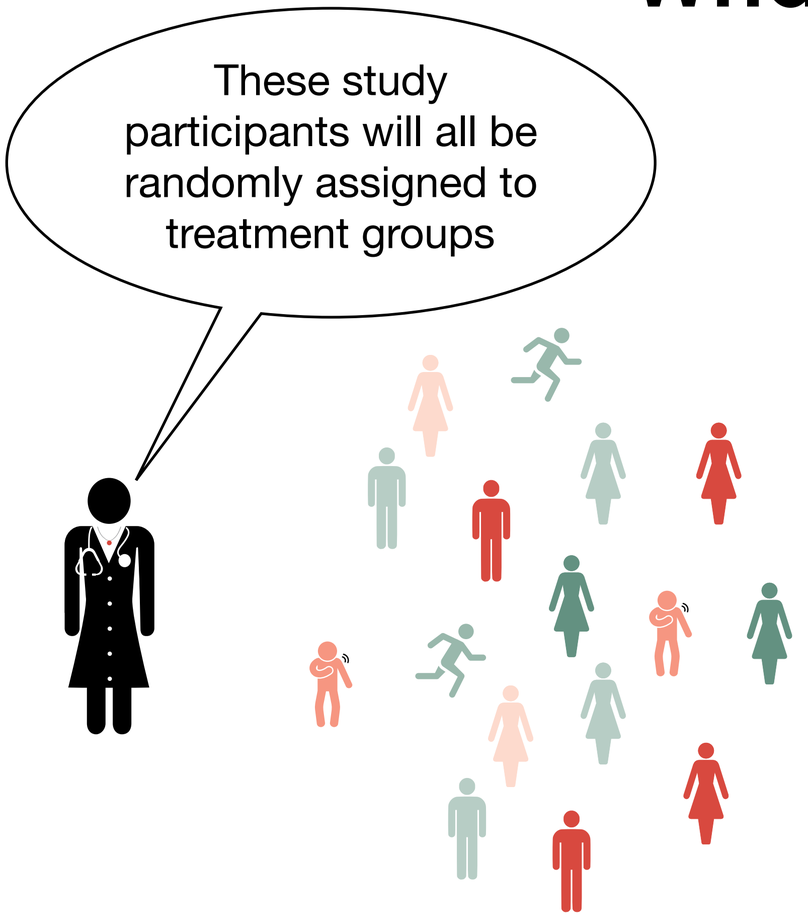
Randomized Trials & Quantifying Treatment Effects

Martina Steurer, MD MAS
10/31/19
With appreciation to Tom Newman & Michael Kohn

What is randomization?



Treatment/Intervention

No Treatment/Intervention

Why randomize?

Exercise

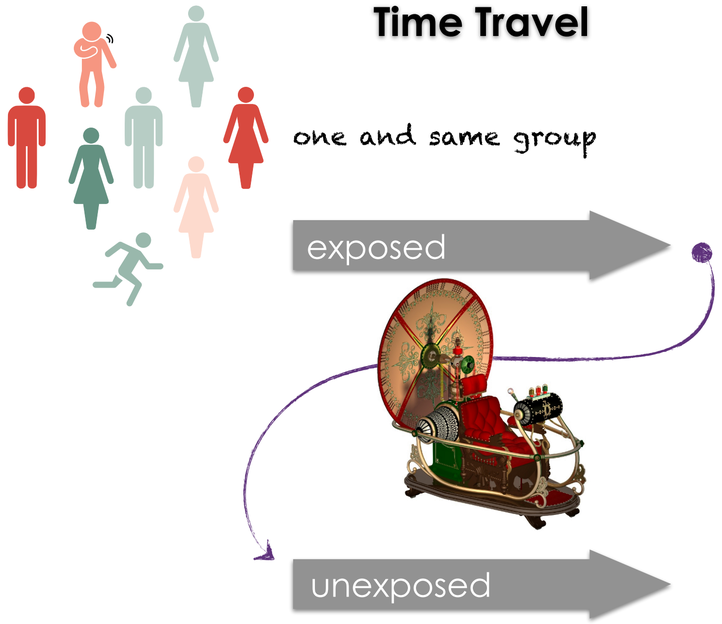
No Exercise

Where is the problem with this study design?

Why randomize?

In order to proof that an effect is causal, the two populations (i.e. exposed and unexposed) need to be **EXCHANGEABLE**

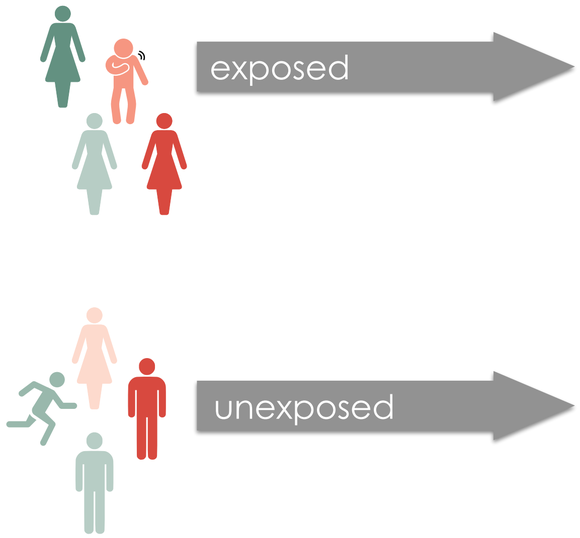
Time Travel



impossible COUNTERFACTUAL

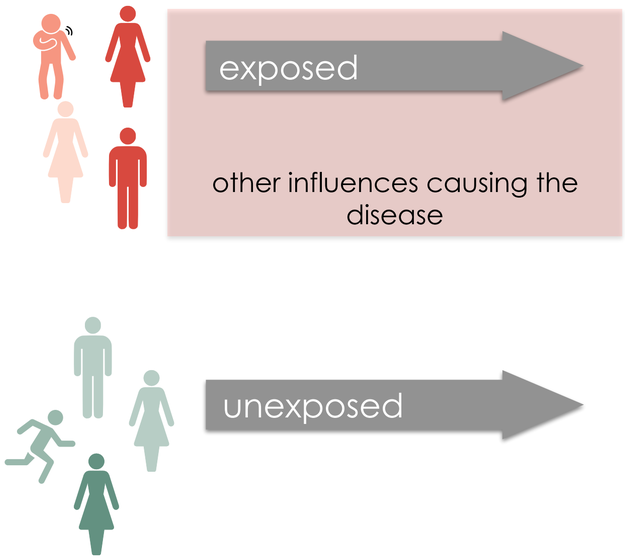
We will let you know immediately when we figured this out, should be soon....

Randomized Trial



TODAY in EPI 204

Cohort study



In order to get at causal interference in cohort studies, you have to deal with confounding, you will learn this in EPI 203

Blinding

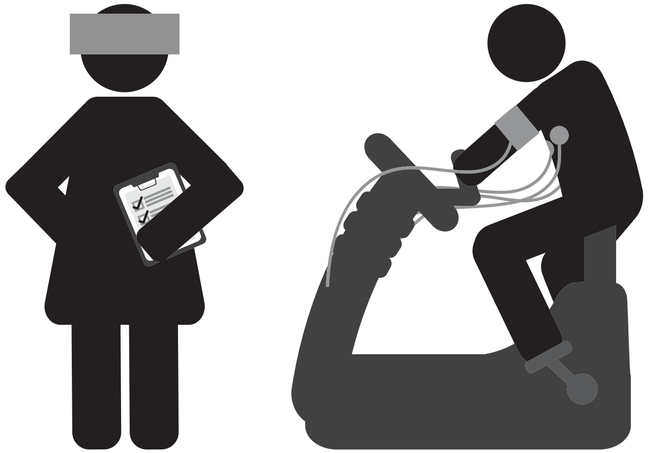
Patient

- Prevents differences due to placebo effect
- Very important for subjective measures
- Getting study drug outside of the trial (controls)

Provider

- Helps avoid co-interventions

Person assessing the outcome



- Prevents observer bias
- More important for subjective measures
- Not so important for objective measures

What about mortality?

Blinding

Patient

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE FREE PREVIEW

Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear

Raine Sihvonen, M.D., Mika Paavola, M.D., Ph.D., Antti Malmivaara, M.D., Ph.D., Ari Itälä, M.D., Ph.D., Antti Joukainen, M.D., Ph.D., Heikki Nurmi, M.D., Juha Kalske, M.D., and Teppo L.N. Järvinen, M.D., Ph.D. for the Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group

Blinding

Person assessing the outcome

January 01, 1994; 44 (1) ARTICLES

The impact of blinding on the results of a randomized, placebo–controlled multiple sclerosis clinical trial

J. H. Noseworthy, G. C. Ebers, M. K. Vandervoort, R. E. Farquhar, E. Yetisir, R. Roberts

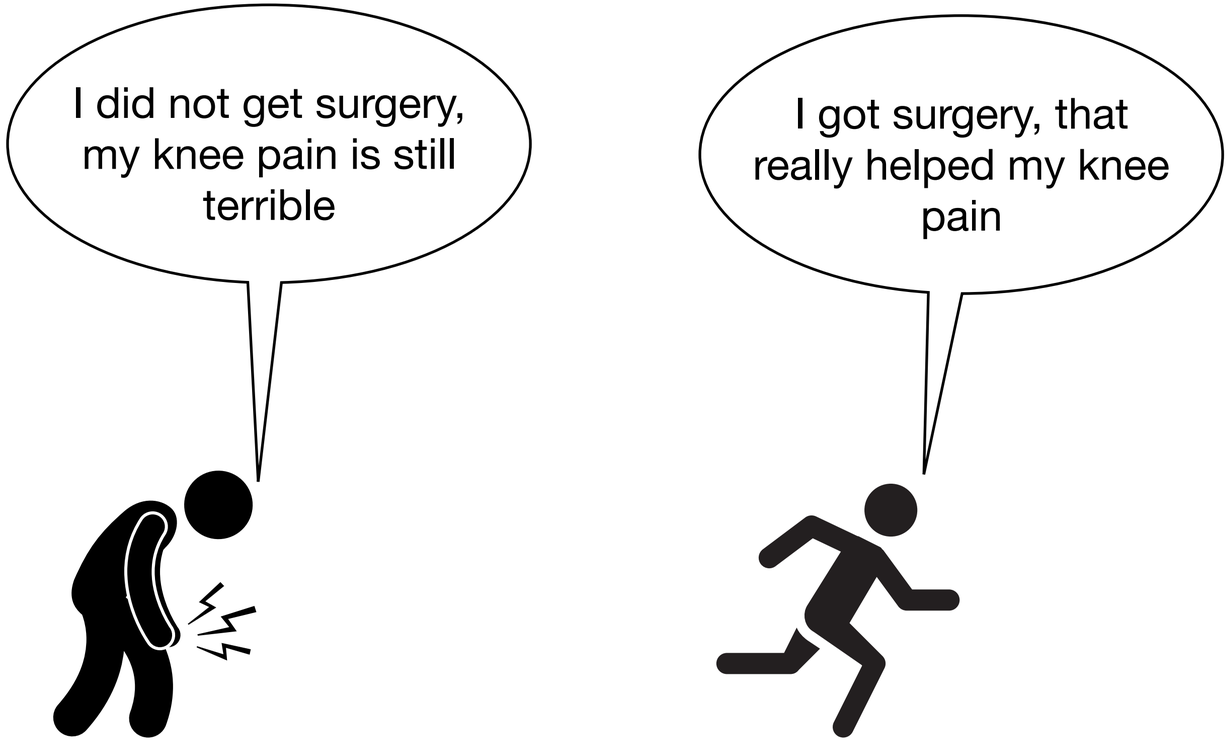
First published January 1, 1994, DOI: https://doi.org/10.1212/WNL.44.1.16

