Duke Clinical Research Institute

Quiz 4

- Which of the following is likely to help in controlling for confounding and obtaining valid estimates in your study assessing the effectiveness of a therapy in real world patients using databases?
  - *Understanding of the clinical question and what factors affect the treatment and the outcome of interests*
  - *Understanding on the data including how information is collected and the content and quality of the information your databases*
  - *Considerations on collecting additional information or potentially linking your database to others to gain information on potential confounders*
  - *Considerations on the design in identifying appropriate study population and restriction of patients as needed*
  - *Employ statistical technique to control for confounding (propensity score, multivariate modeling etc)*
  - *Sensitivity analyses*
  - *All of the above*

79

Cannot find right patients in your databases (Selection bias)

What is Selection Bias?

- **Definition**

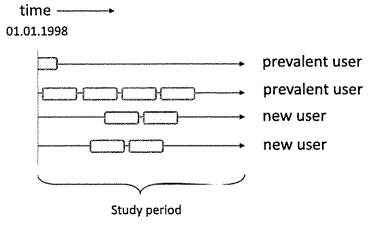
  Distortions that result from procedures used to select subjects and from factors that influence study participation' (Modern Epidemiology)

Potential Sources of Selection Bias

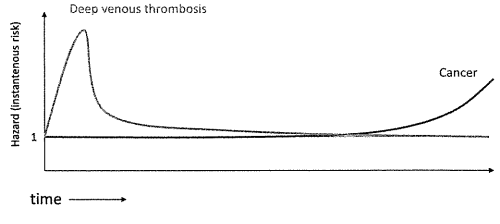
- Participant selection procedure, e.g., exposure affects case ascertainment (**"detection bias"**)
- Differential participation due to death (**'selective survival'**), illness, migration, or refusal (**'nonresponse bias'**)
- Loss to follow-up / attrition / missing data

Cohort studies – start of follow-up

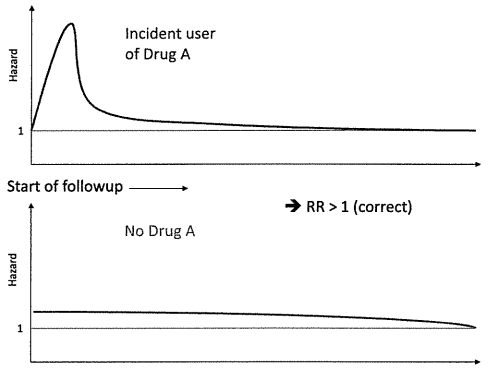
Exposure based cohorts – incident or prevalent user ?



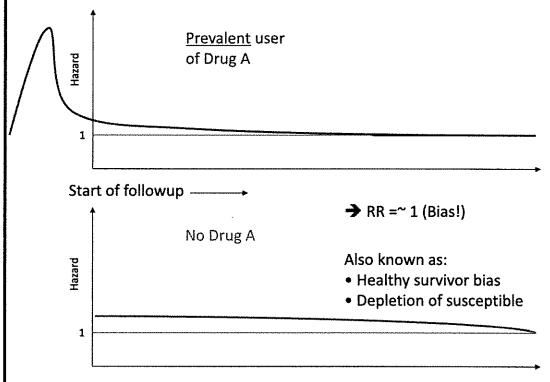
Cohort studies – hazard function



Cohort studies – hazard function for an adverse event

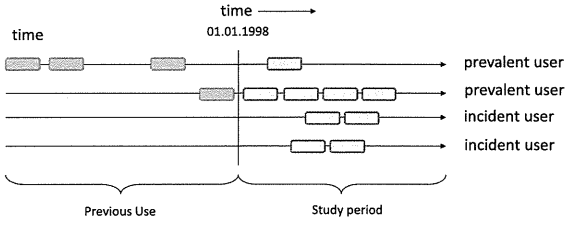


Cohort studies – hazard function



Cohort studies – start of follow-up

Exposure based cohorts – incident or prevalent user ?



