In a cohort study examining the association between daily exercise and a high BMI, it was found that the calculated Relative Risk was 0.48. From this it can be interpreted that:

A. There is no association between daily exercise and BMI
B. Those who exercise daily are 48% less likely to have a high BMI
C. Those who exercise daily are 52% less likely to have a high BMI
D. Those who do not exercise daily are 48 times more likely to have a high BMI

In a case-control study, it was found current oral contraceptive use was a risk factor for developing venous thromboembolism (Odds Ratio 3.3). It can be interpreted that:

A. Current use of contraceptives was associated with a 3.3 times higher risk for developing venous thromboembolism
B. There is a strong association between current oral contraceptive use and venous thromboembolism
C. There is a protective effect of oral contraceptive use on the development of venous thromboembolism
D. All of the above

Relative Risk:

A. Provides a measure of association between an exposure and outcome.
B. Is a ratio of the incidence of disease in the exposed group to the incidence in the non-exposed group
C. Is calculated by dividing the incidence in the exposed by the incidence in the unexposed
D. All of the above

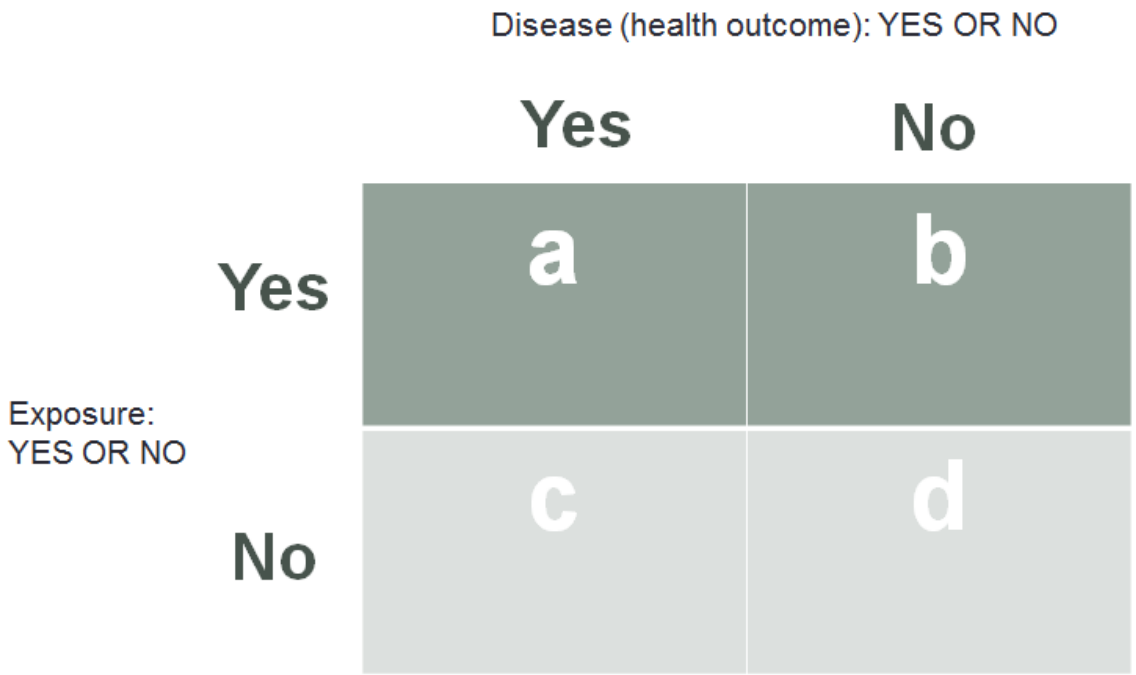
The correct calculation for determining and ODDS RATIO is:

A. $\frac{a/(a+b)}{c/(c+d)}$

B. $\frac{ad}{bc}$

C. $\frac{a/c}{b/d}$

D. Both B. and C.



Class 9 Objectives:

1. Understand and interpret Confidence Intervals (CI) for a relative risk and an odds ratio
2. Understand Experimental study design – elements, ethical considerations, randomization, blinding
3. Distinguish between clinical trials and community trials

Confidence Intervals (CI)

- Odds Ratios and Relative Risk tell are measures of effect and show associations between variables, but remember that these are derived using population samples (not the entire population)
- Samples are only one faction of the target population and, as such, may vary from what characterized the entire population. It is, therefore, only an estimate of what would be true in the target population
- CONFIDENCE INTERVALS are an important tool to help us determine how precise this estimate is

Confidence Intervals (CI)

- Confidence Interval is a *range of values* in which the target population is likely to fall based on statistical probability.
- Most commonly used is 95% CI – which means that, within that range, we are 95% certain that the target population falls somewhere between the lower and upper limit of the range
- Narrow confidence intervals indicate greater precision and can generally be achieved by using larger sample sizes (resulting in less variance between the sample and the target population)

Interpreting Confidence Intervals:

- If the range of the CI contains the value of “no difference” (1 in the case of RR and OR), we would say that the measure of association is NOT statistically significant

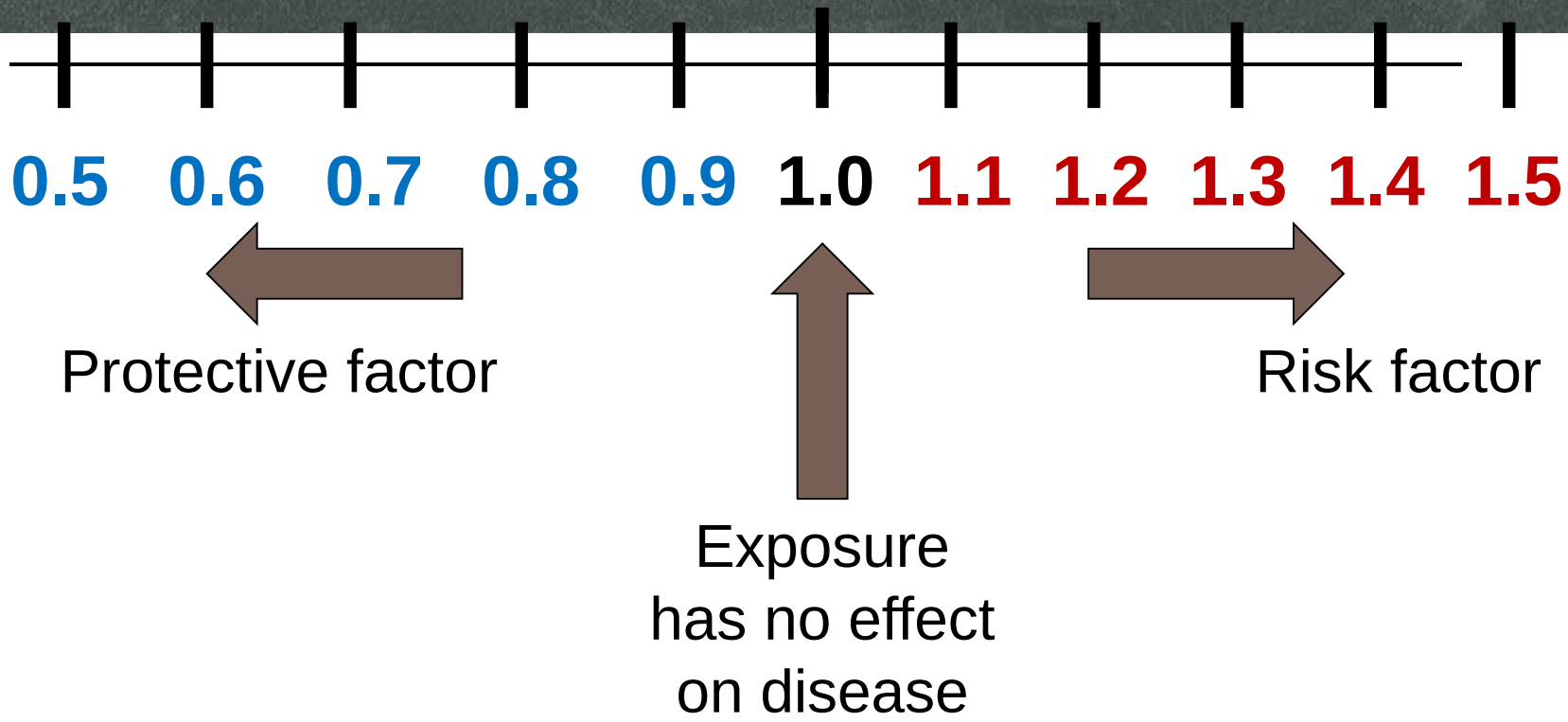
e.g.