Issues with blinding

Patients may be able to tell they are on drug

side effects

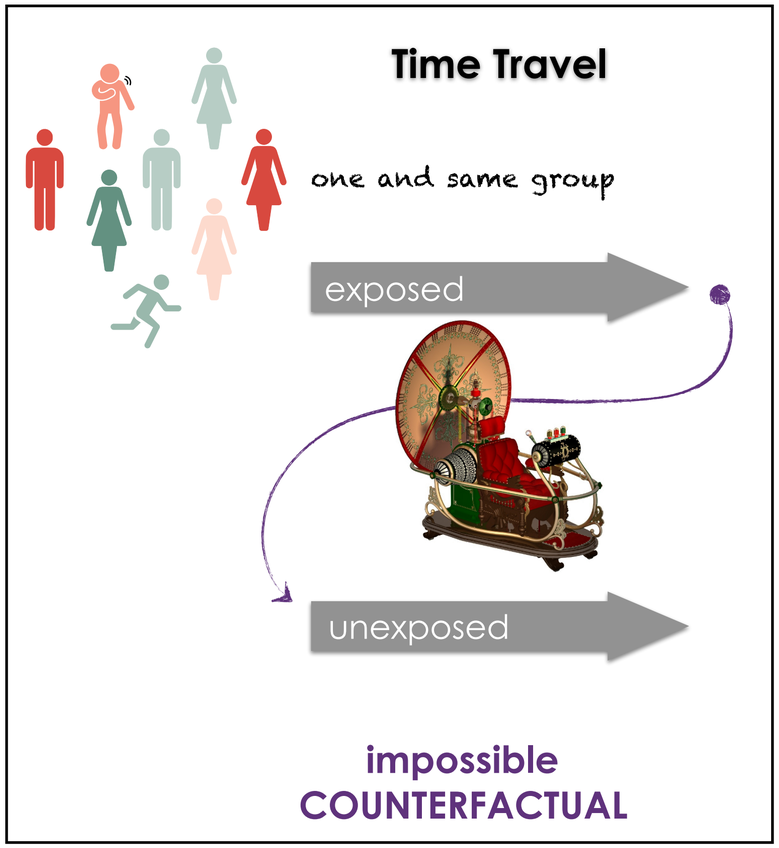
Part of the causal effect of treatment may be related to knowing you are on treatment

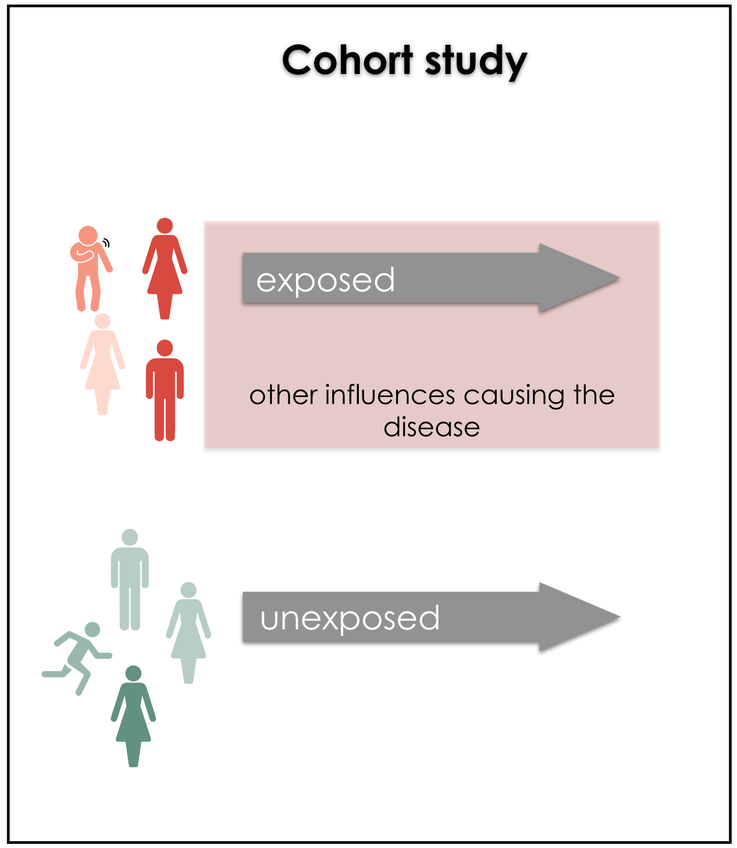


treatment looks better i.e. Meniscus surgery

Issues with RCTs?

In order to proof that an effect is causal, the two populations (i.e. exposed and unexposed) need to be **EXCHANGEABLE**





We will let you know immediately when we figured this out, should be soon....

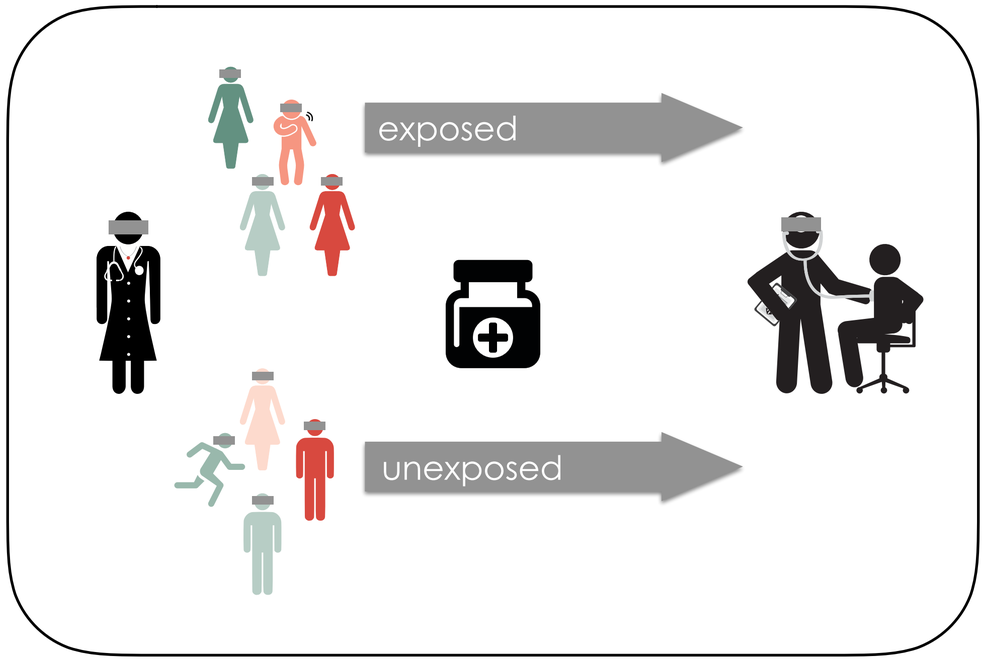
TODAY in EPI 203

In order to get at causal interference in cohort studies, you have to deal with confounding, you will learn this in EPI 203

Issues with RCTs?

Subjects

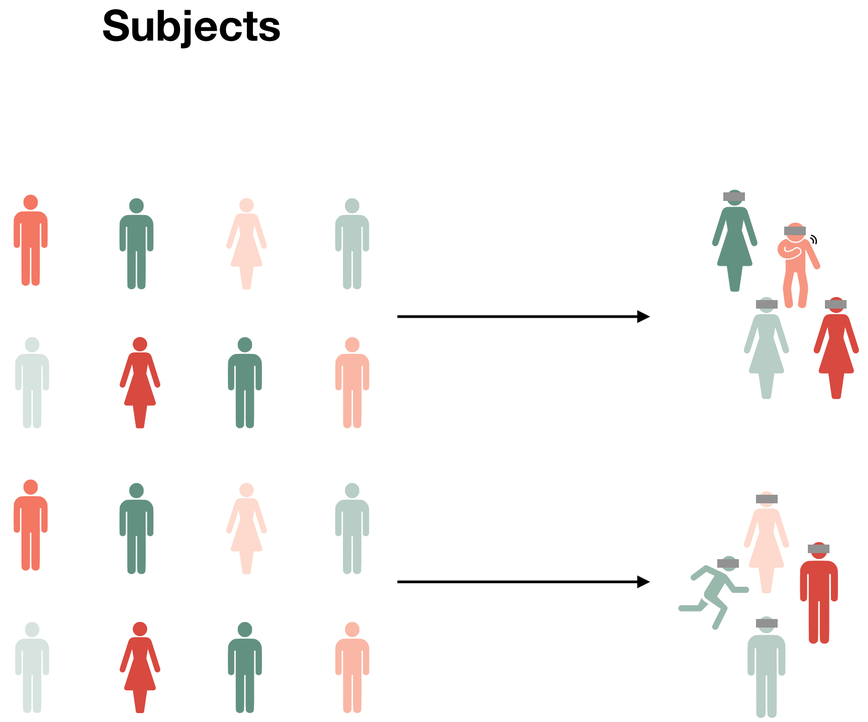
Treatment variable



Outcome variable

Perfect randomization, perfect blinding

Issues with RCTs?