- Prefer incident user over prevalent user
- If pure new user design is infeasible, at least consider sensitivity analyses among new users

Importance of New User Design

- All exposed persons should be new users or initiators
  - RCT is an experimental new user design
  - Follow-up starts after initiation

Reporting

- Follow good examples in well regarded journals
  - They are usually very well written although they may not be free from bias
- Follow guidelines
  - http://www.strobe-statement.org/

Summary

- Best practice of database research require
  - Databases!
  - Framework and tools to avoid bias and produce valid results
  - Knowledge in statistics and skills to analyze data

Need educational opportunities for clinical research

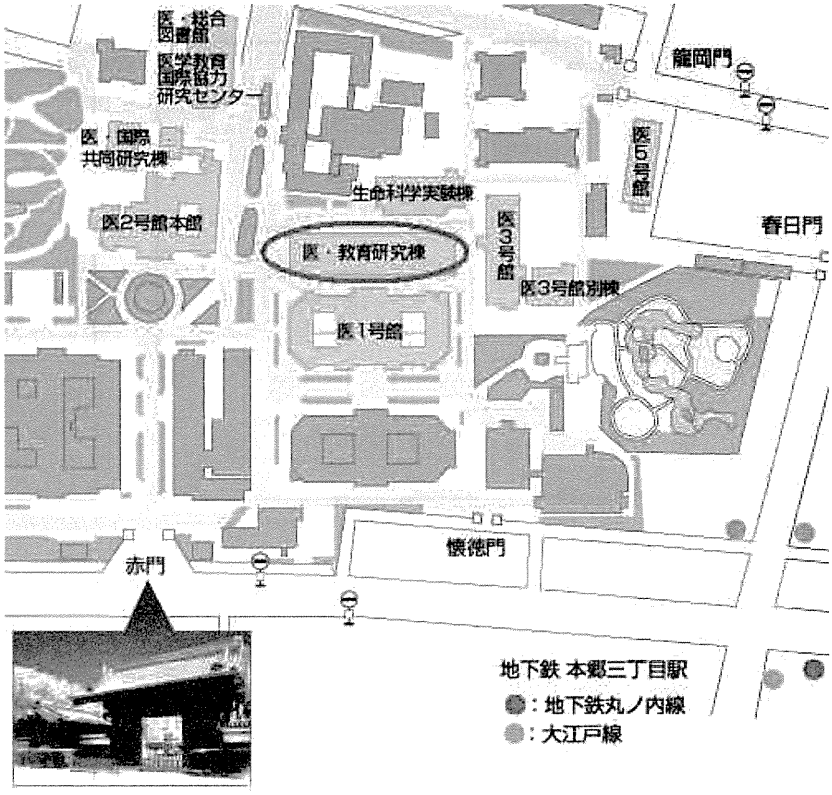
- Best practice of reporting database studies
  - Follow good examples and guidelines

臨床研究・治験の国際化に向けたシンポジウム

(http://cbi.umin.ne.jp/dces/isgcrt_j.pdf)

日　付: 2014 年 2 月 6 日(木)
場　所: 鉄門講堂
東京大学医学部教育研究棟 14F
定員と参加費：　200 名　無料

申込方法及び問い合わせ
お名前、ご所属、電話番号、email アドレスをご記入の上、cbi-secretary@umin.ac.jp にお送りください。
申込締切は 2014 年 1 月 31 日迄とします。



＜プログラム＞

12:30 開場
13:00-13:05(5 分) 開会の辞
東京大学大学院医学系研究科
臨床疫学研究システム講座 特任准教授
小出大介

13:05-13:45 (40 分) 基調講演
研究者主導臨床研究における生物統計家の役割
東京大学大学院医学系研究科 公共健康医学専攻 生物統計学分野 教授 大橋 靖雄

＜メインセッション：研究者主導臨床研究: Up to Date ＞
13:50-14:30 (40 分)
(1) Statistical Methods to Address Confounding in Healthcare Database Research (交絡因子を調整する統計手法)
Dr. M. Alan Brookhart (Associate Professor, Dept. of Epidemiology, Gillings School of Global Public Health,UNC-Chapel Hill)

14:35-15:15 (40 分)
(2) Quality-Driven Investigator-Initiated Clinical Research (質的管理がなされた研究者主導臨床研究)
Dr. Reza Rostami, MBA, CCDM, RAC (Assistant Director, Quality Assurance & Regulatory Compliance, Duke Clinical Research Institute)

