Statistical Concepts for Clinical Research

- PJ Heagerty
- Department of Biostatistics
- University of Washington

CTSA Core Competencies: Statistics

1. Describe the role that biostatistics serves in biomedical and public health research.
2. Describe the basic principles and practical importance of **random variation**, **systematic error**, sampling error, measurement error, **hypothesis testing**, type I and type II errors, and **confidence limits**.
3. Scrutinize the assumptions behind different statistical methods and their corresponding limitations.

4. Generate simple descriptive and inferential statistics that fit the study design chosen and answer research question.
5. Compute **sample size**, **power**, and precision for comparisons of two independent samples with respect to continuous and binary outcomes.
6. Describe the uses of meta-analytic methods.
7. Defend the significance of data and safety monitoring plans.

8. Collaborate with biostatisticians in the design, conduct, and analyses of clinical and translational research.
9. Evaluate computer output containing the results of statistical procedures and graphics.
10. Explain the uses, importance, and limitations of early stopping rules in clinical trials.

Overall Focus

- **Ralph Waldo Emerson**
  - ▷ "If you learn only methods, you'll be tied to your methods, but if you learn principles you can devise your own methods."

A Motivating Example...

- Carpal Tunnel Surgery: Jarvik et al. (2009) *Lancet*
  - Surgical trials often evaluate **pain** and **function** as co-primary outcomes.
  - Comparison of progression / comparison of long-term status
- Key Elements:
  - A research **team**
  - Grant proposal / Protocol
  - Study monitoring / Publication

Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial

Jeffrey G Jarvik, Bryan A Comstock, Michel Kliot, Judith A Turner, Leighton Chan, Patrick J Heagerty, William Hollingworth, Carolyn L Kerrigan, Richard A Deyo

Summary

Background A previous randomised controlled trial reported greater efficacy of surgery than of splinting for patients with carpal tunnel syndrome. Our aim was to compare surgical versus multi-modality, non-surgical treatment for patients with carpal tunnel syndrome without denervation. We hypothesised that surgery would result in improved functional and symptom outcomes.

Methods In this parallel-group randomised controlled trial, we randomly assigned 116 patients from eight academic and private practice centres, using computer-generated random allocation stratified by site, to carpal tunnel surgery (n=57) or to a well-defined, non-surgical treatment (including hand therapy and ultrasound; n=59). The primary outcome was hand function measured by the Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) at 12 months assessed by research personnel unaware of group assignment. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00032227.

Findings 44 (77%) patients assigned to surgery underwent surgery. At 12 months, 101 (87%) completed follow-up and were analysed (49 of 57 assigned to surgery and 52 of 59 assigned to non-surgical treatment). Analyses showed a significant 12-month adjusted advantage for surgery in function (CTSAQ function score: Δ –0·40, 95% CI 0·11–0·70, p=0·0081) and symptoms (CTSAQ symptom score: 0·34, 0·02–0·65, p=0·0357). There were no clinically important adverse events and no surgical complications.

Interpretation Symptoms in both groups improved, but surgical treatment led to better outcome than did non-surgical treatment. However, the clinical relevance of this difference was modest. Overall, our study confirms that surgery is useful for patients with carpal tunnel syndrome without denervation.