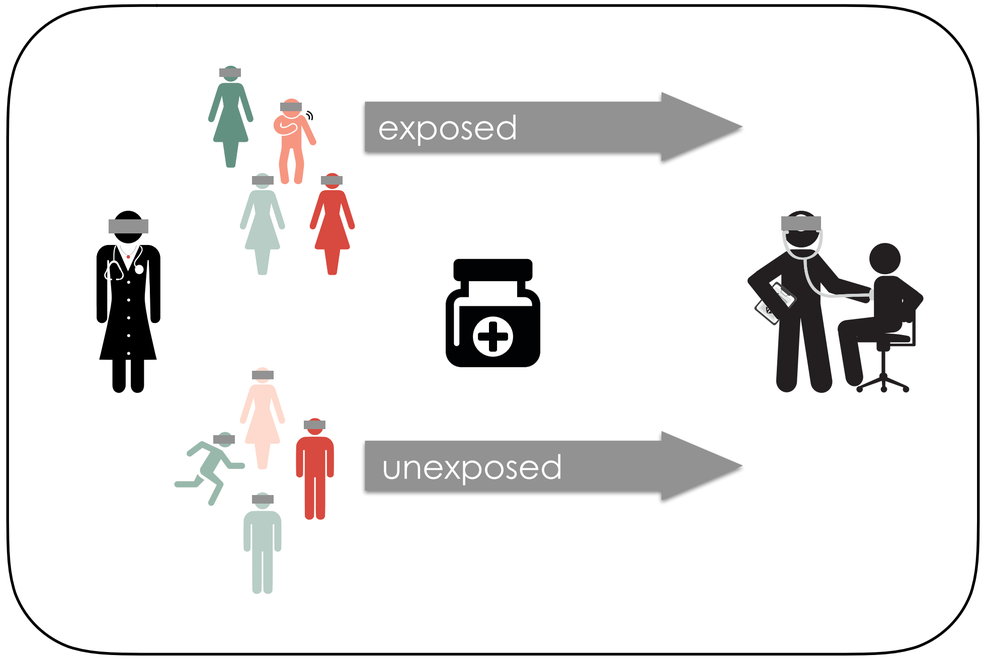
Is the study population representative of the population the results of the study will be applied to?

- Select patient most likely to benefit from treatment and least likely to have adverse effects

- Groups under-represented
  Children
  Elderly
  Women
  Comorbid conditions
  On other meds

Issues with RCTs?

Subjects **Treatment variable** **Outcome variable**



Perfect randomization, perfect blinding

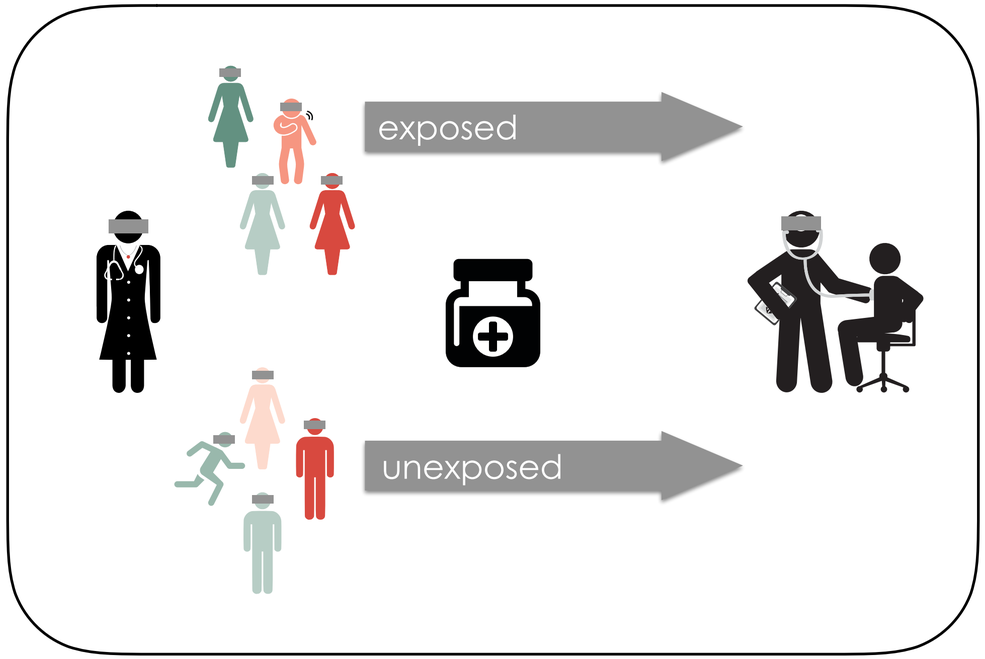
Issues with RCTs?

Treatment variable

Study drug
Dose
Comparator

Issues with RCTs?

Subjects **Treatment variable** **Outcome variable**



Perfect randomization, perfect blinding

Issues with RCTs?

- **Surrogate outcomes**
  - ✓ Presumed to be associated with the outcome of interest
  - ✓ more easily measured
  - ✓ occurs sooner

- **Composite outcomes**
  - ✓ Several bad outcomes grouped into one composite outcome
  - ✓ Can lead to combining outcomes of varying importance:
    Death vs. multiple hospital re-admissions
  - ✓ Can be misleading if individual components of composite outcomes are not reported

Outcome variable

Issues with RCTs?

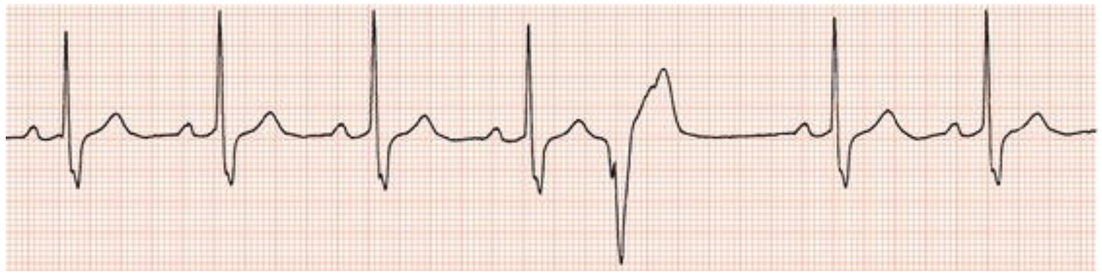
Surrogate outcomes: examples

- Outcome is risk factor rather than disease:
  - ✓Blood pressure instead of stroke

- Outcome is marker of disease severity rather than morbidity/ mortality from disease
  - ✓Viral load instead of morbidity from AIDS
  - ✓HbA1C rather than morbidity from diabetes

Issues with RCTs?

Surrogate outcome: The CAST trial



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT FREE PREVIEW ARCHIVE

Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression after Myocardial Infarction

The Cardiac Arrhythmia Suppression Trial (CAST) Investigators

- Asymptomatic premature ventricular contractions after myocardial infarction increase risk of sudden death
- Surrogate outcome: PVC burden

Issues with RCTs?

Composite outcome: The ACCORD trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

Article Figures/Media

17 References 1874 Citing Articles

April 29, 2010
N Engl J Med 2010; 362:1575-1585
DOI: 10.1056/NEJMoa1001286

Pre-specified primary composite outcome

Nonfatal MI

Nonfatal stroke

Cardiovascular death

Issues with RCTs?

Composite outcome: The ACCORD trial

After 3.5 years…
Non-significant reduction in the risk of the primary composite outcome

But…..
1% decrease in the risk of nonfatal MI (3.6% vs. 4.6%; p= 0.004)
1% increase in risk of cardiovascular death!! (5% vs. 4%, p= 0.04)

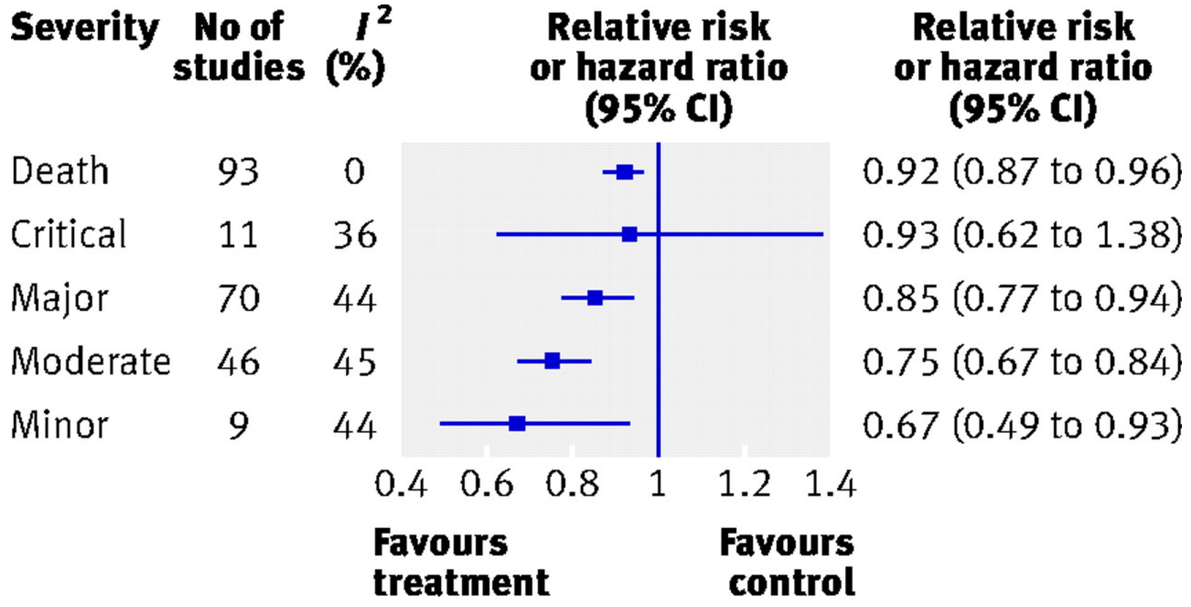
Masked an increase in total mortality!

Issues with RCTs?

Composite outcome: A common problem

I. Ferreira-González et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ 2007.

- Systematic Review of 114 randomized trials of cardiovascular interventions
- 68% of the studies reported results for each component of the composite outcome
- Outcomes of greater importance such as death were associated with smaller relative treatment effects than less important outcomes



Issues with RCTs?

Composite outcome

- Important to ‘decompose’
- Can mask important effects of therapy
  - ✓ No effect on important outcomes
  - ✓ Negative effect on important outcomes

Issues with RCTs?