15:15-15:30 (15 分) 休憩

15:30-16:10 (40 分)
(3)The Differences Between Japan and US regarding Claim Database and Evaluation of Pharmaceuticals / Medical Devices (日米の相違: 医療機器評価とデータベース研究)
Dr.Soko Setoguchi, MD,MPH (Associate Professor of Medicine, Duke Clinical Research Institute)

16:15-16:45 (30 分)
(4)臨床研究・治験のための e-learning
東京大学大学院医学系研究科 臨床疫学研究システム講座 特任准教授 小出大介

16:45-16:50 (5 分) 閉会の辞
東京大学大学院医学系研究科 臨床疫学研究システム講座 特任准教授 小出大介

注：英語の発表には通訳をつける予定です。また本シンポジウムは今後の e ラーニングのコンテンツのために撮影を行いますことをご了承ください。なお聴衆はビデオに収録されないように配慮致します。
主催：厚生労働科学研究費補助金 医療技術実用化総合研究事業 (H24-臨研基-一般-002)代表：小出大介（東京大学）

Statistical Methods to Address Confounding in Healthcare Database Research

M. Alan Brookhart, Ph.D.
Department of Epidemiology,
UNC Gillings School of Global Public Health
University of North Carolina at Chapel Hill

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

Learning Objectives

- To understand some basic features of two very different statistical approaches to confounding control
  - **Propensity score adjustment**
  - **Instrumental variable analysis**

Motivating Example: Observational Study of Non-steroidal Anti-Inflammatory Drugs and GI bleeding risk in an elderly population

- Compare risk of GI outcomes in elderly between
  - Non-selective NSAIDs
  - COX-2 selective NSAIDs
- In RCTs, coxibs were found to be slightly less likely to cause GI problems
- What is the benefit of Coxibs in a real world patient population?

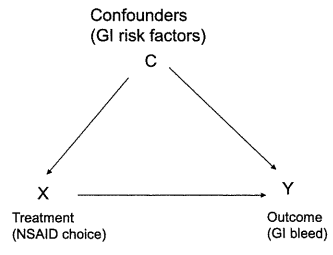
New User Cohort Study

- Population: Medicare beneficiaries in 1 US state
- Cohort of new users of COX-2 inhibitors or non-selective NSAIDs between Jan. 1, 1999 and Jul. 31, 2002
  - Yielded N=49,919
- Captured a variety of covariate from the medical and pharmacy claims
- Do not have measures of laboratory or clinical variables
- Outcome was defined as a hospitalization for peptic ulcer disease or GI bleeding during follow-up (60-days)

Characteristics of Cohort

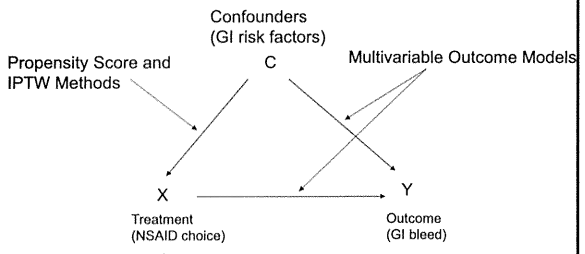
Variable	Coxib	NS NSAID
Female Gender	86%	81%
Age > 75	75%	65%
Charlson Score>1	76%	71%
History of Hospitalization	31%	26%
History of Warfarin Use	13%	7%
History of Peptic Ulcer Disease	4%	2%
History of GI Bleeding	2%	1%
Concomitant GI drug use	5%	4%
History GI drug use	27%	20%
History of Rheumatoid Arthritis	5%	3%
History of Osteoarthritis	49%	33%

Confounding by Indication



Notation: X=treatment (0,1), C=vector of confounders, and Y=outcome

Controlling Remaining Confounding with Statistical Models



Notation: X=treatment (0,1), C=vector of confounders, and Y=outcome

Propensity Score

Propensity score is the probability of receiving treatment (X) given confounders (C)

$$PS = Pr(X=1|C)$$

Propensity scores summarize information about confounding in a single score.

Propensity scores are almost always unknown and must be estimated.