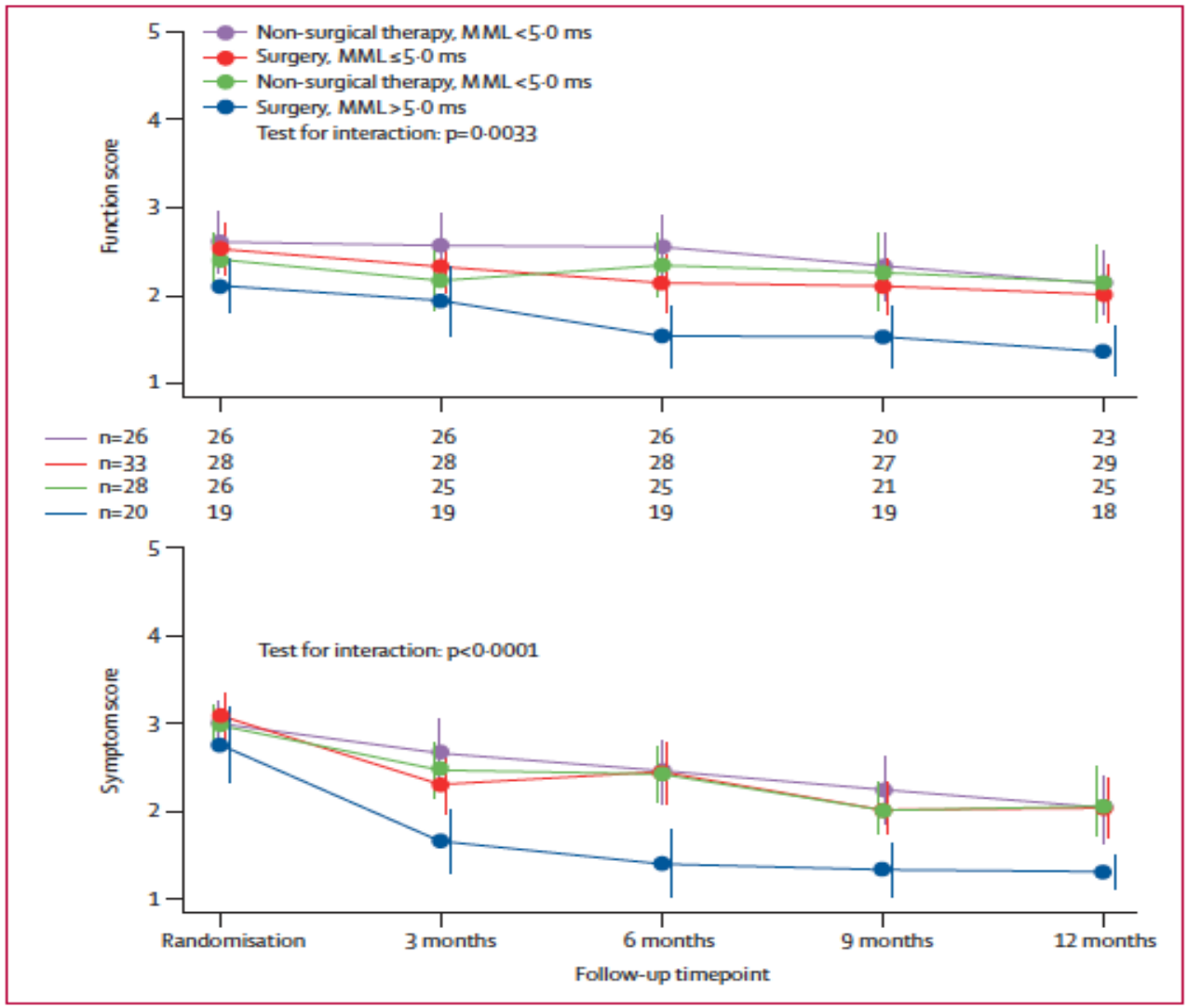


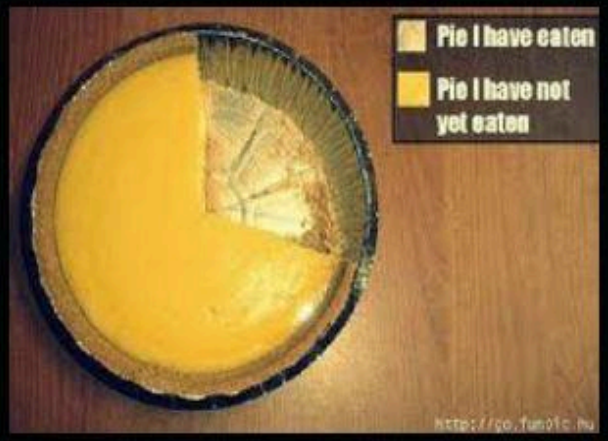
Figure 2: **Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) function and symptom scores**
Scores are stratified by randomised treatment assignment and baseline distal median motor latency. Data are mean (95% CI).

Outline for ITHS Bootcamp

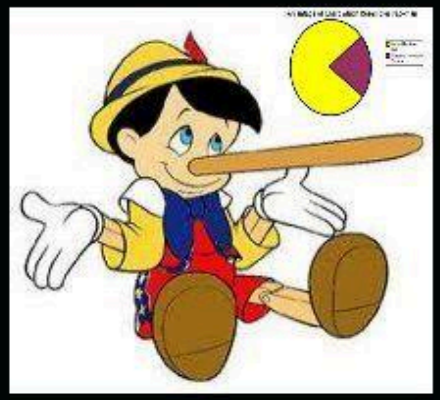
- Why you might want to talk to a statistician.
- How a statistician approaches research aims
- Key considerations in study design
- What you need to know to "bridge the gap"
  - ▷ What data should arise if there is **no association**?
  - ▷ What data should arise if there is **an association**?

STATISTICIAN

What my friends think I do



What my mom thinks I do



What society thinks I do

What my boss thinks I do

What I think I do

What I actually do

SOURCE: http://statswithcats.files.wordpress.com/2012/02/statistician.jpg

Why you might want to talk to a statistician...

- Academic statisticians (faculty) have co-written dozens of grants and have seen what works and what does not work.
- Academic statisticians (faculty) can be really good at helping you to articulate your ideas and to refine your plans.

  question $\rightleftarrows$ **hypothesis** $\rightleftarrows$ **design** $\rightleftarrows$ **analysis**
- Data collection / management and statistics are key collaborative components for most clinical research studies.

Research Question

- What groups do you want to **compare**?
- What do you want to **measure**?
- When will you **measure**?
- What do you need (hope) to **control** (hold fixed) in order to **compare** groups?

Research Goals

- To **describe** associations / patterns.
  - ▷ Moderately easy.
  - ▷ Create an analysis plan ("diary") to document.
- To **make inference** or attribute cause to a condition / exposure.
  - ▷ Moderately difficult.
  - ▷ Require an analysis plan before conduct.
- To **predict** what will happen to individual subjects.
  - ▷ Moderately easy.
  - ▷ Analysis plan to document decisions.

Examples: Descriptive Studies

Spine J. 2012 Feb;12(2):89-97. Epub 2011 Dec 21.

Repeat surgery after lumbar decompression for herniated disc: the quality implications of hospital and surgeon variation.

Martin BI, Mirza SK, Flum DR, Wickizer TM, Heagerty PJ, Lenkoski AF, Deyo RA.