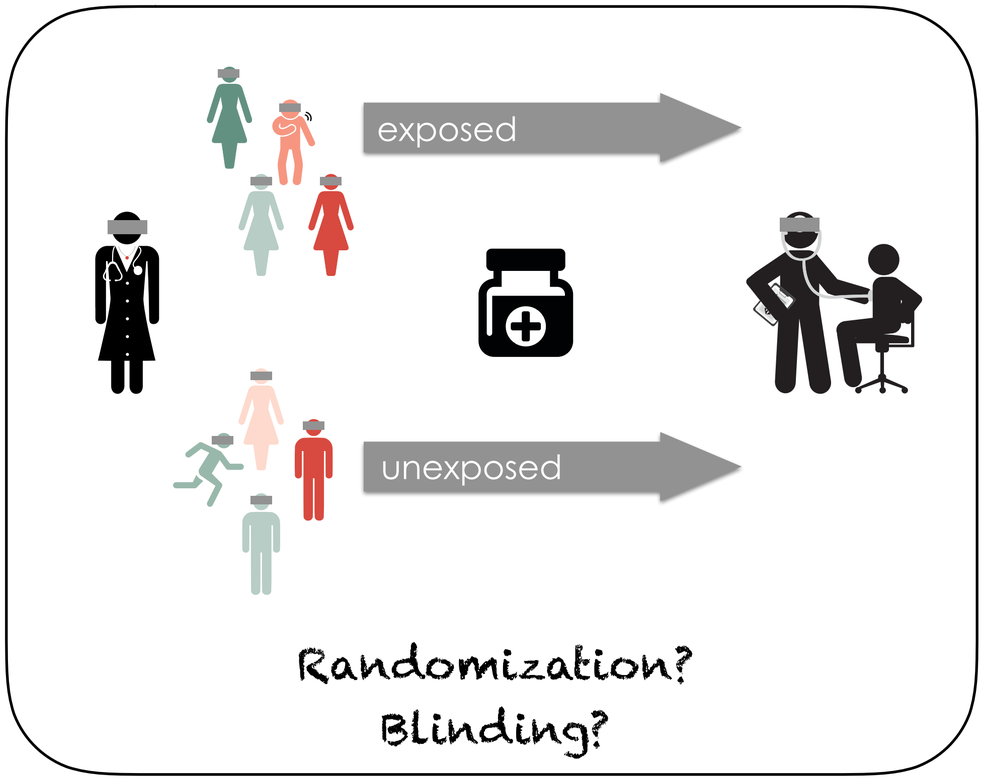
Treatment variable

Study drug?
Dose?
Comparator?

Subjects

Subjects representative of target population?

Underrepresented groups?



Randomization?
Blinding?

Outcome variable

Surrogate outcome?

Composite outcome?

Analysis of RCTs

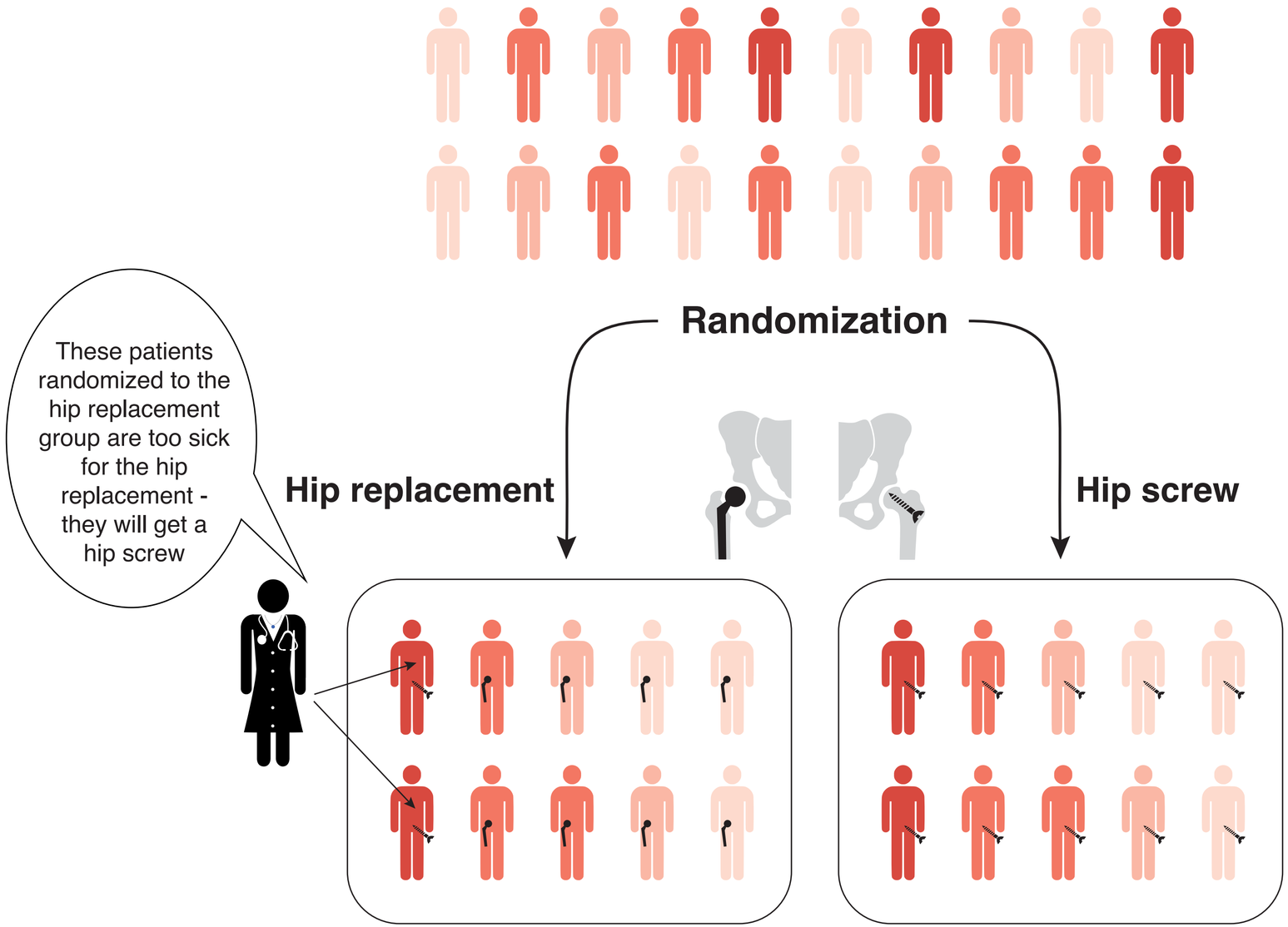
Problem: Subjects don't always stay in the assigned group