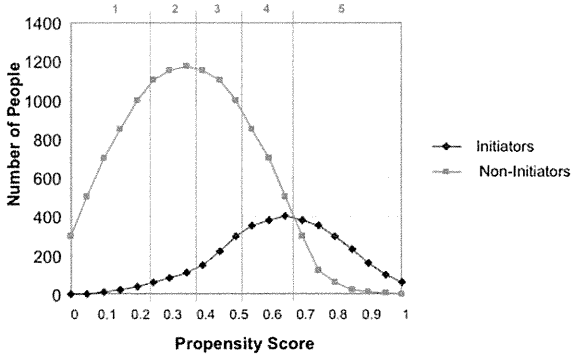
Propensity Score Theory

If all confounders are measured and model for treatment is correct,

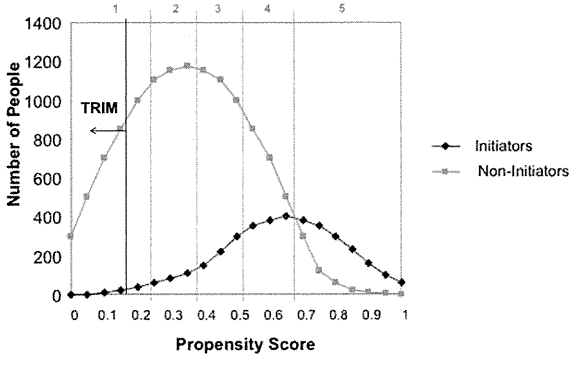
Treatment assignment does not depend on the confounders given the PS.

Among people with the same propensity score, treatment is effectively randomized.

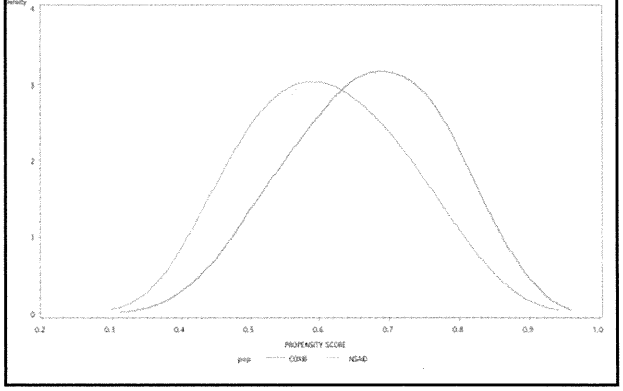
Hypothetical Distribution of Propensity Scores



Hypothetical Distribution of Propensity Scores



Distribution of PS within NSAID Exposure Groups



Inverse Probability of Treatment Weighting (IPTW)

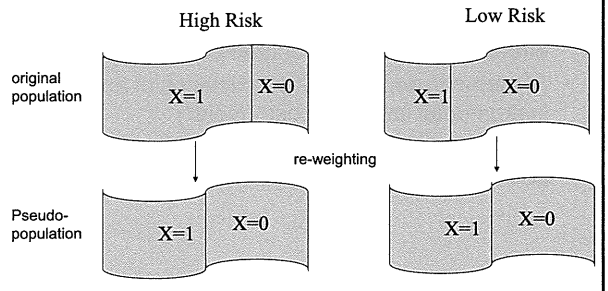
- Each subject weighted by the inverse of the probability that they received their observed treatment
- Inverse probability of treatment (IPTW) estimator
  - Fit a standard regression, but weight by
    1/PS(X), in treated patients
    1/(1- PS(X)), in untreated patients

Inverse Probability of Treatment Weighting (IPTW)

- Fit a standard regression, of the outcome on treatment, but weight with IPTW
- Or can estimate effects by taking difference in weighted means of the outcome between the treated and untreated

$$RD = \frac{1}{n}\left[\sum_{i=1}^{n} Y_i I(X_i = 1) wt_i - \sum_{i=1}^{n} Y_i \{1 - I(X_i = 1)\} wt_i\right]$$

IPTW creates "pseudopopulation" in which treatment is unrelated to covariates



No association between NSAID use (X) and GI risk in pseudopopulation

IPTW estimates the average effect of treatment in the population

- Similar to what is estimated in randomized trial
- Populations in large databases are often ill-defined
- If patients with contraindications are treated, may get hugely up-weighted
- Cause IPTW to give peculiar results
- Other weighting schemes can be used (eg SMR weighting)

NSAIDs & GI Bleeds: Results

Statistical Method	RR (95% CI)
Unadjusted (Crude)	1.09 (0.91-1.30)
Multivariable Regression	0.96 (0.79 -1.15)
Inverse Probability of Treatment Weighting	0.87 (0.71, 1.06)
SMR Weighted Estimator	0.83 (0.66, 1.03)