Department of Orthopaedics, HB7541, Dartmouth-Hitchcock Medical Center, One Medical Center Dr, Lebanon, NH 03756-0001, USA. Brook.I.Martin@Dartmouth.edu

Abstract

BACKGROUND CONTEXT: Repeat lumbar spine surgery is generally an undesirable outcome. Variation in repeat surgery rates may be because of patient characteristics, disease severity, or hospital- and surgeon-related factors. However, little is known about population-level variation in reoperation rates.

PURPOSE: To examine hospital- and surgeon-level variation in reoperation rates after lumbar herniated disc surgery and to relate these to published benchmarks.

STUDY DESIGN/SETTING: Retrospective analysis of a discharge registry including all nonfederal hospitals in Washington State.

METHODS: We identified adults who underwent an initial inpatient lumbar decompression for herniated disc from 1997 to 2007. We then performed generalized linear mixed-effect logistic regressions, controlling for patient characteristics and comorbidity, to examine the variation in reoperation rates within 90 days, 1 year, and 4 years.

RESULTS: Our cohort included 29,529 patients with a mean age of 47.5 years, 61% privately insured, and 15% having any comorbidity. The age-, sex-, insurance-, and comorbidity-adjusted mean rate of reoperation among hospitals was 1.9% at 90 days (95% confidence interval [CI], 1.2-3.1), with a range from 1.1% to 3.4%; 6.4% at 1 year (95% CI, 3.9-10.6), with a range from 2.8% to 12.5%; and 13.8% at 4 years (95% CI, 8.8-19.8), with a range from 8.1% to 24.5%. The adjusted mean reoperation rates of surgeons were 1.9% at 90 days (95% CI, 1.4-2.4) with a range from 1.2% to 4.6%, 6.1% at 1 year (95% CI, 4.8-7.7) with a range from 4.3% to 10.5%, and 13.2% at 4 years (95% CI, 11.3-15.5) with a range from 10.0% to 19.3%. Multilevel random-effect models suggested that variation across surgeons was greater than that of hospitals and that this effect increased with long-term outcomes.

Examples: Descriptive Studies – Martin (2012)

- **Goal**: **describe** variation in reoperation rates.
- **Compare**: hospitals, surgeons.
- **Measurement**: WA registry to capture time-until-reoperation.
- **Control**: age, gender, insurance, comorbidity measures.
- **Additional Comments**:
  - ▷ Reports estimates, confidence intervals, p-values
  - ▷ Required use of multi-level models.