Association between fast food proximity and weight

Sample RR = 3.4 (95% CI between 0.5-15.1)

This means that, although the sample estimate is 3.4, we are 95% confident that the true population value ranges somewhere between 0.7 and 15.1 95 times out of 100.

WHY is it not statistically significant if crosses 1?



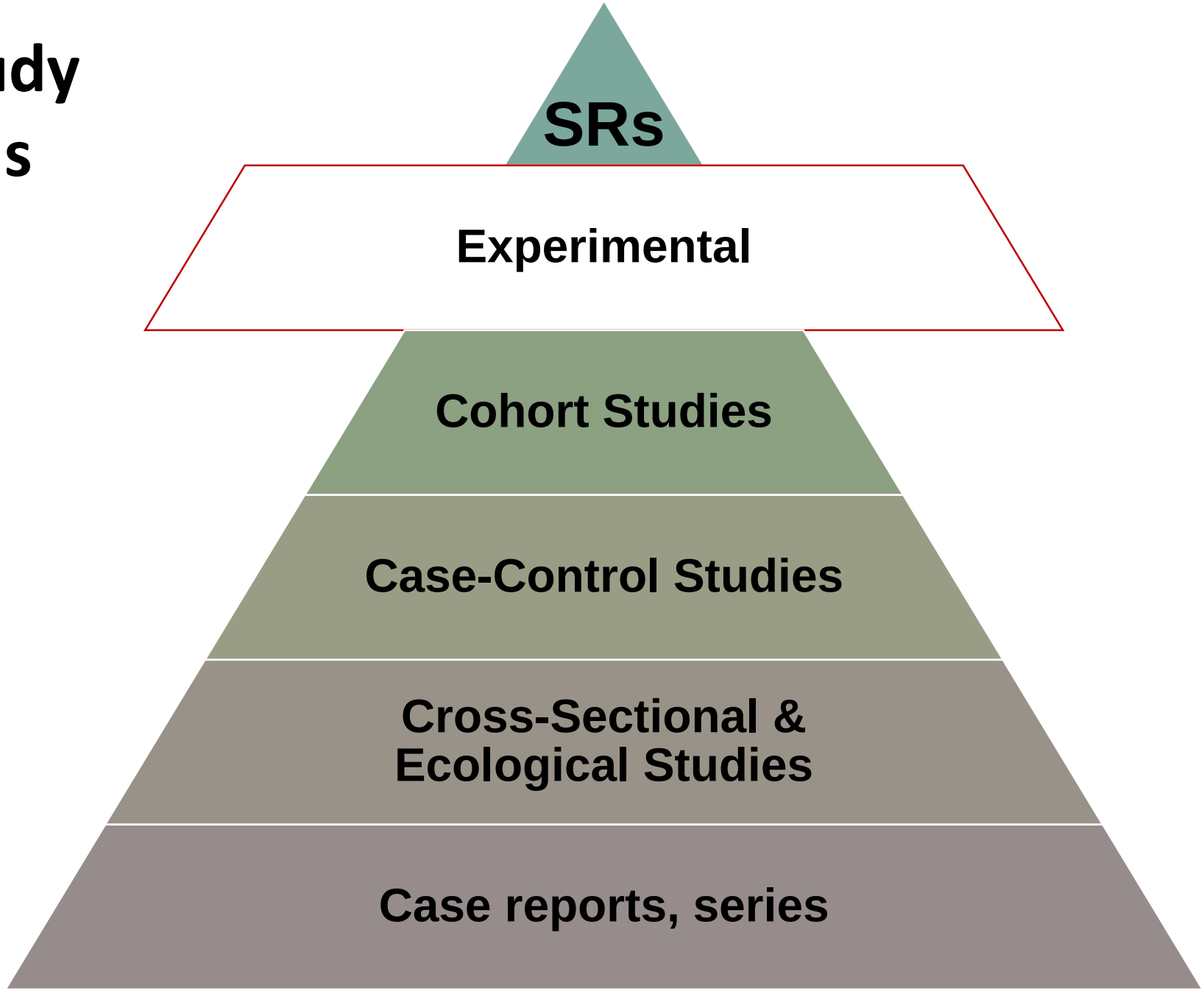
Interpreting Confidence Intervals
Exposure: Smoking; Outcome: Cancer

1. Odds ratio: 1.50 (95% CI = 1.25 to 4.75)	1. Significant
2. Odds ratio: 0.80 (95% CI = 0.50 to 1.90)	2. Not significant
3. Relative risk: 1.15 (95% CI = 1.10 to 1.50)	3. Significant
4. Relative risk: 2.25 (95% CI = 0.75 to 4.50)	4. Not significant
5. Odds ratio: 0.70 (95% CI = 0.10 to 1.35)	5. Not significant

Class 9:
Experimental Studies in Epidemiology

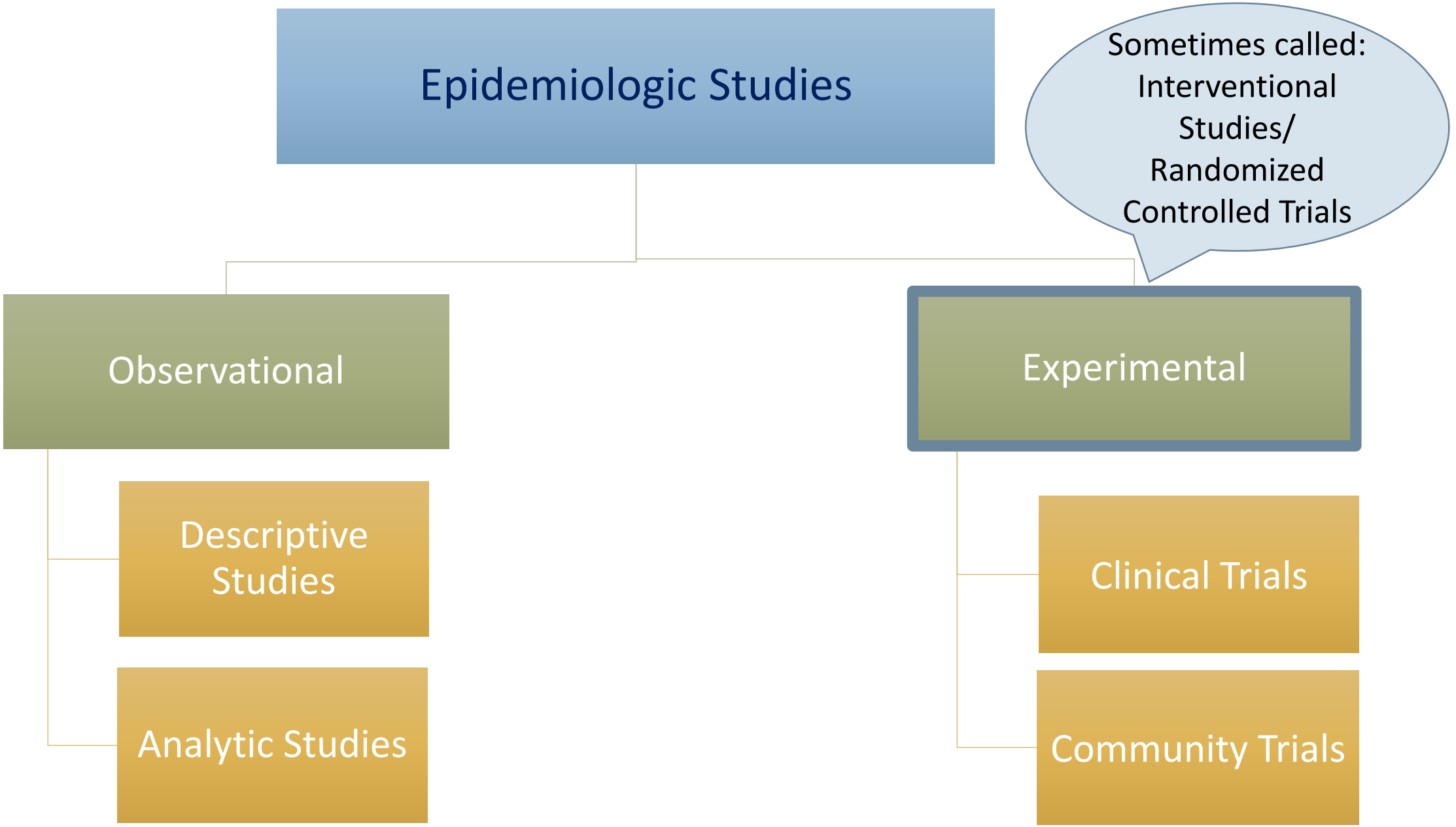
Health Science 2003
Faculty of Health Sciences
University of Lethbridge
Walker