Coxib Example: Unmeasured Confounding

- Many GI risk factors are unmeasured in health care claims data files
  - Tobacco use
  - BMI / Obesity
  - Alcohol consumption
  - Aspirin use
- PS, IPTW methods cannot address this problem

Current Area of Active Research: Automated Approaches to Building Very Large PS Models

ORIGINAL ARTICLE

High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data

Sebastian Schneeweiss, Jeremy A. Rassen, Robert J. Glynn, Jerry Avorn, Helen Mogun, and M. Alan Brookhart

Epidemiology • Volume 20, Number 4, July 2009

Detailed results of coxib study using hd-PS

Table 3: Variations in covariate adjustment and relative risk estimates for the association of selective cox-2 inhibitors and GI complications within 180 days of first medication use.

Model #	Covariates included in propensity score model	Number of covariates adjusted	Variables tested per data source	Data source granularity	Covariate prioriti-zation algorithm	c-statistic of PS model	Outcome model Relative risk	95% CI
							N = 49,653	
1	Unadjusted					-	1.09	0.91-1.30
2	Age, sex, race, year**	*d*=4				0.61	1.01	0.84-1.21
3	+ predefined covars (Tab1)	*d*=4; *l*=14				0.66	0.94	0.78-1.12
4	+ empirical covariates	*d*=4;*l*=14;*k*=200	*n*=200	3-digit ICD	$Bias_{adj}$	0.69	0.86	0.72-1.04
5*	**+ empirical covariates**	***d*=4;*l*=14;*k*=500**	***n*=200**	**3-digit ICD**	**$Bias_{adj}$**	**0.71**	**0.88**	**0.73-1.06**
							Bootstrapped 95% CIs:	0.73-1.06
5b	Only demographics + empirical covariates	*d*=4; *k*=500	*n*=200	3-digit ICD	$Bias_{adj}$	0.71	0.87	0.72-1.05

Schneeweiss et al. Epidemiology, 2009.

Strengths and Limitations of PS Methods

- Identify patients who are always treated/never treated, for removal from analysis
- Results in estimates with clear interpretation
- When treatment is common, PS models can support large numbers of covariates

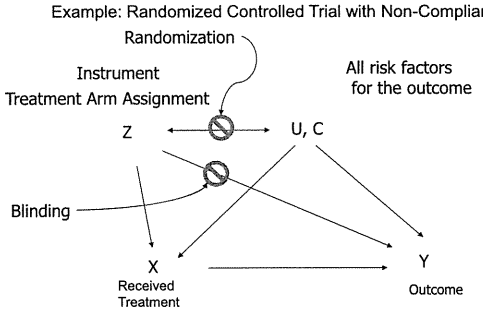
- Require that all confounders are measured and models are correctly specified!

Instrumental Variable Methods

- Developed and widely used by economists
- Can be used to bound and/or estimate treatment effects even when confounders are unmeasured
- IV methods depend on the existence of an instrumental variable ("instrument")
- An IV is a factor that effectively randomizes patients into one group or another

Causal Diagram of Structural IV Assumptions

Example: Randomized Controlled Trial with Non-Compliance



Note: Z can be a valid IV under less restrictive conditions

Note 2: Double headed arrow represents association due to direct causal relation between Z -> C or C <- Z or an assoc. due to a common cause

Intention-to-treat (ITT) Approach

In RCTs with non-compliance, as-treated can be biased estimate of the effect of treatment.

ITT estimates the effect of Z on Y

$$ITT = \Pr[Y = 1 \mid Z = 1] - \Pr[Y = 1 \mid Z = 0]$$

In placebo-controlled trials, ITT estimates tend to be biased towards the null when there is non-compliance.