Intention to treat

As treated

Per protocol

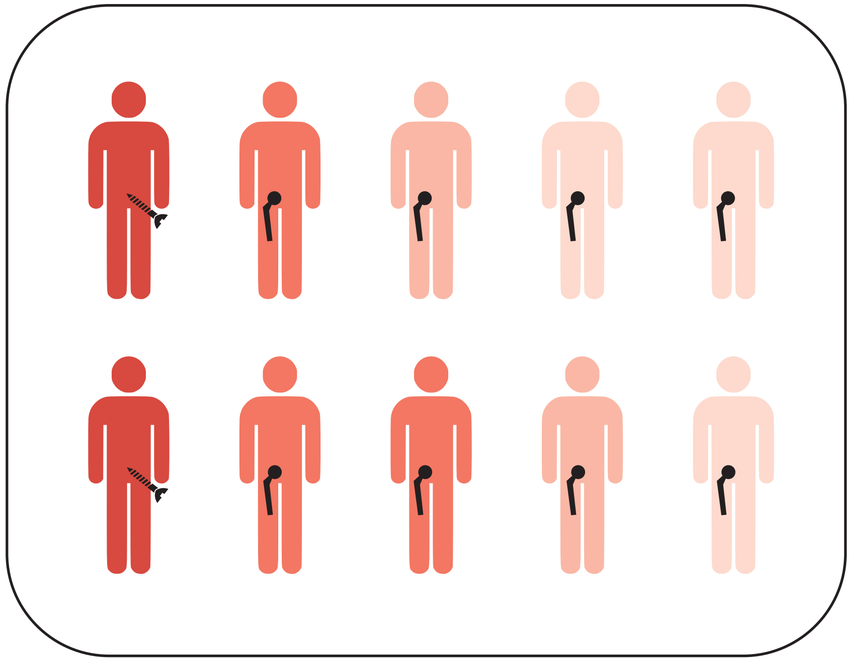
Analysis of RCTs

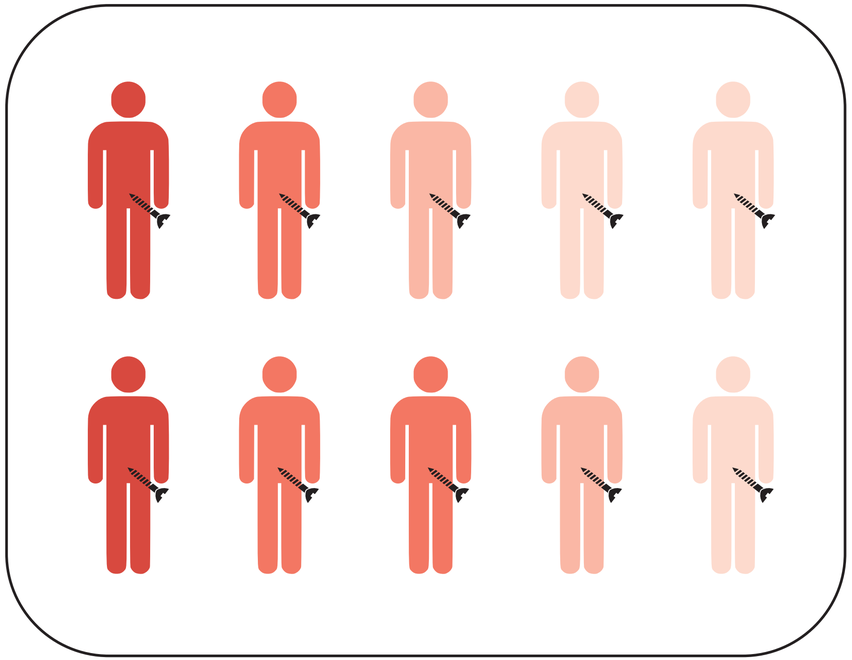


Analysis of RCTs

Intention to treat

All subjects are analyzed according to the randomization group

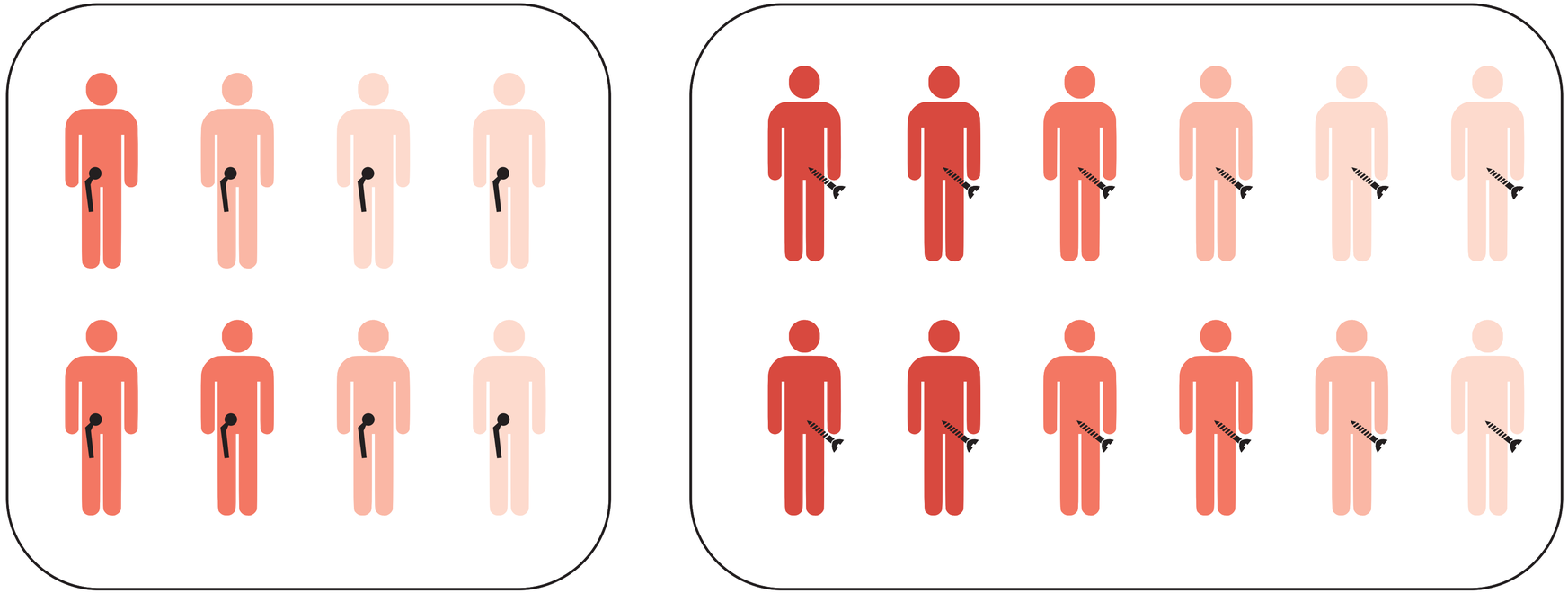




Analysis of RCTs

As treated

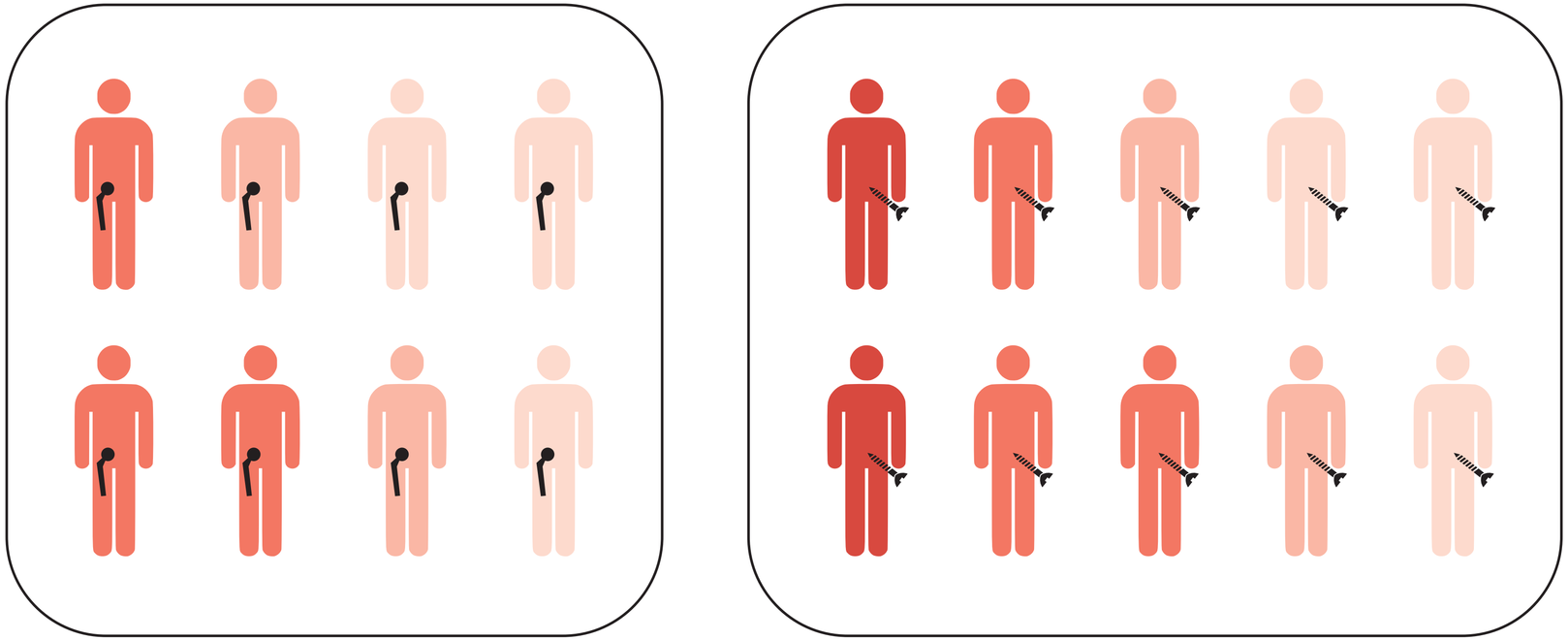
Subjects are analyzed according to treatment received



Analysis of RCTs

Per protocol

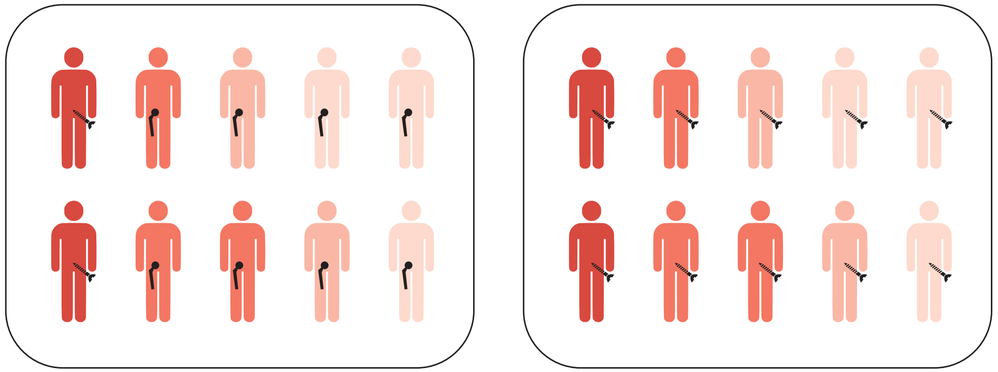
Only subjects treated according to the study protocol are analyzed



Analysis of RCTs

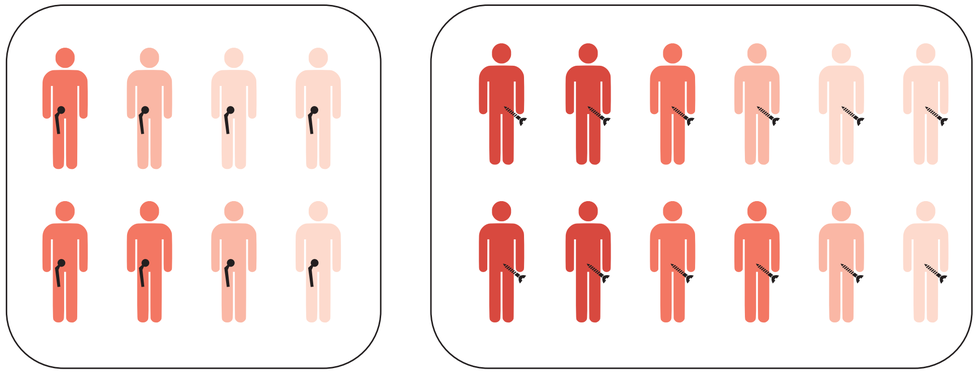
A

Intention to treat
all subjects are analyzed according to the randomization group



B

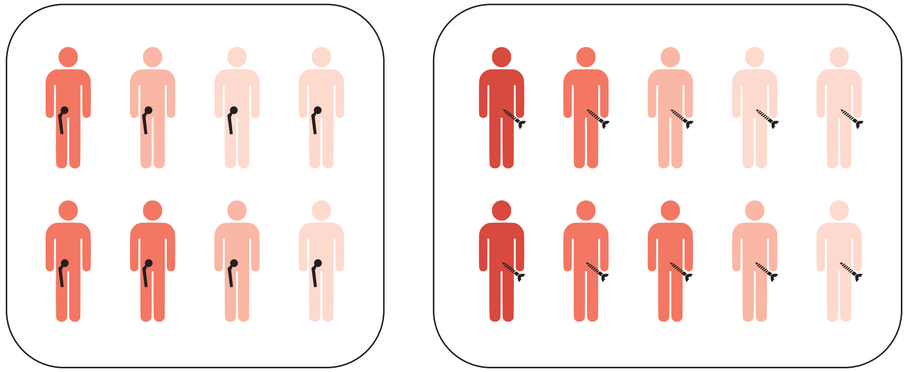
As treated
Subjects are analyzed according to treatment received



Bias in favor of hip replacement

C

Per protocol
Only subjects treated according to the study protocol are analyzed



Bias in favor of hip replacement

Analysis of RCTs: Pitfalls

- Sub-group analysis
- Multiple Comparisons
- Between- vs. within-group comparisons

Analysis of RCTs: Pitfalls

Sub-group analysis

Presenting results within a particular subgroup of subjects (bound to find something interesting)

THE LANCET
Volume 332, Issue 8607, 13 August 1988, Pages 349-360

RANDOMISED TRIAL OF INTRAVENOUS STREPTOKINASE, ORAL ASPIRIN, BOTH, OR NEITHER AMONG 17 187 CASES OF SUSPECTED ACUTE MYOCARDIAL INFARCTION: ISIS-2

Aspirin therapy (one month of 160 mg/day) in patients with acute myocardial infarction (AMI) reduced 30-day cardiovascular mortality from 11.8% in the placebo group to 9.4% in the aspirin group.