Examples: Descriptive Studies

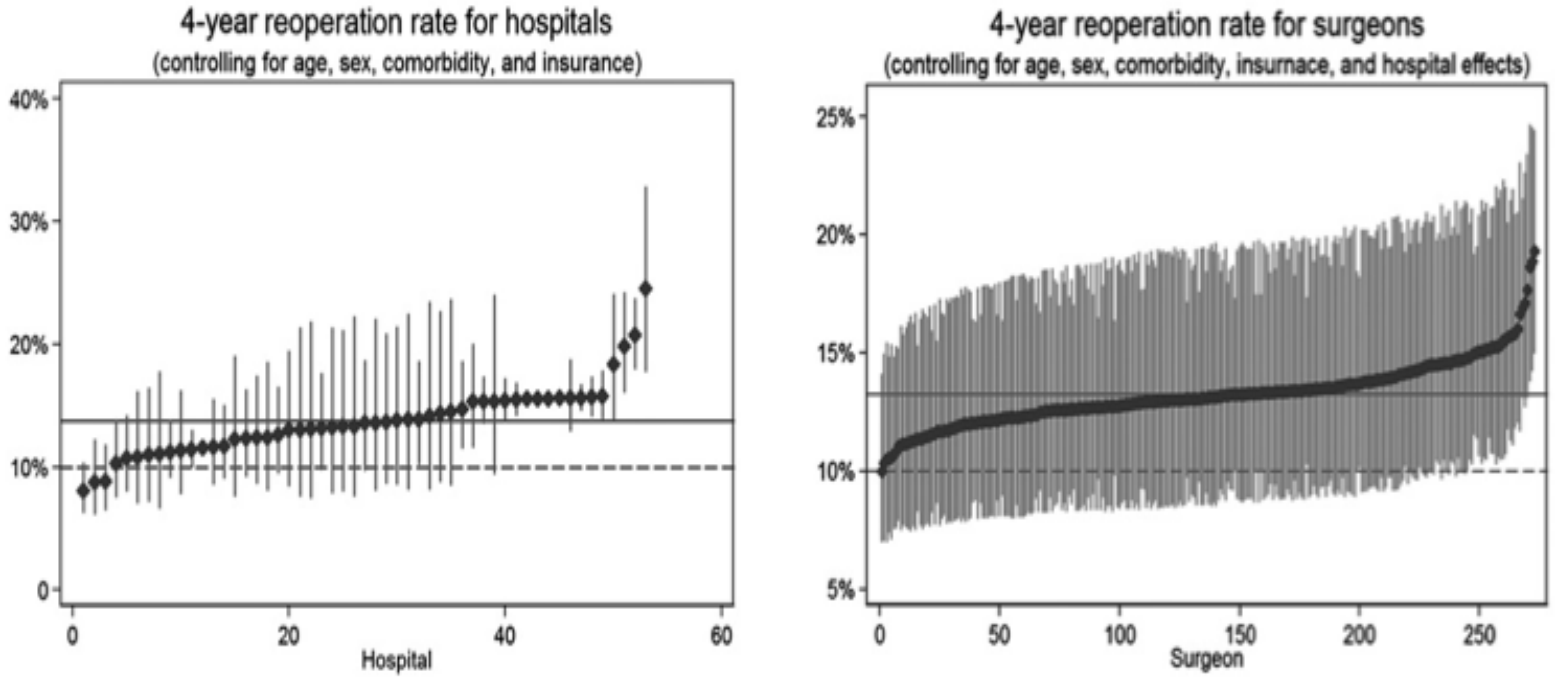


Fig. 2. The reoperation rates within 90 days, 1 year, and 4 years after inpatient lumbar decompression surgery for herniated disc. Each spike represents 95% Bayesian confidence interval for the probability of reoperation within hospitals (figures on left) and surgeons nested within hospitals (figures on right) in Washington State. For the purposes of presentation, we excluded those surgeons who have fewer than 10 cases (because of their uninformative low volumes, we could not identify any of them as being significantly above or below the Spine Patient Outcomes Research Trial [SPORT] benchmark). The solid horizontal line represents the overall reoperation rate, whereas dashed lines represent the reoperation benchmark from SPORT.

Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial

Jeffrey G Jarvik, Bryan A Comstock, Michel Kliot, Judith A Turner, Leighton Chan, Patrick J Heagerty, William Hollingworth, Carolyn L Kerrigan, Richard A Deyo

Summary

Background A previous randomised controlled trial reported greater efficacy of surgery than of splinting for patients with carpal tunnel syndrome. Our aim was to compare surgical versus multi-modality, non-surgical treatment for patients with carpal tunnel syndrome without denervation. We hypothesised that surgery would result in improved functional and symptom outcomes.

Methods In this parallel-group randomised controlled trial, we randomly assigned 116 patients from eight academic and private practice centres, using computer-generated random allocation stratified by site, to carpal tunnel surgery (n=57) or to a well-defined, non-surgical treatment (including hand therapy and ultrasound; n=59). The primary outcome was hand function measured by the Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) at 12 months assessed by research personnel unaware of group assignment. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00032227.

Findings 44 (77%) patients assigned to surgery underwent surgery. At 12 months, 101 (87%) completed follow-up and were analysed (49 of 57 assigned to surgery and 52 of 59 assigned to non-surgical treatment). Analyses showed a significant 12-month adjusted advantage for surgery in function (CTSAQ function score: Δ –0·40, 95% CI 0·11–0·70, p=0·0081) and symptoms (CTSAQ symptom score: 0·34, 0·02–0·65, p=0·0357). There were no clinically important adverse events and no surgical complications.

Interpretation Symptoms in both groups improved, but surgical treatment led to better outcome than did non-surgical treatment. However, the clinical relevance of this difference was modest. Overall, our study confirms that surgery is useful for patients with carpal tunnel syndrome without denervation.

Examples: Inferential Studies – Jarvik (2009)

- **Goal**: **evaluate** impact of surgery
- **Compare**: surgery versus standard-of-care
- **Measurement**: disease-specific functional measure
- **Control**: baseline status
- **Additional Comments**:
  - **Randomized** trial – comparisons are simple
  - Pre-post data analysis (and longitudinal)

Example: Inferential Studies

	6 months				12 months			
	Surgical (n=50)	Non-surgical (n=54)	Treatment effect* (95% CI)	p value	Surgical (n=49)	Non-surgical (n=52)	Treatment effect* (95% CI)	p value
Primary outcome								
CTSAQ function (1–5)	1·91(0·88)	2·44 (0·87)	0·46 (0·20 to 0·72)	0·0006	1·74 (0·79)	2·17 (0·96)	0·40 (0·11 to 0·70)	0·0081
Secondary outcomes								
CTSAQ symptom (1–5)	2·02 (1·03)	2·42 (0·80)	0·42 (0·07 to 0·77)	0·0181	1·74 (0·76)	2·07 (0·88)	0·34 (0·02 to 0·65)	0·0357
Days of reduced work or housework (0–28)	4·3 (8·8)	6·3 (9·4)	2·3 (–1·0 to 5·6)	0·1638	2·2 (5·6)	5·2 (8·8)	2·7 (–0·0 to 5·4)	0·0524
Days of lost work (0–28)	0·7 (4·3)	2·8 (8·1)	2·3 (–0·6 to 5·3)	0·1174	0·1 (0·7)	1·6 (5·8)	0·9 (–0·4 to 2·3)	0·1641
Pain intensity (0–10)	4·7 (3·2)	5·7 (3·1)	1·0 (–0·2 to 2·1)	0·0993	3·5 (3·0)	4·3 (3·3)	0·9 (–0·3 to 2·1)	0·1590
Pain interference (0–10)	2·8 (3·0)	3·4 (3·2)	0·1 (–0·8 to 1·1)	0·8068	2·1 (6·9)	3·1 (3·3)	0·6 (–0·3 to 1·6)	0·1957
SF-36 (version 2.0)† PCS	39 (12)	37 (11)	1·5 (–1·7 to 4·7)	0·3608	39 (14)	37 (12)	1·6 (–2·8 to 6·0)	0·4762
SF-36 (version 2.0)† MCS	47 (16)	47 (14)	0·9 (–3·5 to 5·4)	0·6833	45 (15)	47 (15)	–0·5 (–6·0 to 5·0)	0·8520