Classic IV estimator is a rescaled ITT estimator

$$\hat{\alpha}_{IV} = \frac{\Pr[Y=1|Z=1] - \Pr[Y=1|Z=0]}{\Pr[X=1|Z=1] - \Pr[X=1|Z=0]}$$

X is received treatment

- Numerator is the intention to treat (ITT) estimate of the risk difference
- Denominator is estimate of the effect of the instrument on treatment on the risk difference scale

Interpretation of IV Results

- When treatment effects are heterogeneous, IV estimator may not be estimating the average treatment effect
- Under 'monotonicity,' IV estimates the average treatment effect in 'marginal' patients
- Marginal patients are those whose treatment status is influenced by the instrumental variable
- In an RCT with non-compliance, IV estimates the average effect of treatment in the "compliers"

Examples of Instruments Used in Non-Experimental Settings

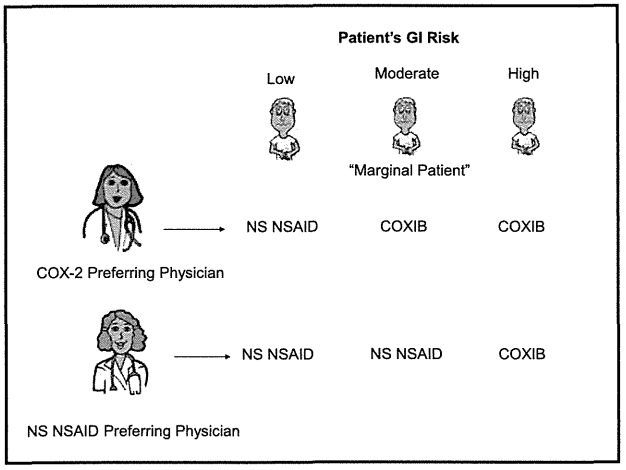
- Change in policy, regulation, or guidelines that create a sharp uptake in use of treatment
- Distance to specialty care providers
- Variation in medical practice across regions, hospitals, physicians – "preference-based"

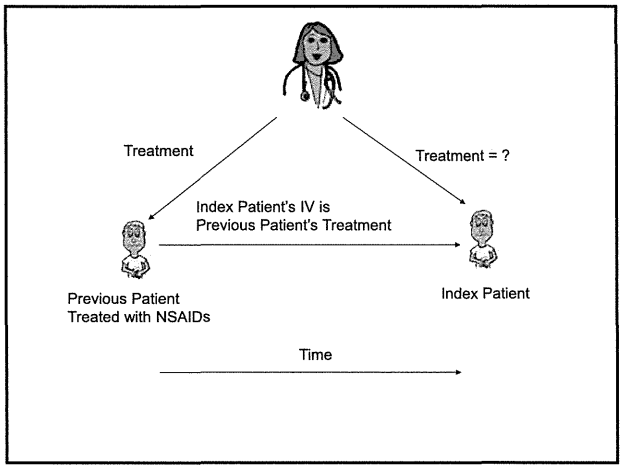
ORIGINAL ARTICLE

Evaluating Short-Term Drug Effects Using a Physician-Specific Prescribing Preference as an Instrumental Variable

M. Alan Brookhart, Philip S. Wang, Daniel H. Solomon, and Sebastian Schneeweiss

- NSAID prescribing is driven strongly by MD preference (Solomon DH, et. al. 2003)
- Implication: Some patients would be treated with new drugs by some physicians and with older drugs by others
- Differences in medication prescribing patterns is the natural experiment that we exploit





Instrument should be related to treatment

NSAID Preference (IV)	Current Prescription (Actual Treatment)	
	Coxib X=1	**Non-Selective NSAID X=0**
Coxib Z=1	(73%)	(27%)
Non-Selective NSAID Z=0	(50%)	(50%)

Instrument should be unrelated to observed patient risk factors

Variable	Patients of Coxib Preferring Docs Z=1	Patients of NS NSAID Preferring Docs Z=0
Female Gender	84%	84%
Age > 75	73%	72%
Charlson Score > 1	75%	73%
History of Hospitalization	29%	27%
History of Warfarin Use	12%	10%
History of Peptic Ulcer Disease	3%	3%
History of GI Bleeding	1%	1%
Concomitant GI drug use	5%	5%
History GI drug use (e.g., PPIs)	25%	24%
History of Rheumatoid Arthritis	4%	4%
History of Osteoarthritis	45%	41%

IV estimate of the effect of coxib exposure on GI outcome

$$\frac{E[Y|Z=1]-E[Y|Z=0]}{E[X|Z=1]-E[X|Z=0]} = \frac{-0.21\%}{22.8\%} = -0.92\%$$

95% CI (-1.75, 0.10%)