Epi Study Designs



Considered the "Rolls Royce" of all study designs.

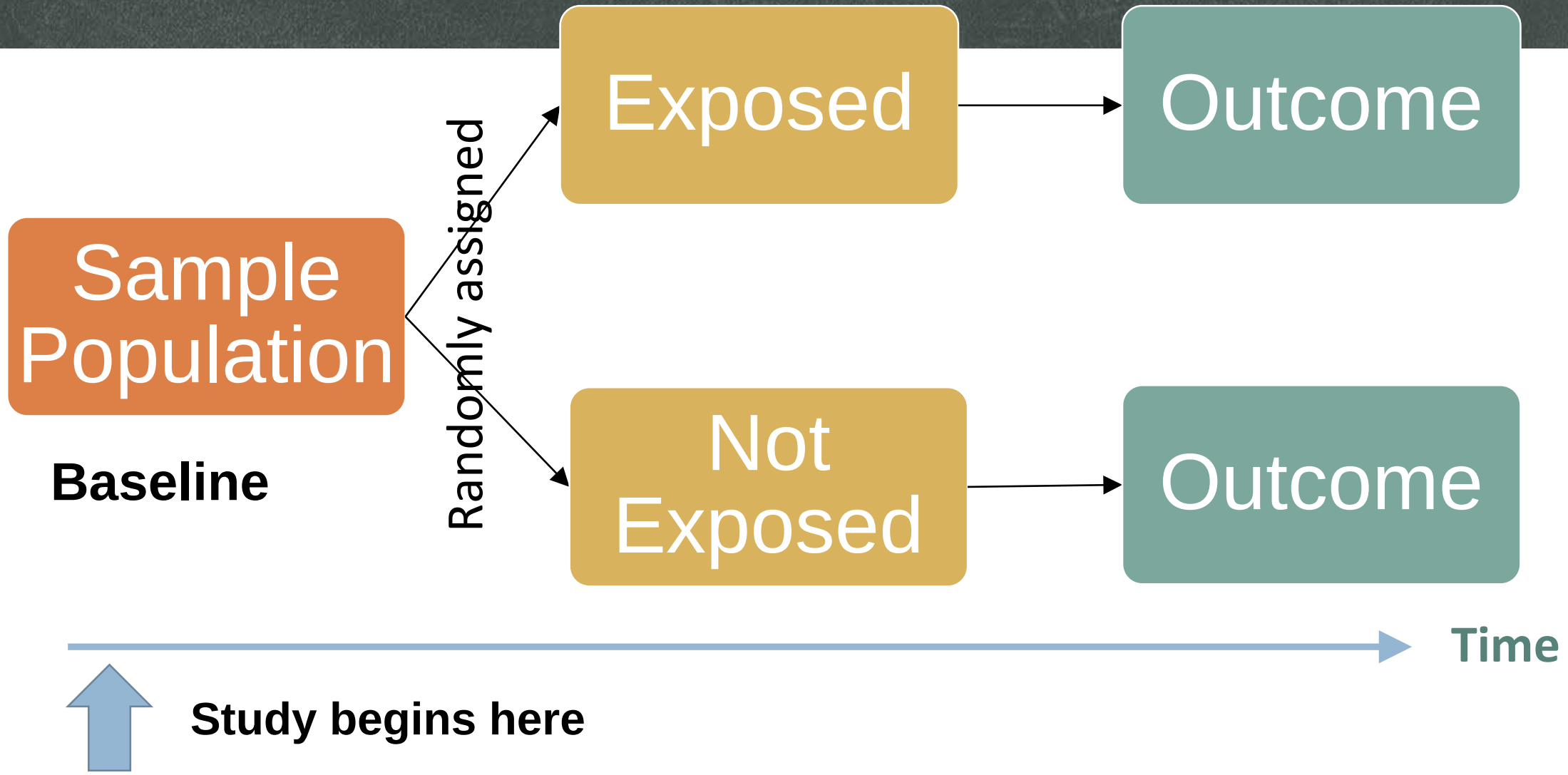
Used to **test hypothesis (analytical)**, but the difference is that the investigator has **control** over the study conditions and the **exposure status**.


Epidemiologic Studies
Sometimes called: Interventional Studies/ Randomized Controlled Trials
Observational
Experimental
Descriptive Studies
Analytic Studies
Clinical Trials
Community Trials

Experimental Studies:

- Offer the strongest evidence for causation in Epi study design and the best evidence for preventative measures available to prevent/delay death or disability, or bring about recovery in the diseased.
- Are often used in the trial of new drugs, treatments, or interventions to prevent or cure disease
- Have numerous ethical considerations

Experimental Study Design



Early Experimental Study: Ambroise Pare (1537)