Analysis of RCTs: Pitfalls

Sub-group analysis

Presenting results within a particular subgroup of subjects (bound to find something interesting)

ISIS-2	**30-day mortality**		
	Overall	Geminis and Libras	Other signs
Aspirin	9.4%	11.1%	9.0%
Placebo	11.8%	10.2%	12.1%

Analysis of RCTs: Pitfalls

Multiple comparison

Looking at multiple different outcomes in multiple different groups in multiple different ways (need to adjust for this)

ELSEVIER

Journal of the American Academy of Child & Adolescent Psychiatry

Volume 40, Issue 7, July 2001, Pages 762-772

Articles

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

MARTIN B. KELLER M.D., NEAL D. RYAN M.D., MICHAEL STROBER PH.D., RACHEL G. KLEIN PH.D., STAN P. KUTCHER M.D., BORIS BIRMAHER M.D., OWEN R. HAGINO M.D., HAROLD KOPLEWICZ M.D., GABRIELLE A. CARLSON M.D., GREGORY N. CLARKE PH.D., GRAHAM J. EMSLIE M.D., DAVID FEINBERG M.D., BARBARA GELLER M.D., VIVEK KUSUMAKAR M.D., GEORGE PAPATHEODOROU M.D., WILLIAM H. SACK M.D., MICHAEL SWEENEY PH.D., KAREN DINEEN WAGNER M.D., PH.D. ... JAMES P. MCCAFFERTY B.S.

Glaxo-Smith Kline funded study on depression in adolescents concluded that Paroxetine "generally well-tolerated and effective for major depression in adolescents”

Analysis of RCTs: Pitfalls

Multiple comparison

Looking at multiple different outcomes in multiple different groups in multiple different ways (need to adjust for this)

- Independent analysis: 20 outcome measures had been added to the 8 original outcomes
- Only highlighted those that were favorable!
- GSK paid a fine of $3 billion (which was a fraction of the sales from this drug– $27.9 billion)

Analysis of RCTs: Pitfalls

Within group comparison

Comparing multiple time points within the treatment group

JAMA Network

November 5, 2003

Effect of Recombinant ApoA-I Milano on Coronary Atherosclerosis in Patients With Acute Coronary Syndromes

A Randomized Controlled Trial

Steven E. Nissen, MD; Taro Tsunoda, MD; E. Murat Tuzcu, MD; et al

» Author Affiliations

JAMA. 2003;290(17):2292-2300. doi:10.1001/jama.290.17.2292

Analysis of RCTs: Pitfalls

Within group comparison

Comparing multiple time points within the treatment group

Percent Atheroma Volume in the Target Coronary Segment					
	N	**Baseline**	**Follow-Up**	**Change**	**P Value***
Placebo	11	34.8	34.9	0.1	0.97
ApoA-I Milano					
15 mg/kg	21	39.7	38.4	-1.3	0.03
45 mg/kg	15	37.9	37.2	-0.7	0.45
Combined	36	39.0	37.9	-1.1	0.02
*P values for within-group comparison from Wilcoxon signed rank test. For between-group comparison, P = 0.29					

Issues with RCTs?

Design and Execution

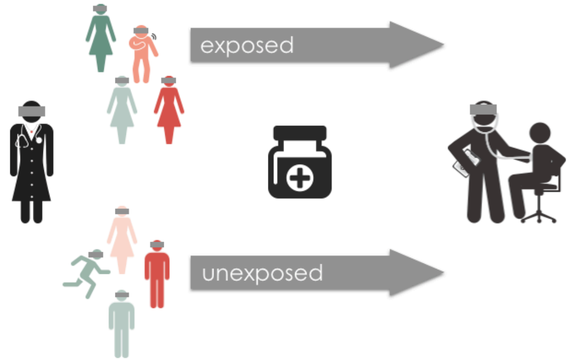
Treatment variable

Study drug?
Dose?
Comparator?

Subjects

Subjects representative of target population?

Underrepresented groups?



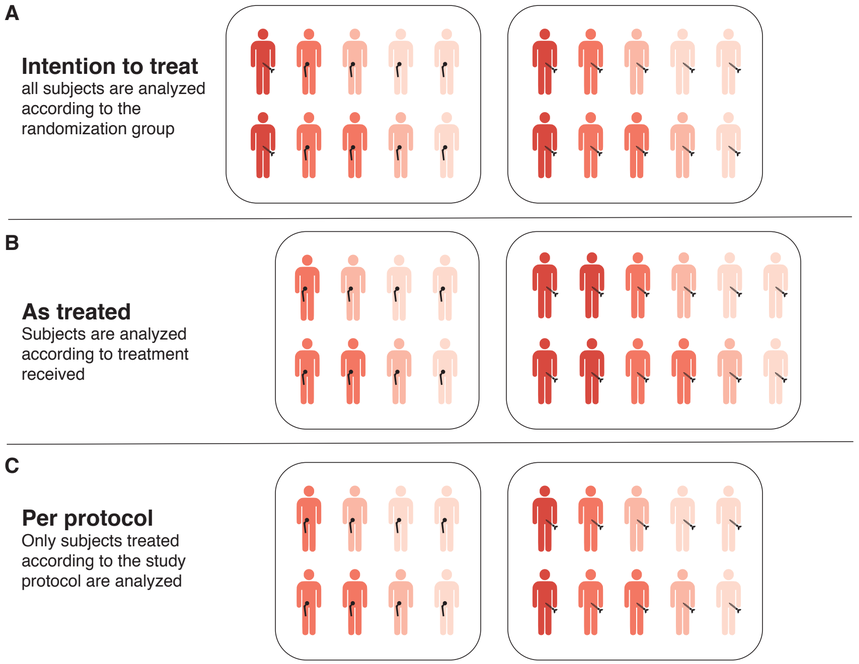
Outcome variable

Surrogate outcome?

Composite outcome?

Randomization?
Blinding?

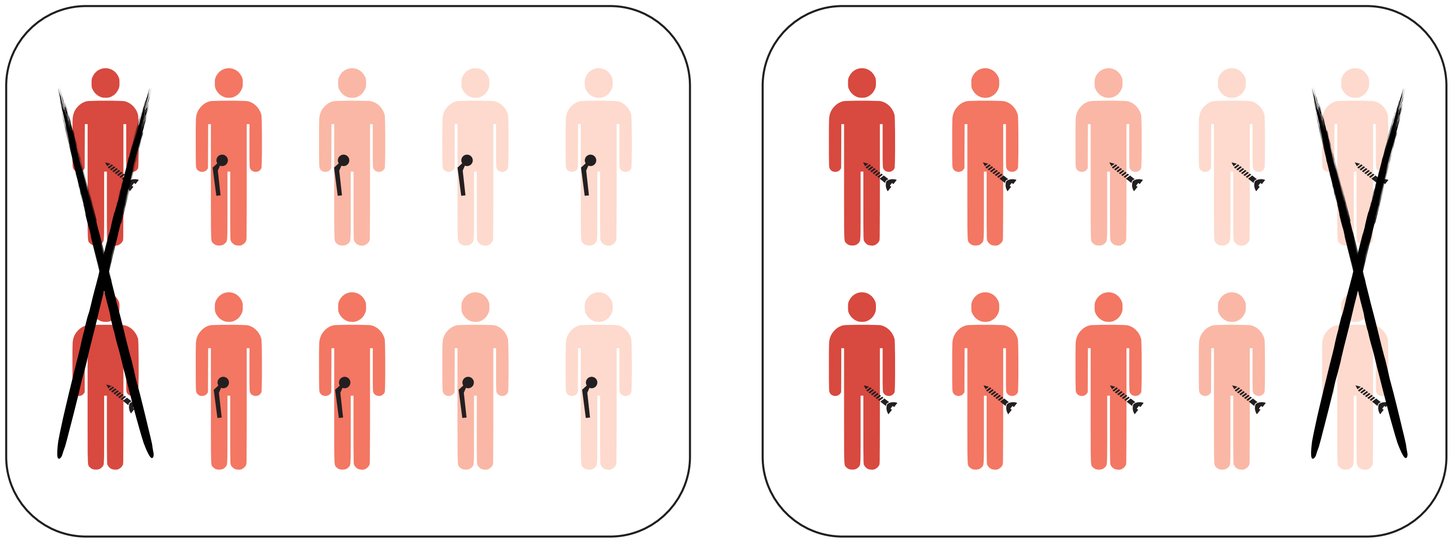
Analysis



Subgroup analysis?
Multiple comparison?
Within group comparison?

Loss to follow-up in RCTs

- Reduces power
- May introduce bias



Loss to follow-up in RCTs

Solution:

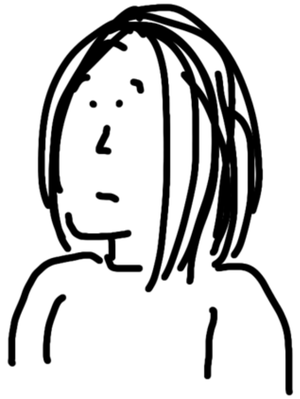
1. Sensitivity Analysis

Worst case scenario analysis (extreme): Poor outcomes for all losses in Tx group & good outcomes for all losses in control group

2. **Compare subjects that remained in the study vs. lost to follow up (similar or different?)**

Break

Do you know about any RCTs that provide evidence that we should use RCTs?



Quantifying Treatment Effects

	Poor outome	No poor outcome
Treatment	A	B
Control	C	D

R_T = Risk in Treatment Group = a/(a+b)
R_c = Risk in Control Group = c/(c+d)

RR = R_t/R_c = a/(a+b)/c/(c+d)
RRR = 1- RR

ARR = - Risk Difference = - (R_T - R_C)= R_c - R_T = c/(c+d) – a/(a+b)
NNT= 1/ARR

OR= ad/bc

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Quantifying Treatment Effects

ORIGINAL ARTICLE

Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone

David A. Stempel, M.D., Ibrahim H. Raphiou, Ph.D., Kenneth M. Kral, M.S., Anne M. Yeakey, M.D., Amanda H. Emmett, M.S., Charlene M. Prazma, Ph.D., Kathleen S. Buaron, B.S.N., and Steven J. Pascoe, M.B., B.S. for the AUSTRI Investigators*

Article Figures/Media Metrics

28 References 80 Citing Articles Letters

May 12, 2016
N Engl J Med 2016; 374:1822-1830
DOI: 10.1056/NEJMoa1511049

	Astma exacerbation	No Asthma exacerbation	Total
Fluticasone + Salmeterol	480	5354	5834
Fluticasone alone	597	5248	5845

R_T = Risk (Fluticasone+Salmeterol) = 480/5834= 8.2%
R_c = Risk (Fluticasone alone) = c/(c+d) = 597/5845 = 10.2%

RR = R_t/R_c = a/(a+b)/c/(c+b) = 8.2%/10.2%= 0.81

RRR = 1- RR = 1-0.81 = 19%

ARR = - Risk Difference = - (R_T - R_C) = -(8.2%-10.2%) = 2.0% (over 6 months)

NNT= 1/ARR = 1/0.02 = 50 for 6 months

Meaning of NNT?