- Numerator is the intention to treat (ITT) estimate of the risk difference
- Denominator is estimate of the effect of the instrument on treatment on the risk difference scale

Strengths and Limitations of Instrumental Variable Methods

- **IV may address unobserved confounding**
- **IV methods are often statistically inefficient**
- **IV could result in highly biased estimate if assumptions aren't met**
  - Differences in patient case-mix
  - Differences in medical practice or case-mix
- **IVs are difficult to find**

Propensity Score vs Instrumental Variables

- Ultimately we cannot know which method is correct (each depends on assumptions that are not testable)
- We must use subject matter information and good judgment
- If there is little confounding, PS methods are certainly preferable
- If there is very strong unmeasured confounding and a good instrumental variable is available, IV methods may be preferable
- In some examples, PS and IV methods agree.

Thank you

Quality-Driven Investigator-Initiated Clinical Research

Reza Rostami, MBA,
CCDM, CQA, CQE, CMQ/OE, CSSBB, RAC

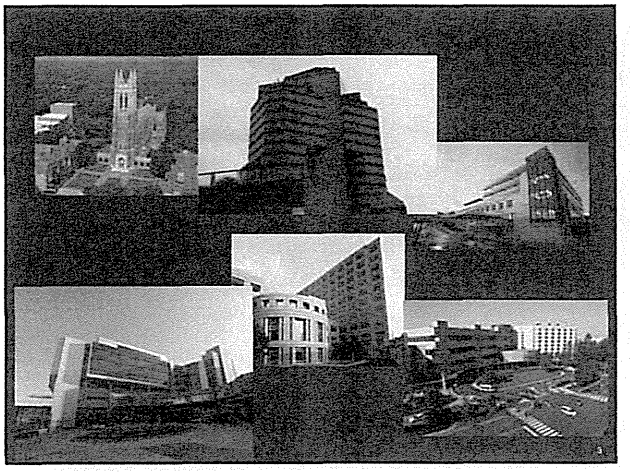
Assistant Director
Quality Assurance/Regulatory Compliance
Duke Clinical Research Institute
Duke University

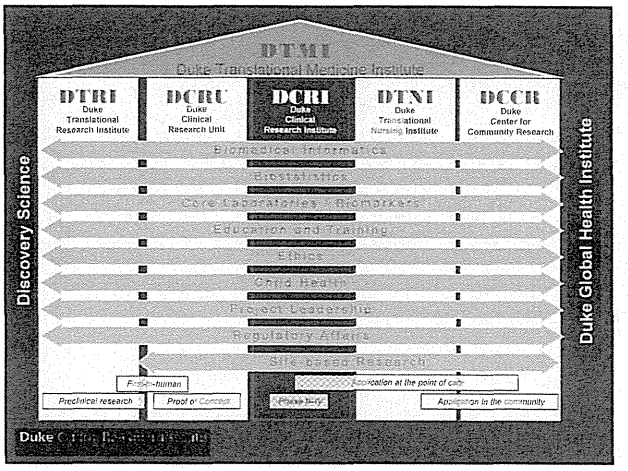
Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

International Symposium on Globalization of Clinical Research and Trial
Tokyo, Feb. 6, 2014

Topics

- An ARO Model
- Investigator-Initiated Clinical Trial
- Quality Assurance Model
- Data Integrity
- Principals of GCP
- Quality System





Academic Research Organization

- **Academic focus / University based**
  - Collaborative group of investigators (atypical of academic model)
  - Provide scientific leadership in the conduct of clinical research
  - Advanced clinical research methodology
  - True patient connection
- **Clinical research**
  - Research: A systematic evaluation to develop generalizable knowledge
  - Clinical Research: Research involving human participants
  - Extensive knowledge of regulatory requirements
  - High quality of data
  - Best-in-class statistics and quantitative science
- **Operational capability**
  - Shared resource (atypical of academic model)
  - Focus on knowledge dissemination through publications and high impact presentation venues

Visionary Leadership

- 1969 Founding of the Duke Databank for Cardiovascular Diseases
- 1970s Observational research
- 1980s Coordination of multi-center clinical trials in cardiology
- 1990s Extensive experience in coordinating large global multicenter clinical trials
- 2000s Therapeutic diversification, clinical trial networks, public-private partnerships, relationships with professional societies