Injured Soldiers

Baseline

New Treatment: egg yolk, oil of roses, turpentine

Wound Healing

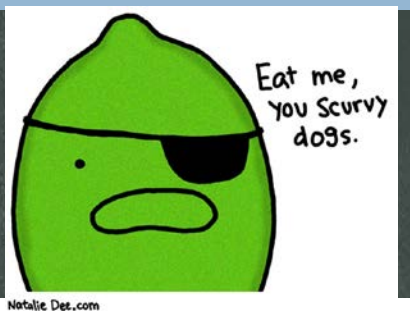
Standard Treatment: hot oil

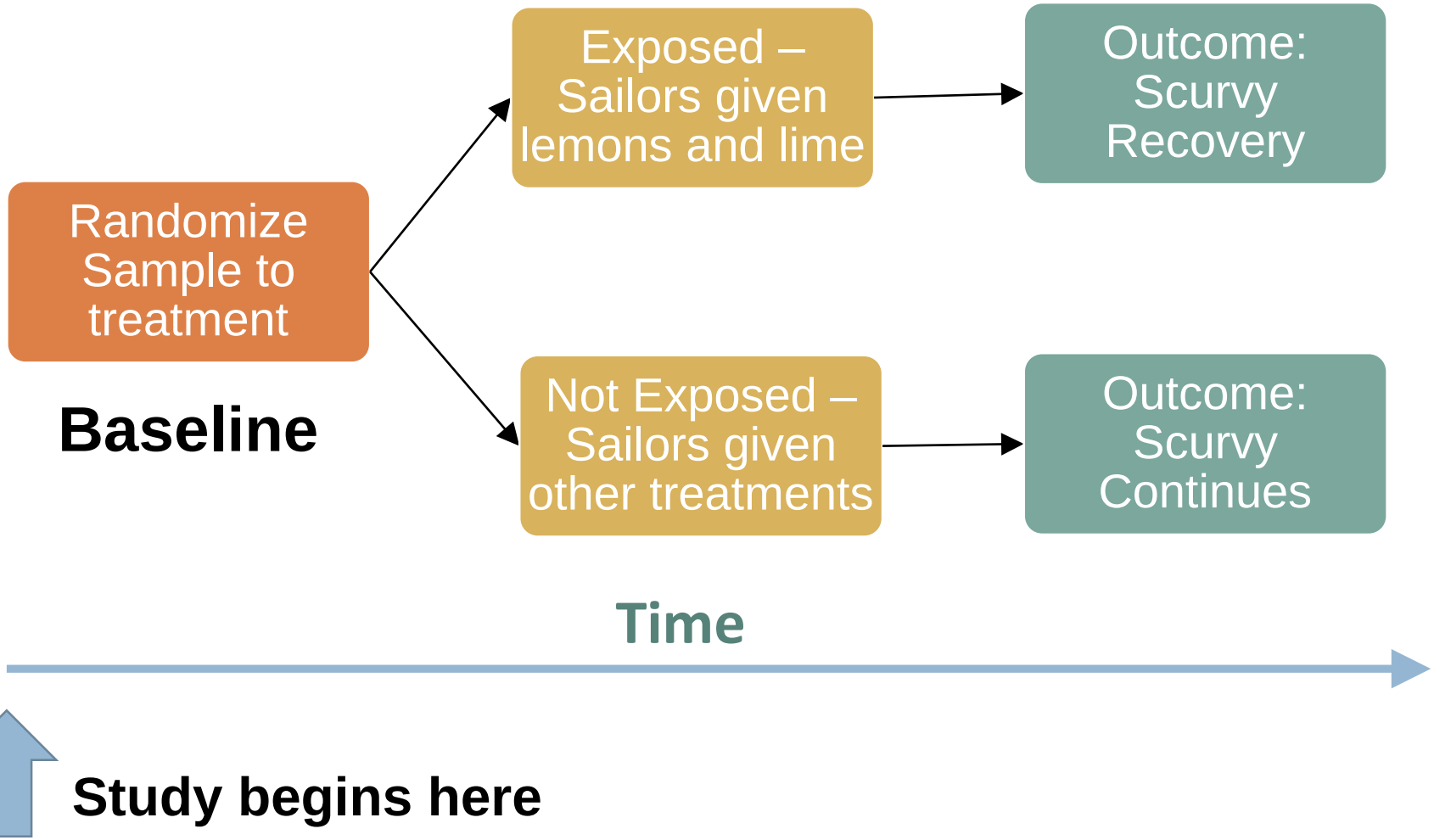
Wound Healing

Time

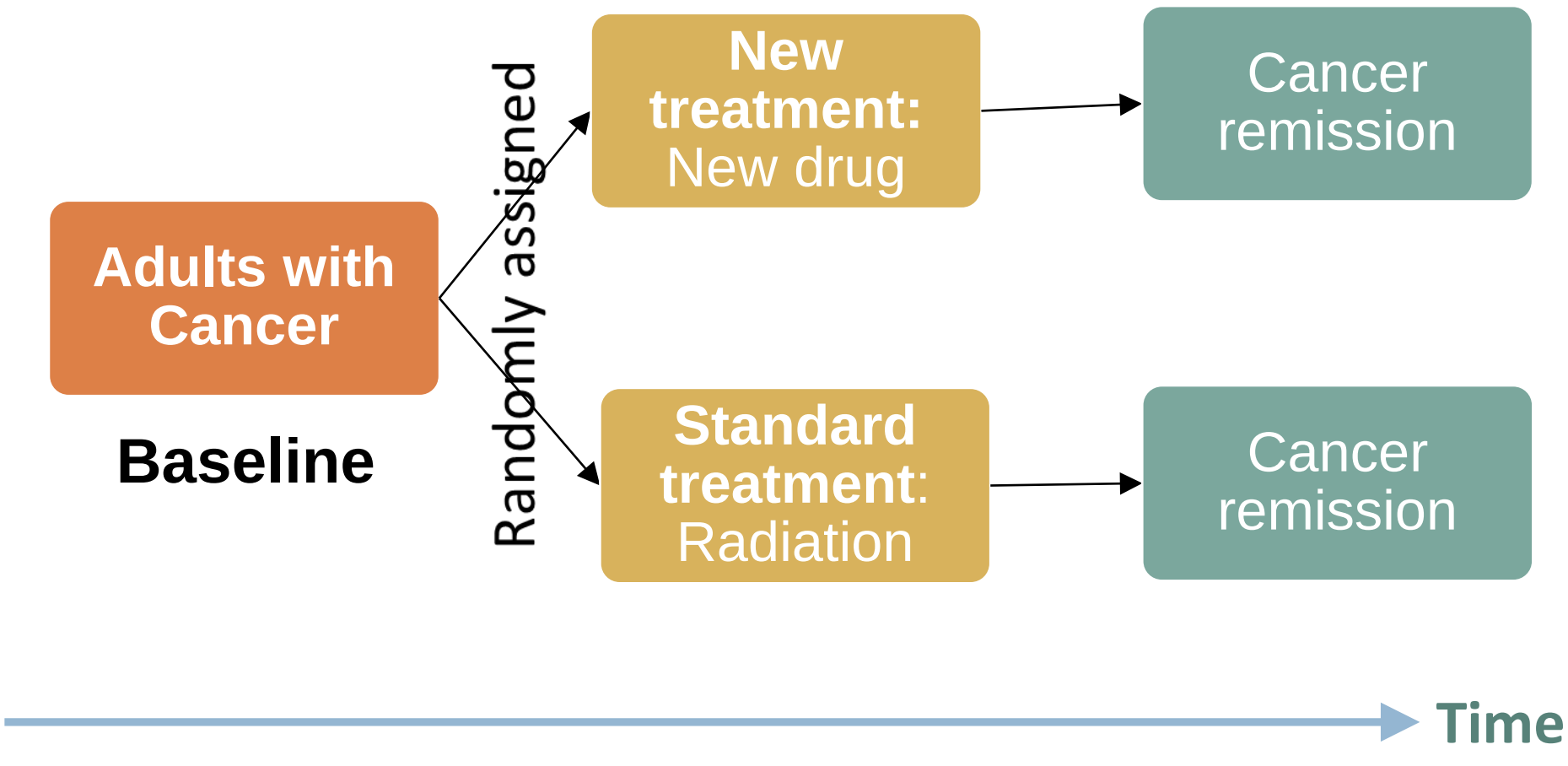
Study begins here

Early Experimental Study: James Lind (1747)





Modern Day Experimental Study: 2014



Randomized Controlled Trials: (clinical trials)

- Individuals receive random assignment to either a **treatment group** or a **control group**
- Can compare therapy vs no therapy; therapy vs placebo; therapy A vs therapy B
- Can be
  1. Preventative trials (healthy individuals)
  2. Intervention trials (high risk individuals)
  3. Therapeutic trials (diseased individuals)

Selecting a Study Sample -

Participants:

- Must be selected based on clear, written out, inclusion and exclusion criteria prior to study initiation
- May be selected from a group that will have increased levels of compliance (i.e. nurses)

Reasons for exclusion from study:

- Potential harm
- Poor compliance
- Inability to participate
- Do not met inclusion criteria
- Unwilling to be randomized

The Importance of Controls

- Must have a comparison group (i.e. controls) if we are to derive a causal inference between the treatment and the outcome, otherwise we cannot attribute the improvement to the treatment.

"results can always be improved by omitting controls"

- Hugo Muensch, as cited by Gordis (2014)

Controls may be:

- Historical Controls
- Simultaneous non-randomized controls (*predictable)
- Simultaneous randomized controls

The Importance of Randomization

- Randomization ensures all groups are **as similar as possible** at the start of study.
- Exposure: **Exercise**
  - If we let participants choose group (exercise or no exercise) those who are healthier more likely to choose the exercise group.
  - SURPRISE!! At end of study, exercise group has better health outcomes –is this because they were healthier before study began or if it was exercise intervention?

Importance of Randomization cont.