Quantifying Treatment Effects

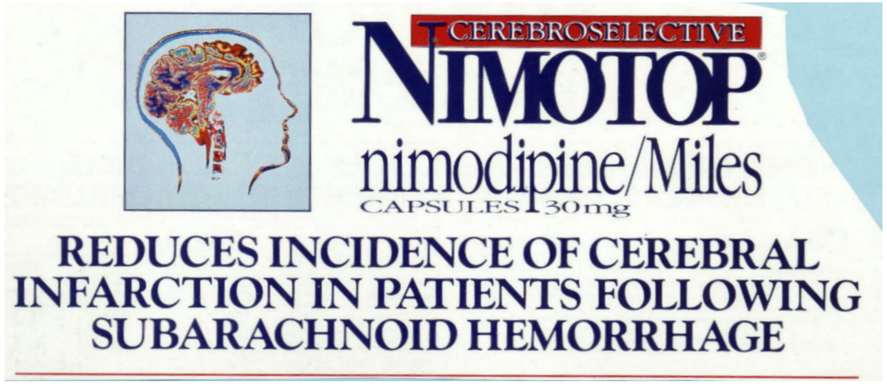
Number Needed to Treat (NNT)

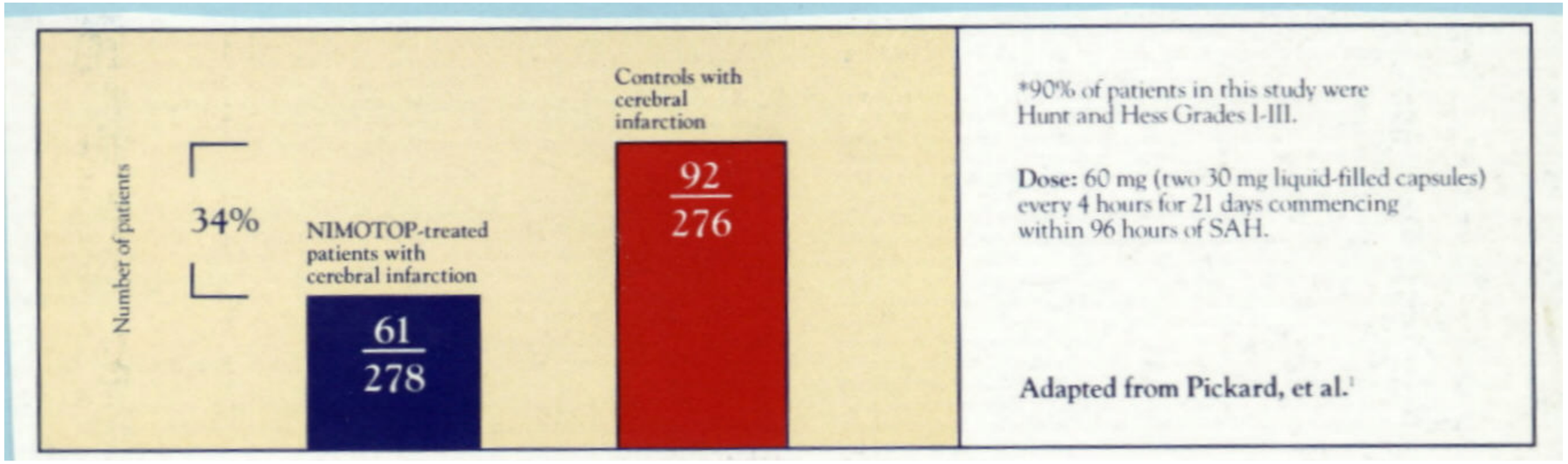
- Number needed to treat to prevent one bad outcome
- Lower the # the better
- Specify the follow-up time, the bad outcome being prevented and the characteristics of the people being treated
- Round to the nearest integer (since talking about people) especially when talking to patients

.

Quantifying Treatment Effects

Relative and Absolute Risk Reduction

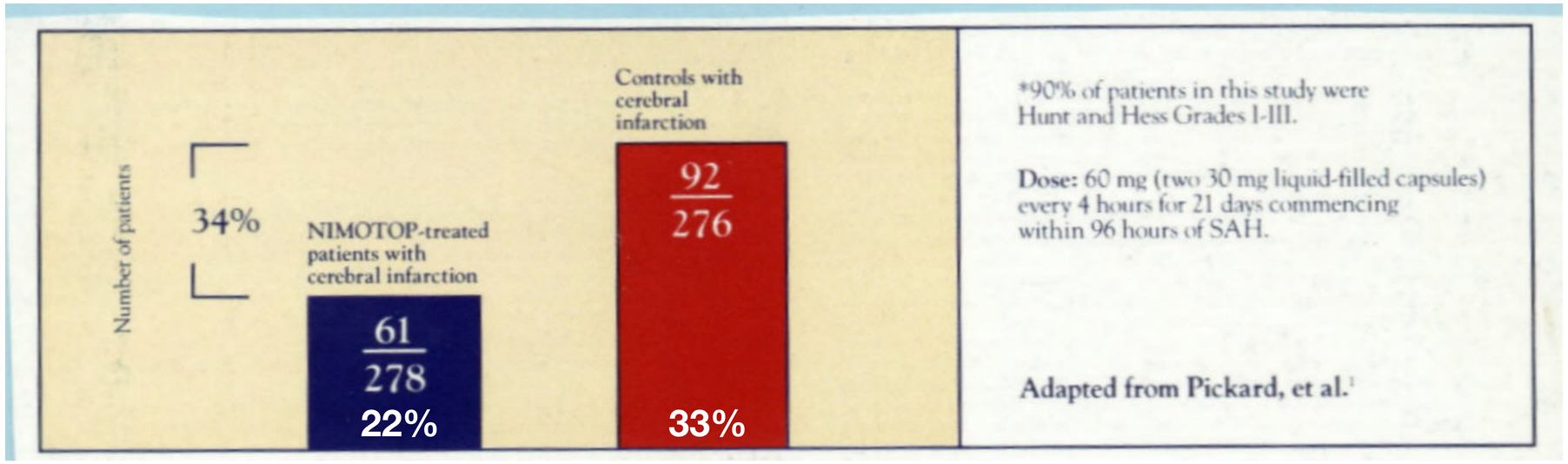




Quantifying Treatment Effects

Relative and Absolute Risk Reduction

RR = 22%/33% = 0.66
RRR = 1-0.66 = 34%
ARR = 33% - 22% = 11%



Quantifying Treatment Effects

Relative and Absolute Risk Reduction

- Relative risk reduction will always appear more impressive than absolute risk reduction
- Absolute risk reduction takes into account baseline risk (of control group)

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Quantifying Treatment Effects

Relative and Absolute Risk Reduction

ORIGINAL ARTICLE

Intravascular Gamma Radiation for In-Stent Restenosis in Saphenous-Vein Bypass Grafts

Ron Waksman, M.D., Andrew E. Ajani, M.D., R. Larry White, M.D., Rosanna C. Chan, M.D., Lowell F. Satler, M.D., Kenneth M. Kent, M.D., Augusto D. Pichard, M.D., Ellen E. Pinnow, M.S., Anh B. Bui, M.D., Steven Ramee, M.D., Paul Teirstein, M.D., and Joseph Lindsay, M.D.

Article Figures/Media

19 References 100 Citing Articles Letters

April 18, 2002
N Engl J Med 2002; 346:1194-1199
DOI: 10.1056/NEJMoa012579

"At 12 months, the rate of revascularization of the target lesion was 70 percent lower in the iridium-192 group than in the placebo group".

After cleaning out blocked bypass graft, how many do we have to treat with iridium to prevent one revascularization procedure (of the target lesion)?

You need to calculate NNT

The NEW ENGLAND JOURNAL of MEDICINE

Quantifying Treatment Effects

Number Needed to Treat

$$RRR = 1-(R_t/R_c)$$
$$RRR \times R_c = 1 \times R_c - 1(R_t/R_c) \times R_c$$
$$RRR \times R_c = R_c - R_t$$

$$ARR = RRR \times Risk_{control}$$

$$NNT = 1/ARR$$

The NEW ENGLAND JOURNAL of MEDICINE

Quantifying Treatment Effects

Relative and Absolute Risk Reduction

ORIGINAL ARTICLE

Intravascular Gamma Radiation for In-Stent Restenosis in Saphenous-Vein Bypass Grafts

Ron Waksman, M.D., Andrew E. Ajani, M.D., R. Larry White, M.D., Rosanna C. Chan, M.D., Lowell F. Satler, M.D., Kenneth M. Kent, M.D., Augusto D. Pichard, M.D., Ellen E. Pinnow, M.S., Anh B. Bui, M.D., Steven Ramee, M.D., Paul Teirstein, M.D., and Joseph Lindsay, M.D.

Article Figures/Media

19 References 100 Citing Articles Letters

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"At 12 months, the rate of revascularization of the target lesion was 70 percent lower in the iridium-192 group than in the placebo group".

The **baseline risk** (i.e., risk in the placebo group) was **57%**.

After cleaning out blocked bypass graft, how many do we have to treat with iridium to prevent one revascularization procedure (of the target lesion)?

The NEW ENGLAND JOURNAL of MEDICINE

Quantifying Treatment Effects

Relative and Absolute Risk Reduction

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Baseline 12-month risk of revascularization = 57%
RRR = 0.70

$$ARR = RRR \times Risk_{control}$$

ARR = 0.70 × 0.57 = 0.40
NNT = 1/0.40 = 2.5

Need to treat 2.5 unclogged grafts with radiation to prevent 1 from needing revascularization of the target lesion in the next 12 months.