Data are mean (SD) unless otherwise stated. CTSAQ=Carpal Tunnel Syndrome Assessment Questionnaire. SF-36=short-form-36. PCS=physical component summary. MCS=mental component summary. *Treatment effect indicates the difference between surgical and non-surgical groups on the outcome measure at 6 and 12 months, based on ANCOVA adjusted for the baseline value of the outcome measure and treatment site. A positive effect indicates that patients assigned to surgery had better outcomes than did those assigned to non-surgical care. †SF-36 PCS and MCS scores are norm-based with mean (SD) of 50 (10) in a healthy population. Higher scores indicate better function.

***Table 2:* Primary and secondary outcomes and adjusted treatment effect at 6 and 12 months by randomised treatment assignment (intention-to-treat comparisons)**

Validation of case-mix measures derived from self-reports of diagnoses and health

Vincent S. Fan[a,b,*], David Au[a,b], Patrick Heagerty[c], Richard A. Deyo[b], Mary B. McDonell[a], Stephan D. Fihn[a,b]

[a]*Health Services Research and Development Center of Excellence, VA Puget Sound Health Care System, Seattle, WA, USA*
[b]*Department of Medicine, University of Washington, Seattle, WA, USA*
[c]*Department of Biostatistics, University of Washington, Seattle, WA, USA*

Abstract

Self-reported chronic diseases and health status are associated with resource use. However, few data exist regarding their ability to predict mortality or hospitalizations. We sought to determine whether self-reported chronic medical conditions and the SF-36 could be used individually or in combination to assess co-morbidity in the outpatient setting. The study was designed as a prospective cohort study. Patients were enrolled in the primary care clinics at seven Veterans Affairs (VA) medical centers participating in the Ambulatory Care Quality Improvement Project (ACQUIP). 10,947 patients, ⩾ 50 years of age, enrolled in general internal medicine clinics who returned both a baseline health inventory checklist and the baseline SF-36 who were followed for a mean of 722.5 (±84.3) days. The primary outcome was all-cause mortality, with a secondary outcome of hospitalization within the VA system. Using a Cox proportional hazards model in a development set of 5,469 patients, a co-morbidity index [Seattle Index of Co-morbidity (SIC)] was constructed using information about age, smoking status and seven of 25 self-reported medical conditions that were associated with increased mortality. In the validation set of 5,478 patients, the SIC was predictive of both mortality and hospitalizations within the VA system. A separate model was constructed in which only age and the PCS and MCS scores of the SF-36 were entered to predict mortality. The SF-36 component scores and the SIC had comparable discriminatory ability (AUC for discrimination of death within 2 y 0.71 for both models). When combined, the SIC and SF-36 together had improved discrimination for mortality (AUC = 0.74, p-value for difference in AUC < 0.005). A new outpatient co-morbidity score developed using self-identified chronic medical conditions on a baseline health inventory checklist was predictive of 2-y mortality and hospitalization within the VA system in general internal medicine patients.

Example: Predictive Studies – Fan (2002)

- **Goal**: **predict** hospitalization / death
- **Compare**: different sources of information
- **Measurement**: time-until-event / comorbidities
- **Control**: not key – just measure predictive ability!
- **Additional Comments**:
  - ▷ **Development / validation** data
  - ▷ Assessment of predictive accuracy

Table 2
Prevalence of self-reported chronic medical conditions

Disease Condition, %	Development Sample (N = 5469) %	Validation Sample (N = 5478) %	P-value
Number of Co-morbidities*			
Mean (SD)	3.75 (0.03)	3.79 (0.03)	0.4
Cardiac Disease Variables:			
Angina	31.2	30.6	0.5
Coronary Artery Disease	20.2	19.2	0.2
Prior Myocardial Infarction	21.9	21.7	0.8
CABG/PTCA	20.7	19.6	0.1
Any Heart Disease**	41.8	41.7	0.9
Arthritis	58.1	58.7	0.5
Cancer	14.3	13.2	0.09
Lung disease	23.8	24.1	0.8
Heartburn	18.1	18.4	0.7
Congestive heart failure	9.2	9.4	0.8
Depression	22.4	23.3	0.3
Diabetes	24.9	23.6	0.1
Drug abuse	1.4	1.5	0.5
Enlarged Prostate	27.7	28.0	0.7
Hypertension	57.4	59.4	0.04
HIV disease	0.6	0.4	0.3
Renal insufficiency	12.1	11.3	0.2
Liver disease	6.3	5.5	0.1
Osteoporosis	3.6	3.4	0.7
Pneumonia	13.7	14.9	0.07
Post-Traumatic Stress Disorder	8.1	8.6	0.3
Seizure	3.5	3.4	0.7
Ulcer disease	17.9	17.3	0.4
Stroke	10.9	12.9	0.001
Thyroid disease	4.1	4.9	0.04