- Exposure: **New cancer drug**
  - If we let participants choose, those with more advanced cancer more likely to choose to take risky new drug.
  - At end of study – those who took drug more likely to die, not sure if drug caused it, if the drug was ineffective, or if it was simply because they were the sickest and the least likely to survive anyway
- Exposure: **New form of in vitro fertilization**
  - Which couples will be most likely to choose the new treatment vs. the standard treatment _____

The Importance of Randomization cont.

- Randomization also makes groups similar on **sociodemographic factors** (eliminates selection bias and confounders)
- This is important as factors like age, education & income are all strongly associated with health.
- Can use **Stratified Randomization** if concerned that characteristics will cluster

"Do a double-blind test. Give the new drug to rich patients and a placebo to the poor. No sense getting their hopes up. They couldn't afford it even if it works."

Electronic cigarettes for smoking cessation: a randomised controlled trial

Christopher Bullen, Colin Howe, Murray Laugesen, Hayden McRobbie, Varsha Parag, Jonathan Williman, Natalie Walker

Summary

Background Electronic cigarettes (e-cigarettes) can deliver nicotine and mitigate tobacco withdrawal and are used by many smokers to assist quit attempts. We investigated whether e-cigarettes are more effective than nicotine patches at helping smokers to quit.

Methods We did this pragmatic randomised-controlled superiority trial in Auckland, New Zealand, between Sept 6, 2011, and July 5, 2013. Adult (≥18 years) smokers wanting to quit were randomised (with computerised block randomisation, block size nine, stratified by ethnicity [Māori; Pacific; or non-Māori, non-Pacific], sex [men or women], and level of nicotine dependence [>5 or ≤5 Fagerström test for nicotine dependence]) in a 4:4:1 ratio to 16 mg nicotine e-cigarettes, nicotine patches (21 mg patch, one daily), or placebo e-cigarettes (no nicotine), from 1 week before until 12 weeks after quit day, with low intensity behavioural support via voluntary telephone counselling. The primary outcome was biochemically verified continuous abstinence at 6 months (exhaled breath carbon monoxide measurement <10 ppm). Primary analysis was by intention to treat. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000866000.

Findings 657 people were randomised (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) and were included in the intention-to-treat analysis. At 6 months, verified abstinence was 7·3% (21 of 289) with nicotine e-cigarettes, 5·8% (17 of 295) with patches, and 4·1% (three of 73) with placebo e-cigarettes (risk difference for nicotine e-cigarette *vs* patches 1·51 [95% CI −2·49 to 5·51]; for nicotine e-cigarettes *vs* placebo e-cigarettes 3·16 [95% CI −2·29 to 8·61]). Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. We identified no significant differences in adverse events, with 137 events in the nicotine e-cigarettes group, 119 events in the patches group, and 36 events in the placebo e-cigarettes group. We noted no evidence of an association between adverse events and study product.

Interpretation E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events. Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels.

Lancet 2013; 382: 1629–37

Published Online
September 7, 2013
http://dx.doi.org/10.1016/S0140-6736(13)61842-5

See **Comment** page 1614

National Institute for Health Innovation, School of Population Health, The University of Auckland, Auckland, New Zealand (C Bullen MBChB, C Howe PhD, V Parag MSc, N Walker PhD); **Health New Zealand, Lyttelton, Christchurch, New Zealand** (M Laugesen MBChB); **Wolfson Institute of Preventive Medicine, UK Centre for Tobacco Control Studies, Queen Mary University of London, Charterhouse Square, London, UK** (H McRobbie MBChB); **and Department of Public Health and General Practice, University of Otago, Christchurch, New Zealand** (J Williman PhD)

Correspondence to:
Dr Christopher Bullen, The National Institute for Health Innovation, School of Population Health, The University of Auckland, Private Bag 92019,

Link

HOW to Randomize

- If we assigned the first half of the participants arriving to the class, and everyone who arrived after them (or arrived late) to the control group – is that randomization?
    - NO…People must have the same chance of being selected for the experimental or control group, independent of their behaviour or characteristics.
    - Usually we use a random number table, computer algorithms, or a coin is flipped for each person.

The Importance of Blinding (masking)

- Participants who learn they are randomly assigned to get the placebo may be less motivated to take them, or may drop out of study.
- Knowing what group you are in may influence disease outcome independent of effects of exposure:
  - Power of the placebo effect

- **Single-blind** study – participant does not know what group they are in
- **Double-blind** study – participant and experimenter do not know group assignment
- **Triple-blind Study** – participants, investigator, and those analyzing the data do not know the group assignment

Phases of a Clinical Trials: Clinical Trials Registry

Preclinical trial – animal studies or lab trials

Phase I – SAFETY OF DRUG - Establish the effects (e.g. toxicity, absorption, metabolism) of a new drug or treatment in small groups; typically 20-80 healthy participants

Phase II – EFFICACY - Tested in larger groups for safety and efficacy; typically 100-300 participants

Phase III – EFFICACY and SAFETY - Larger populations tested, often using placebo as a comparison; typically 1000-3000 participants

Phase IV - LONG TERM EFFECTS – After drug is approved, studies are conducted to compare the drug to competitors, explore new patient populations, and study adverse reactions from long term use (post marketing surveillance)

Epi in the NEWS
January 17th, 2016

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1 dead after botched clinical drug trial in France, 5 still in hospital

Man was already brain dead after ingesting painkiller based on a compound similar to cannabis

The Associated Press Posted: Jan 17, 2016 1:44 PM ET | Last Updated: Jan 17, 2016 4:11 PM ET

French Health Minister Marisol Touraine and Gilles Hedan, professor of clinical neurology, attend a news conference in Rennes, France, January 15, 2016. (Stephane Mahe/Reuters)

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A man died in a French hospital Sunday after taking part in a drug trial for a painkiller being tested that blocks a naturally occurring enzyme to mimic a cannabis-like effect, such as pain relief. Five other participants remain hospitalized after one of France's most troubling medical incidents.

French prosecutors have launched a manslaughter investigation into the unusual case, which shone a spotlight on the practice of testing drugs on paid, healthy human volunteers. Scores of others were also given the drug.