The NEW ENGLAND JOURNAL of MEDICINE

Quantifying Treatment Effects

Odds Ratio

- OR not necessary to report in clinical trials
- Often reported since always further from 1 than the RR
- Inflates the apparent effect size

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	Major Cardiac Event	No Major Cardiac Event	Total
Irradiation	19	41	60
Placebo	38	22	60

RR = (19/60)/(38/60) = 0.50
OR = (19/41)/(38/22) = 0.27

Quantifying Treatment Effects

Incorporating Cost

NNT= # needed to treat to prevent one bad outcome

C= cost to treat one patient

NNT x C= treatment cost to prevent one bad outcome = CBOP

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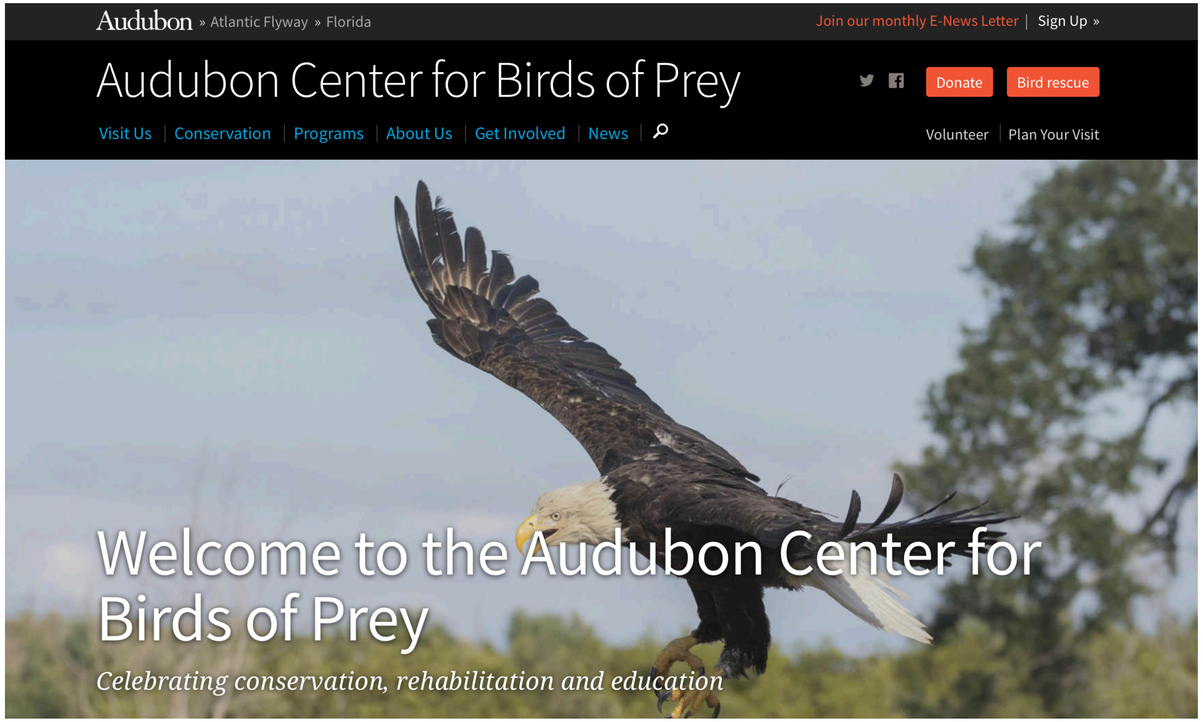
Quantifying Treatment Effects

CBOP

https://www.shopcbop.com



https://cbop.audubon.org

Quantifying Treatment Effects

JAMA Network

February 14, 2001

Effectiveness of Oseltamivir in Preventing Influenza in Household Contacts

A Randomized Controlled Trial

Robert Welliver, MD; Arnold S. Monto, MD; Otmar Carewicz, MD; et al

Index case Proven Flu +

	Flu + Contact	Flu – Contact	Totals
Tamiflu	3	206	209
Placebo	26	180	206

$Risk_T$= 3/209 = 1.4%
$Risk_C$= 26/206= 12.6%

RR= 1.4%/12.6%= 11%
RRR= 1-11%= 89%

ARR= 12.6%-1.4%= 11.2%

Why is ARR different?

Index case NOT Proven Flu +

	Flu + Contact	Flu – Contact	Totals
Tamiflu	1	283	284
Placebo	8	248	256

$Risk_T$= 1/284 = 0.35%
$Risk_C$= 8/256= 3.1%

RR= 0.35%/3.1%= 11%
RRR= 1-11%= 89%

ARR= 3.1%-0.35%= 2.7%

Quantifying Treatment Effects

Incorporating Cost

Tamiflu prophylaxis $40

Index case Proven Flu +

	Flu + Contact	Flu – Contact	Totals
Tamiflu	3	206	209
Placebo	26	180	206

ARR= 12.6%-1.4%= 11.2%
NNT= 1/11.2%= 9
Cost= 9*$40= $360

It costs about $360 to prevent a case of flu in household contacts

Index case NOT Proven Flu +

	Flu + Contact	Flu – Contact	Totals
Tamiflu	1	283	284
Placebo	8	248	256

ARR= 3.1%-0.35%= 2.7%
NNT= 1/ 2.7%= 37
Cost= 37*$40

It costs about $1480 to prevent a case of flu in household contacts

Quantifying Treatment Effects

Incorporating Cost

CBOP: Is it worth it?

INTRODUCING BBOP

INTRODUCING BBOP

HearthSong
6.54K subscribers

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Bump with the stars—or feel like you are! The fun begins the minute kids step inside our colorful, confetti-filled Bright Lights BBOP (Buddy Bounce Outdoor Play) ball—and skyrockets when they start bumping their chums (nanoseconds later). The more kids run and bump, the more the balls' motion-activated LEDs and colorful foil confetti light up like starbursts! Keeps kids on the move and laughter on a roll (available in Blue and Red). Use our Electric Pump for quick, easy inflation and deflation. Adult supervision recommended.

Quantifying Treatment Effects

Incorporating Cost

CBOP: Is it worth it?

Depends on BBOP= Benefit per Bad Outcome Prevented

BBOP= $1080

BBOP>CBOP= treat!

Quantifying Treatment Effects

Incorporating Cost

Treatment Threshold

If BBOP>CBOP, at what probability of disease would benefits outweigh costs?
What is the treatment threshold (P_{TT})?

P_{TT}= C/C+B

We know C ($40), but what is B?

Quantifying Treatment Effects

Incorporating Cost

What is B?

B = expected benefit of treatment

B = BBOP X ARR - C

Benefit of preventing a bad outcome

Absolute Risk Reduction (how much does treatment reduce the risk)

Cost

Quantifying Treatment Effects

Incorporating Cost

Treatment Threshold

$B = BBOP \times ARR - C$

$ARR = 1/NNT$

$B = BBOP/NNT - C$

$P_{TT} = C/(C + BBOP/NNT - C) = C/(BBOP/NNT)$

$P_{TT} = C \times NNT/BBOP$

$P_{TT} = CBOP/BBOP$

Quantifying Treatment Effects

Incorporating Cost

Back to the Flu example

Treatment cost = $40
BBOP = $1080
NNT= 9
P_{TT}= 9*40/1080= 0.33

If you treat household contacts when the index cases's probability of the flu is 33% or higher, you will not spend more than the BBOP of $1080 to prevent a case of flu

Quantifying Treatment Effects

Number Needed to Harm

Adverse effects of treatment

Trade-off between side effects and outcome prevention

Example:

Plecanatide (Trulance) to treat chronic constipation

Unintended side effect: Diarrhea

Quantifying Treatment Effects

Number Needed to Harm

	Diarrhea	No Diarrhea	Total	Risk
Plecanatide	28	446	474	5.9%
Placebo	6	452	458	1.3%

RR = 5.9%/1.3% = 4.5
ARR = 1.3%-5.9% = -4.6%

ARI = 5.9%-1.3% = 4.6%
NNH = 1/ARI = 21.7

For every 22 patients treated , we will cause one additional case of diarrhea

Quantifying Treatment Effects

Number Needed to Harm

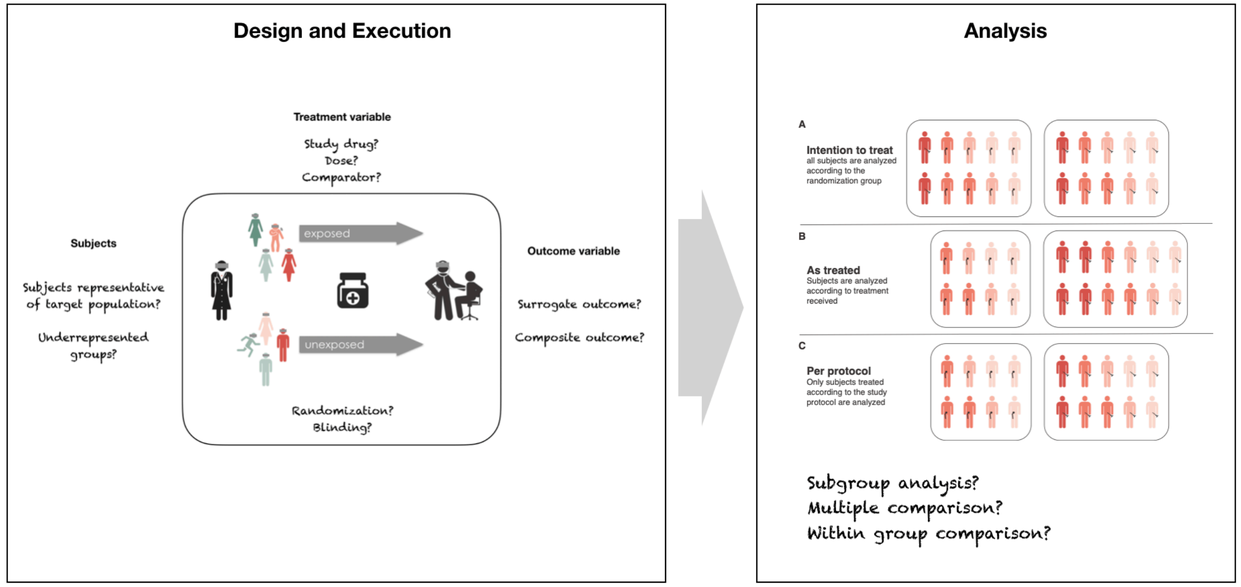
The Trade Off

Trade-off between side effects and primary outcome prevention
Harms/Bad outcome prevented= ARI/ARR or NNT/NNH

Trulance example:
NNT for primary outcome 9.3
NNH: 22
NNT/NNH = 9.3/21.7 = 0.43
We cause 0.43 cases of diarrhea for each durable responder

Conclusions

Design, Execution and Analysis of RCTs



Treatment Effects in RCTs

- ARR takes baseline risk into account
- Practical results:
  - NNT
  - CBOP, BBOP
  - ARI and NNH