*angina, cad, prior MI and CABG/PTCA are counted only once

**If a subject has any of the following: angina, coronary artery disease, Prior myocardial infarction, or CABG/PTCA

CABG/PTCA=coronary artery bypass graft surgery or percutaneous trans coronary angioplasty; HIV=Human Immunodeficiency Virus

Table 3
Univariate hazard ratio for mortality associated with each chronic medical condition on the health inventory questionnaire

Disease Condition, %	Hazard Ratio	P-Value
Age (continuous)	1.05	0.000
Gender	1.29	0.474
Cardiac Disease Variables:		
Angina	1.47	0.000
Coronary Artery Disease	1.69	0.000
Prior Myocardial Infarction	1.93	0.000
CABG/PTCA	1.71	0.000
Any Heart Disease	1.69	0.000
Arthritis	0.92	0.382
Cancer	2.02	0.000
Lung disease	1.70	0.000
Heartburn	1.06	0.626
Congestive heart failure	2.65	0.000
Depression	1.29	0.026
Diabetes	1.64	0.000
Drug abuse	1.52	0.243
Enlarged Prostate	0.90	0.354
Hypertension	0.90	0.294
HIV disease	0.89	0.910
Renal insufficiency	1.54	0.001
Liver disease	1.38	0.079
Osteoporosis	1.96	0.001
Pneumonia	1.91	0.000
Post-Traumatic Stress Disorder	1.03	0.890
Seizure	1.41	0.141
Ulcer disease	1.40	0.005
Stroke	2.01	0.000
Thyroid disease	0.78	0.389
Smoking		
Never	1.00	—
Former	1.58	0.004
Current	1.95	0.000

*CABG=Coronary Artery Bypass Grafting, PTCA=Percutaneous Transluminal Coronary Angioplasty, HIV=Human Immunodeficiency Virus

Summary of Study Goals

- One framework organized according to:
  - Descriptive
  - Inferential / Confirmatory
  - Predictive
- Statisticians can help connect the study **goals** to a chosen **study design** and appropriate **analysis plan**
- Key elements of study design include:
  - Choice of target population
  - Choice of **measurements**
  - Elements under the control of the research team

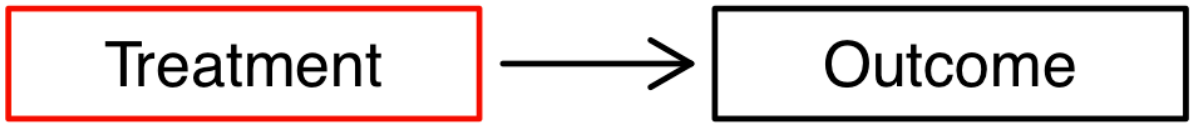
The Measurements

- The major categories for variables are:
- **Outcome** – variable that reflects the clinically meaningful **result** for the subject (unit) under study.
  - ▷ e.g. time-until-death
  - ▷ e.g. function (disability) status
- **Predictor of Interest** – the variable that you want to study as possible **cause** of outcome.
  - ▷ e.g. genotype(s)
  - ▷ e.g. treatment group

The Measurements

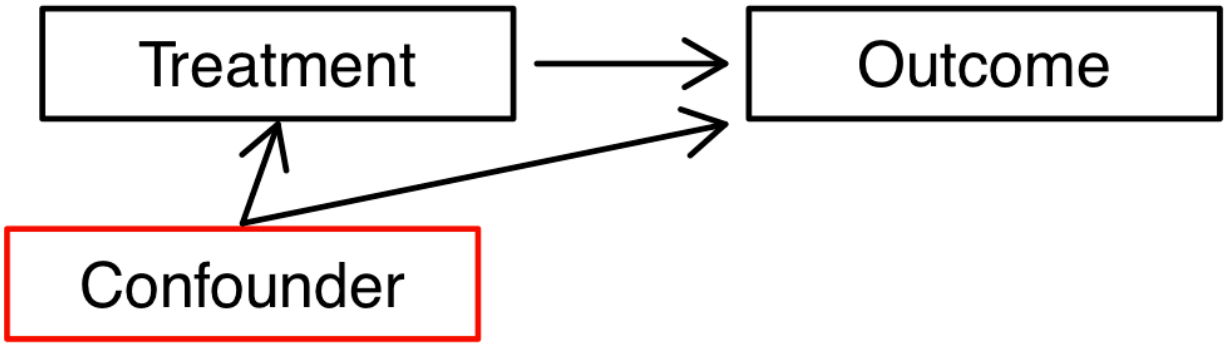
- The major categories for variables are:
- **Potential Confounder** – variable that is possibly **"confused"** with the predictor of interest.
  - ▷ e.g. clinical indications for treatment
  - ▷ e.g. recruitment site
- **Precision Variable** – used to explain some of the **variance** of outcome.
  - ▷ e.g. baseline (pre-randomization) health status
  - ▷ e.g. age of child

Variables [1]