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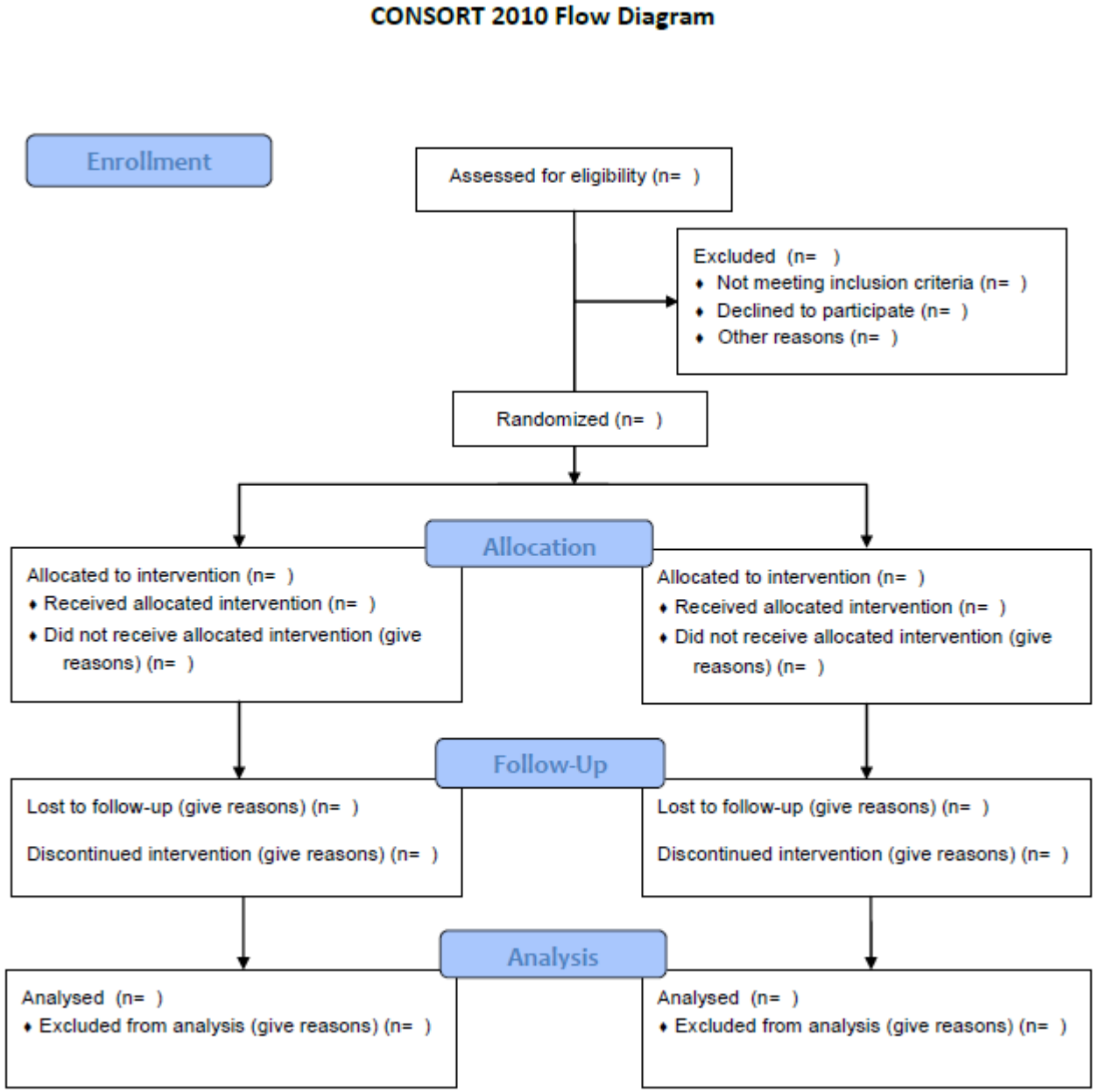
- Woman sent Ghomeshi emails, bikini pic a

LINK

Reporting Clinical Trials:
Quality Control

CONSORT (consolidated Standards of Reporting Trials)

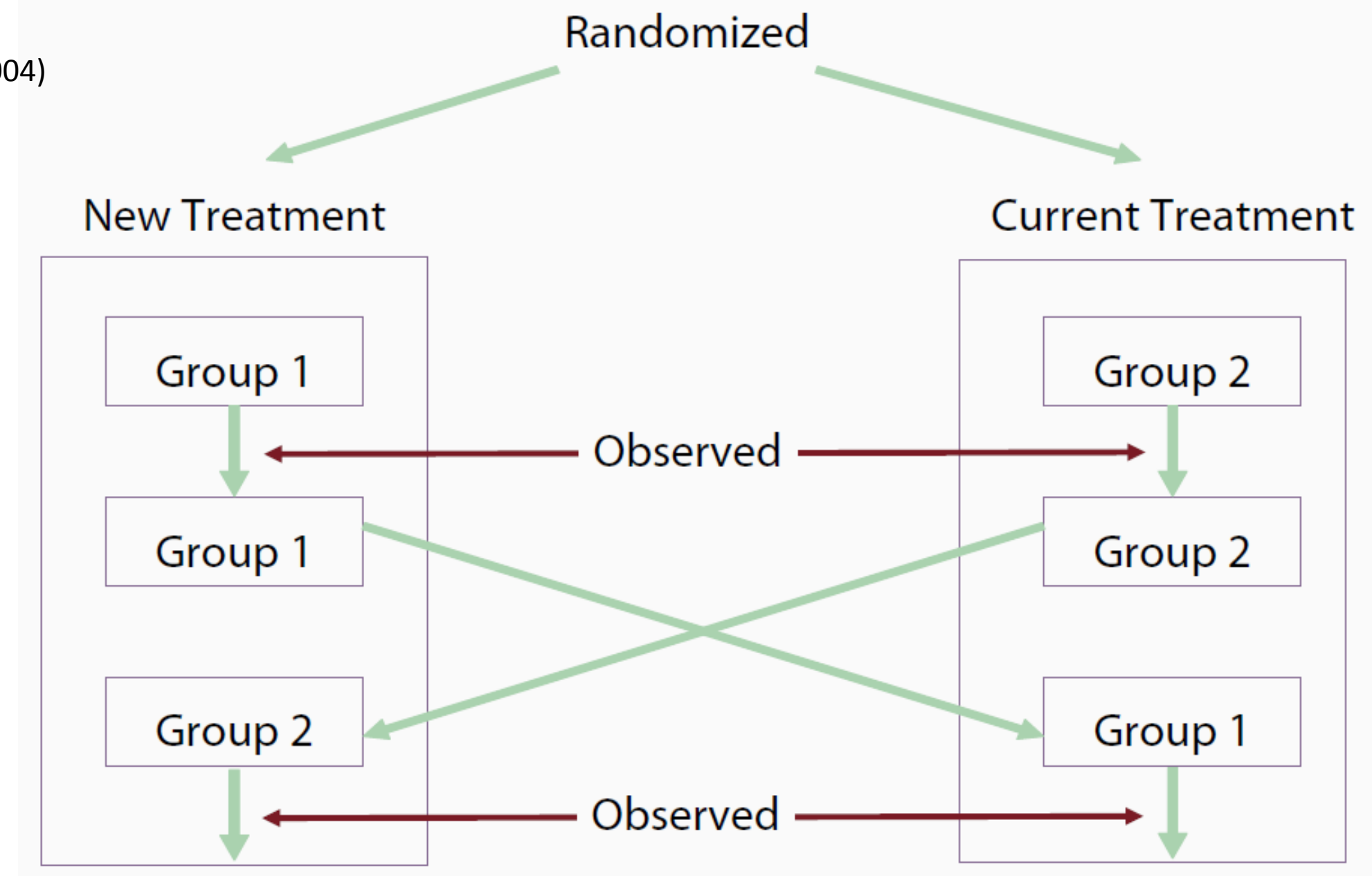
- Developed to alleviate problems which arise from inadequate reporting of RCTs
- Checklist and Flow Diagram



CROSSOVER in RCTs: *Planned*

- Each study participant gets **both** the intervention and the placebo
- Randomized to treatment group or control group, but after a period of time are switched to the other group
- Patients serve as their own controls
- Need to ensure there is no "carryover" – residual from the first intervention – so a "**washout period**" is needed
- Not possible if therapy is not reversible, or if the new therapy cures the disease

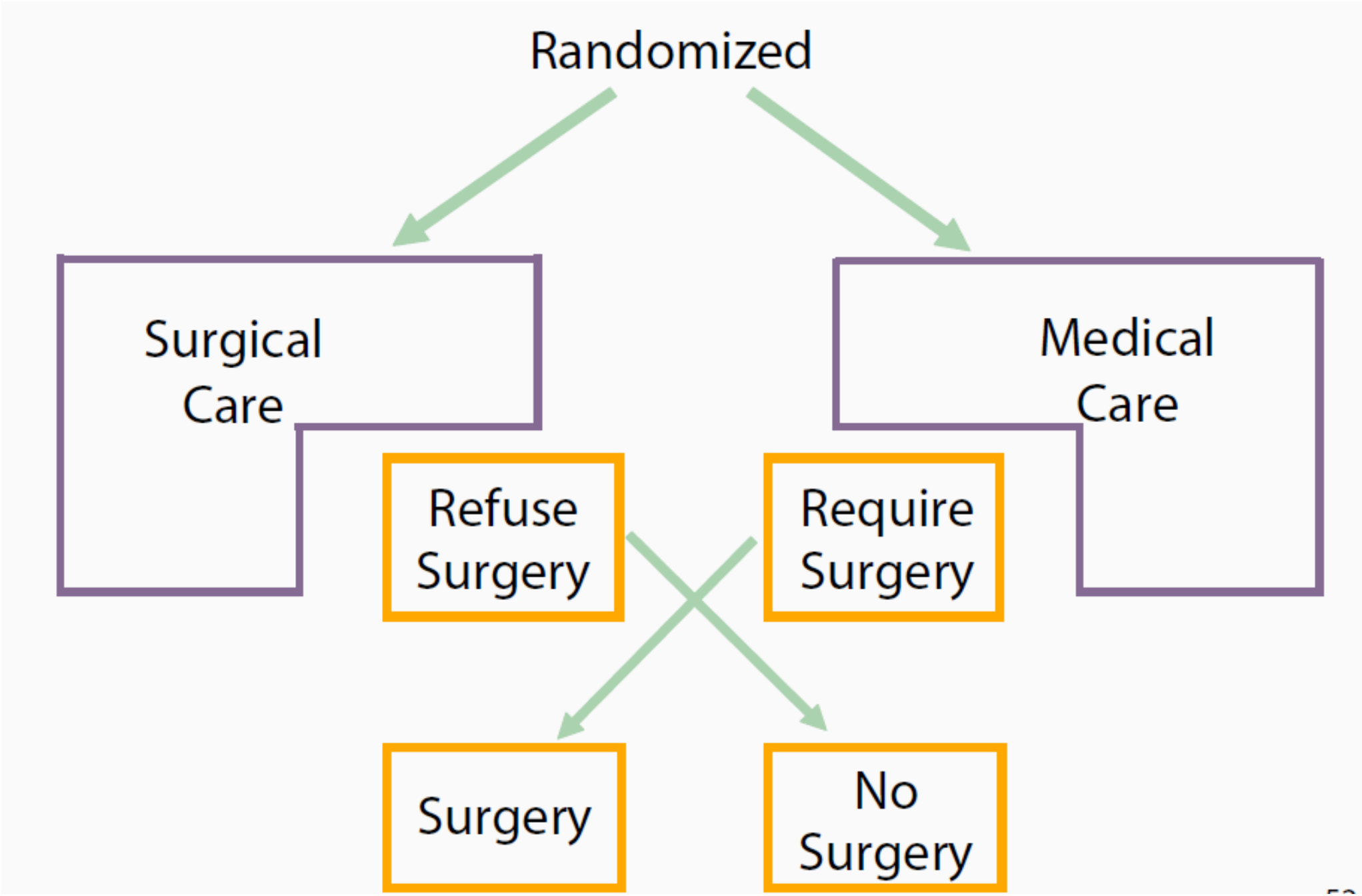
Planned Crossover
(image from Gordis, 2004)



CROSSOVER in RCTs: *Unplanned*

- Patients are randomized to treatment or control group
- Participants may need to be reassigned based on deterioration of health condition or their wavering about treatment
- Best to analyse data based on "**Intention To Treat**" (according to the original randomized assignment) rather than what was actually received to avoid losing the benefits of randomization

Unplanned Crossover
(Gordis, 2004)



Notable Events in the development of ethical guidelines:

- Nuremberg Code
- Declaration of Helsinki
- Beecher Report
  - Tuskegee Syphilis Study
- Belmont Report

Webb and Bain p. 118

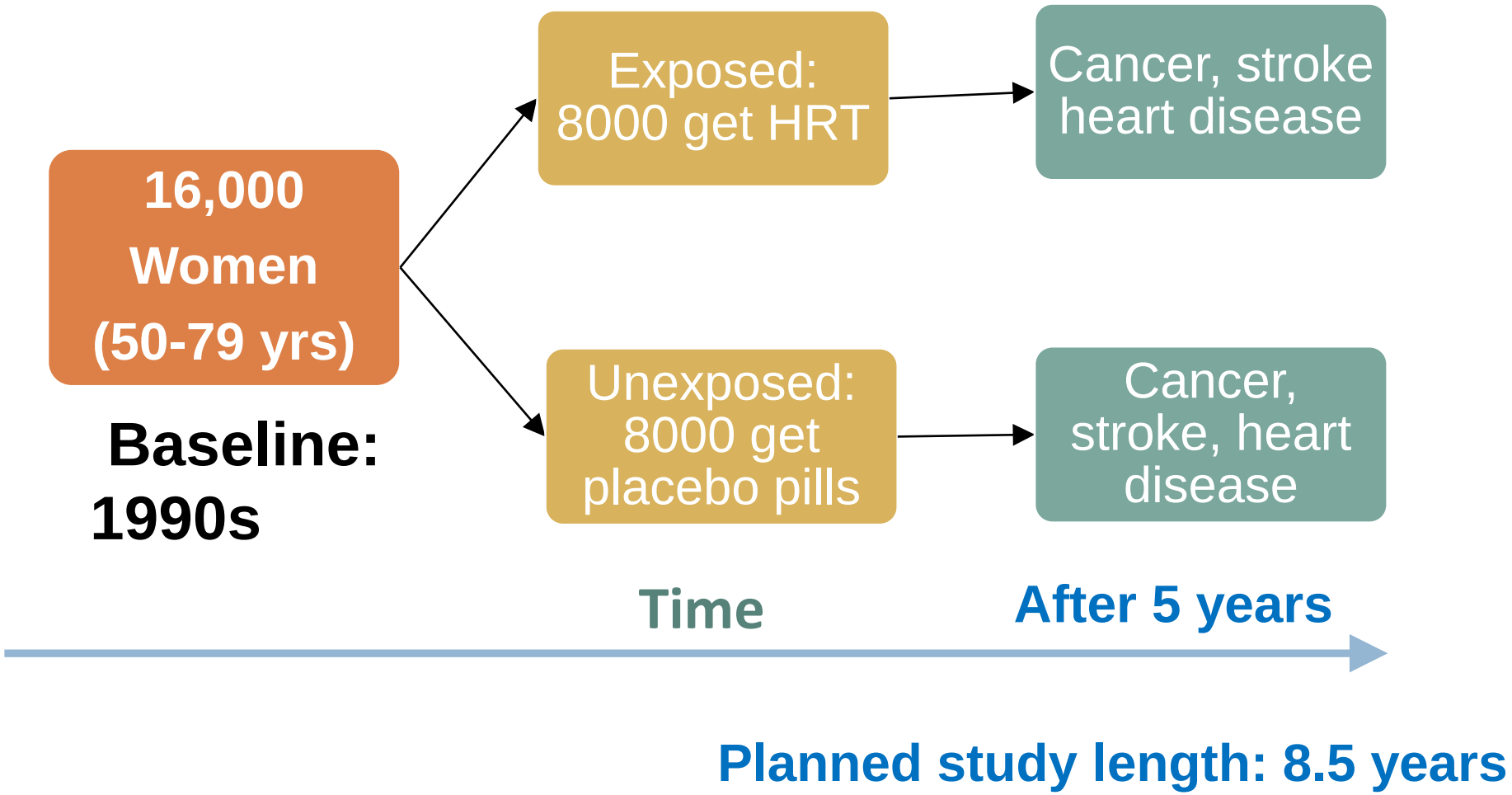
Moral Principles as a Basis for Ethical Research:

1. **Beneficence** – do good
2. **Non-Maleficence** – do no harm; potential benefits should outweigh potential risks
3. **Respect for Autonomy** – respect the rights of the individual; right to privacy; right to informed decisions
4. **Justice** – equity, impartiality, and fairness

Ethics in Experimental Research

1. **Informed consent**
   - Patients must know purpose of trial, length, procedures involved, and potential risks.
2. **Cannot withhold treatment known to be effective**
   - Cannot provide control group no treatment if a standard treatment is available.
3. **Must protect the interests of participants**
   - Must monitor findings and stop trials showing a strong negative effect, or remove people showing dangerous signs.