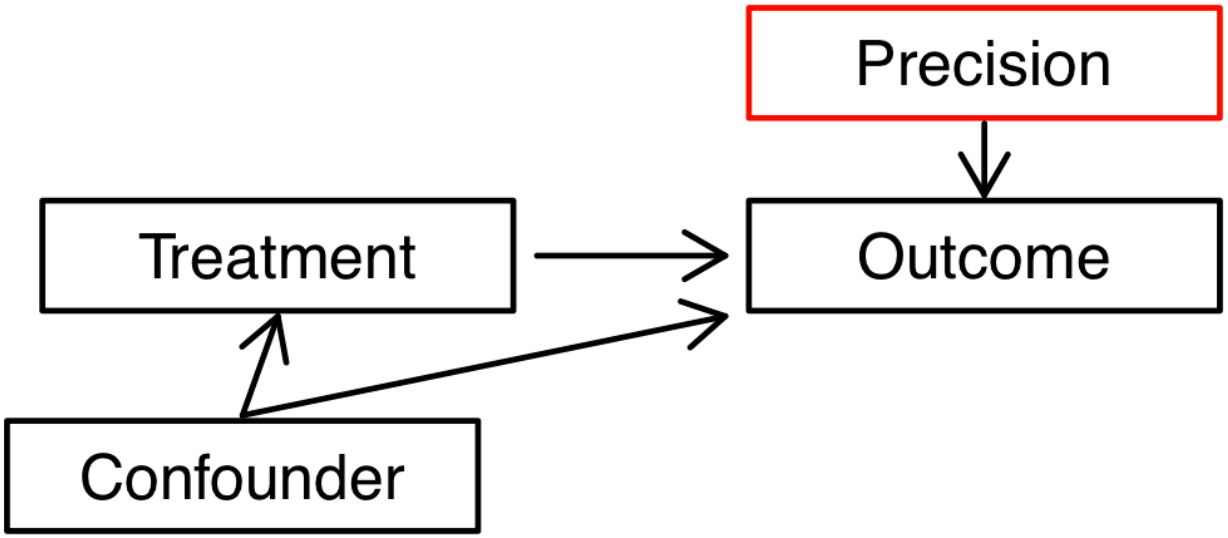
- Surgery $\rightarrow$ CTSAQ function
- Genotype $\rightarrow$ diabetes

Variables [2]



- **[surgery]** Pre-treatment pain (observational study)
- **[genes]** Continent of origin

Variables [3]



- **[surgery]** Pre-treatment pain (randomized trial)
- **[genes]** Smoking

More on Variables...

- **Definition**: Confounding refers to the presence of an additional factor, Z, which when not accounted for leads to an association between treatment, X, and outcome, Y, that does not reflect a causal effect. Counfounding is ultimately a "confusion" of the effects of X and Z. For a variable Z to be a confounder it must: be associated with X in the population; be a predictor of Y in the control $(X = 0)$ group; and not be a consequence of either X or Y.
- **a selection bias**: van Belle, Fisher, Heagerty & Lumley (2004)

A Perfect Situation

- Suppose that we are interested in the effect of surgery for low back pain.
- Suppose we measure function (or pain) for each person Y_i (i is individual subject)
- Suppose **somehow** we could measure what would happen to each person if they were **surgically treated**, $Y_i(1)$, and if they were non-surgically treated, $Y_i(0)$.
- We would then have the information that we wanted!

Subject	Potential Outcomes		Causal Effect
i	$Y_i(0)$	$Y_i(1)$	Δ_i
1	4.5	2.7	-1.8
2	3.1	1.0	-2.1
3	3.9	2.0	-1.9
4	4.3	2.2	-2.1
5	3.3	1.5	-1.9
6	3.3	0.8	-2.5
7	4.0	1.5	-2.5
8	4.9	3.2	-1.7
9	3.8	2.0	-1.9
10	3.6	2.0	-1.6

11	7.5	5.1	-2.3
12	6.7	5.2	-1.5
13	6.0	4.4	-1.6
14	5.6	3.2	-2.4
15	6.5	4.0	-2.4
16	7.7	6.0	-1.8
17	7.1	5.1	-2.1
18	8.3	6.0	-2.3
19	7.0	4.6	-2.4
20	6.9	5.3	-1.5
Mean	5.40	3.39	**-2.01**

A Randomized Trial

- Suppose that we are interested in the effect of surgery for low back pain.
- Suppose we **randomly** assign surgery or non-surgery. (with all conduct caveats)
- Now we only "see half" of what we'd like, but the comparison of surgical to non-surgical subjects is perfectly fair.
- We have no **selection bias**.

Subject	**Randomized**	Observed		
i	Assignment	$Y_i(0)$	$Y_i(1)$	Difference
1	0	4.5		
2	1		1.0	
3	1		2.0	
4	1		2.2	
5	0	3.3		
6	1		0.8	
7	1		1.5	
8	0	4.9		
9	0	3.8		
10	0	3.6		

11	1		5.1	
12	0	6.7		
13	0	6.0		
14	0	5.6		
15	0	6.5		
16	1		6.0	
17	1		5.1	
18	0	8.3		
19	1		4.6	
20	1		5.3	
Mean		5.32	3.37	**-1.95**

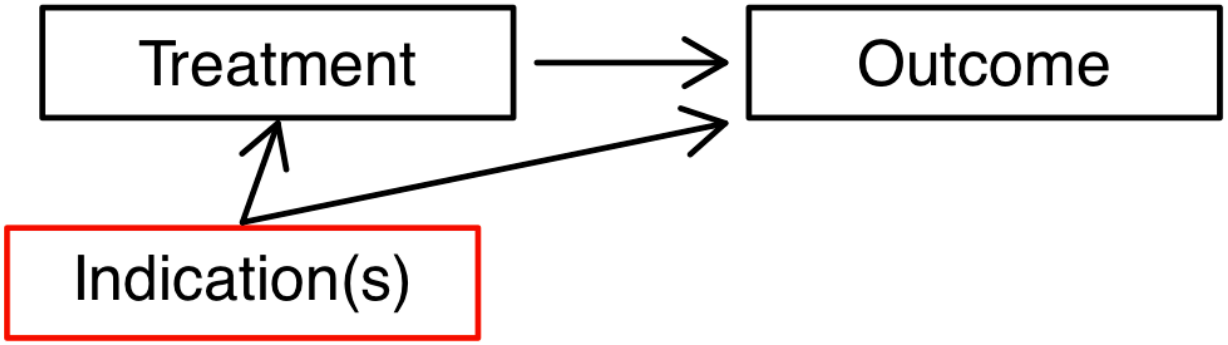
An Observational Trial

- Suppose that we are interested in the effect of surgery for low back pain.
- Suppose we **have available** subjects that have had surgery or non-surgical treatment.
- **Q**: what leads some subjects to get treatment?
- Suppose we know that there are "poor" and "good" functioning patients based on their pre-treatment clinical assessment, and that this status is highly related to moving to surgery.
- **Q**: can we **control** for baseline-status?

Subject	**Observational**	Observed			
i	Assignment	$Y_i(0)$	$Y_i(1)$	**Strata**	Difference
1	1		2.7	1	
2	0	3.1		1	
3	0	3.9		1	
4	1		2.2	1	
5	0	3.3		1	
6	0	3.3		1	
7	0	4.0		1	
8	0	4.9		1	
9	0	3.8		1	
10	0	3.6		1	
Mean		3.74	2.45		**-1.29**

	11	1		5.1	2
	12	1		5.2	2
	13	1		4.4	2
	14	0	5.6		2
	15	1		4.0	2
	16	0	7.7		2
	17	1		5.1	2
	18	1		6.0	2
	19	1		4.6	2
	20	1		5.3	2
	Mean		6.65	4.96	**-1.69**
Overall Mean			4.32	4.46	**0.14**

Surgical Study



Summary of These Scenarios

- The **design** of the study is important.
- Understanding the **variables** at play in relation to your **research goal** is critical.
- For observational studies **confounding** (e.g. by indication) is important to consider when planning the research.
- Control of confounding: **design**, or **analysis**.

Ann Intensive Care. 2012 Jun 13;2(1):15.

Design, conduct, and analysis of a multicenter, pharmacogenomic, biomarker study in matched patients with severe sepsis treated with or without drotrecogin Alfa (activated).

Annane D, Mira JP, Ware LB, Gordon AC, Sevransky J, Stüber F, Heagerty PJ, Wellman HF, Neira M, Mancini ADj, Russell JA.

Service de reanimation medicale, CIC-IT805 (INSERM), Hopital R, Poincare (AP-HP), 104 Bd Raymond Poincare, 92380, Garches, France. djillali.annane@rpc.aphp.fr.

Abstract

ABSTRACT:

BACKGROUND: A genomic biomarker identifying patients likely to benefit from drotrecogin alfa (activated) (DAA) may be clinically useful as a companion diagnostic. This trial was designed to validate biomarkers (improved response polymorphisms (IRPs)). Each IRP (A and B) contains two single nucleotide polymorphisms that were associated with a differential DAA treatment effect.

METHODS: DAA is typically given to younger patients with greater disease severity; therefore, a well-matched control group is critical to this multicenter, retrospective, controlled, outcome-blinded, genotype-blinded trial. Within each center, DAA-treated patients will be matched to controls treated within 24 months of each other taking into account age, APACHE II, cardiovascular, respiratory, renal, and hematologic dysfunction, mechanical ventilation status, medical/surgical status, and infection site. A propensity score will estimate the probability that a patient would have received DAA given their baseline characteristics. Two-phase data transfer will ensure unbiased selection of matched controls. The first transfer will be for eligibility and matching data and the second transfer for outcomes and genotypic data. The primary analysis will compare the effect of DAA in IRP + and IRP - groups on in-hospital mortality through day 28.

DISCUSSION: A design-based approach matching DAA-free to DAA-treated patients in a multicenter study of patients who have severe sepsis and high risk of death will directly compare control to DAA-treated groups for mortality by genotype. Results, which should be available in 2012, may help to identify the group of patients who would benefit from DAA and may provide a model for future investigation of sepsis therapies.

Examples: Inferential – Annane (2012)

- **Goal**: **evaluate** the effect of Xigris treatment on mortality, and to compare genotype subgroups.
- **Compare**: Treatment effect across genotype groups.
- **Measurement**: mortality (28-day), treatment
- **Control**: age, gender, APACHE, SAPS, site
- **Additional Comments**:
  - ▷ Uses **matching** of treated to non-treated.
  - ▷ Complete protocol and analysis plan drafted prior to data collection.

Summary: Goals and Variables

- Orienting your primary and secondary goals:
  - Descriptive
  - Inferential / Confirmatory
  - Prediction
- Grouping variables according to role:
  - **outcomes**,
  - **exposures (POI)**
  - **confounders**, **precision** or predictors
- Preparation /organization can help to maximize successful communication and collaboration.