Ethics in Experimental Study (Famous Example)



Planned study length: 8.5 years

Women`s Health Initiative Study (USA, 2002)

- **Relative risk** for women exposed to HRT compared to women not exposed in study.
  - Breast cancer: **1.26**
  - Cardiovascular disease: **1.29**
  - Hip fractures: **0.66**
  - Stroke: **1.41**
  - Endometrial cancer: **0.92**
  - Pulmonary embolism: **2.13**
- Study was stopped based on these findings: http://www.youtube.com/watch?v=HEJxiDc8Ufw

Randomized Controlled Trials Overview

Strengths

- Can demonstrate causal relationship with high level of confidence
- Allow investigators to control exposure levels
- Randomization reduces selection bias

Limitations

- Costly and time consuming
- May be difficult to find sample sizes large enough based on eligibility criteria
- Ethical considerations
- Adherence to treatment

Experimental Study: Community Trials

- Groups, rather than individual, are the unit of analysis

(e.g. cities, counties, states, occupational groups, schools)

- Appropriate for diseases influenced by social conditions and where prevention can target group behaviour.
- Determine eligible communities (and willingness to participate) and then randomly assign to treatment or control
- Communities should be similar and have stable population

Translating a Fall Prevention Intervention Into Practice: A Randomized Community Trial

LINK

Clare E. Guse, MS, Donna J. Peterson, PhD, Ann L. Christiansen, MPH, Jane Mahoney, MD, Purushottam Laud, PhD, and Peter M. Layde, MD, MSc

Objectives. We examined whether community translation of an effective evidence-based fall prevention program via standard monetary support can produce a community-wide reduction in fall injuries in older adults and evaluated whether an enhanced version with added technical support and capacity building amplified the fall reduction effect.

Methods. We completed a randomized controlled community trial among adults aged 65 and older in (1) 10 control communities receiving no special resources or guidance on fall prevention, (2) 5 standard support communities receiving modest funding to implement Stepping On, and (3) 5 enhanced support communities receiving funding and technical support. The primary outcome was hospital inpatient and emergency department discharges for falls, examined with Poisson regression.

Results. Compared with control communities, standard and enhanced support communities showed significantly higher community-wide reductions (9% and 8%, respectively) in fall injuries from baseline (2007–2008) to follow-up (2010–2011). No significant difference was found between enhanced and standard support communities.

Conclusions. Population-based fall prevention interventions can be effective when implemented in community settings. More research is needed to identify the barriers and facilitators that influence the successful adoption and implementation of fall prevention interventions into broad community practice. (*Am J Public Health*. Published online ahead of print January 20, 2015: e1–e7. doi:10.2105/AJPH.2014.302315)

In 2010, injuries resulting from unintentional falls in adults aged 65 years and older accounted for 21 649 deaths nationally (54 per 100 000 population), which was the leading cause of fatal injury in that age group and the ninth overall cause of death.[1] On the basis of 2011 emergency department data, the Centers for Disease Control and Prevention (CDC) estimated that more than 2.4 million unintentional fall injuries required treatment in emergency departments in adults aged 65 years and older, appreciably more than any other injury-related cause of emergency department visits.[1] The CDC estimated that fatal and nonfatal unintentional falls in adults aged 65 years and older have lifetime costs greater than $18.6 billion (according to 2005 prices).[2]

Wisconsin has a higher fall injury mortality rate than does the nation as a whole.[3,4] In 2010, Wisconsinites aged 65 years and older had the second highest rate of unintentional fall injury fatality among all states for that age group, a rate of 111 per 100 000 population.[1]

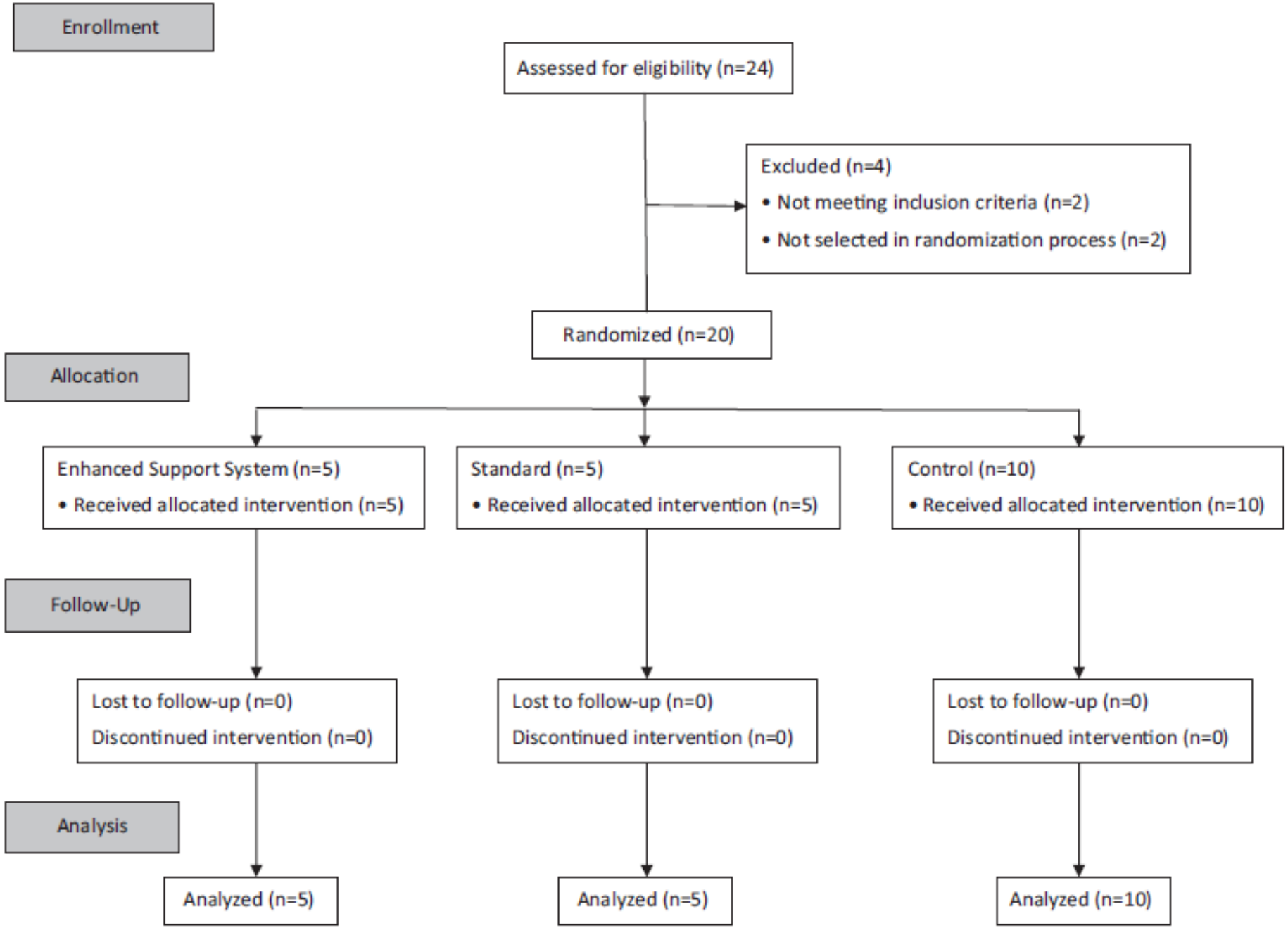


FIGURE 1—Flow diagram of study communities: Wisconsin, May 2008 through January 31, 2012.

Community Trials

Strengths

- Realistic estimate of exposure effect in the real world.
- Can randomize exposure
- Good way to determine benefits of new program or policy intervention within a community.

Weaknesses

- Difficult to blind participants
- Randomize a group, not an individual (e.g., schools) - sample size can be a problem.
- Differences in outcomes may be due to other causes
- Selection bias (if randomization not possible)
- Ecological fallacy

In a cohort study examining the association between childhood exposure to CT scans and leukemia, it was found that the relative risk was 3.18 (95% CI 1.46-6.94). Is this statistically significant?

A. YES

B. NO

Randomization in RCT

A. Minimizes ethical concerns
B. Masks the participants to knowledge of assignment group
C. Ensures participants are as similar to each other as possible
D. Minimizes loss to follow up

A Crossover Study design would be best suited for which of the following interventions?

A. Vaccination

B. Surgical Treatment

C. Drug therapy

D. None of the above