Univerza v Ljubljani
Fakulteta za farmacijo

Načrtovanje raziskav

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Uvod v načrtovanje raziskav

Randomizirana kontrolirana klinična raziskava (RCT)

- Zgodovina
- Randomizacija
- Faze RCT
- Osnovni načrti RCT
- Elementi RCT
- Etična načela

Zgodovinska perspektiva

Kontrolirana klinična raziskava...

Prove thy servants, I beseech thee, ten days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the King's meat; and as thou seest, deal with thy servants. So he consented to them in this matter, and proved them ten days. And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the King's meat.

Book of Daniel, Chapter 1, Verses 12 -15

I raised myself very early to visit them when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses.

Ambroise Paré (1510 – 1590)

Kontrolirana klinična raziskava...

James Lind: Zdravljenje skorbuta

No of Patients: 12

Test Treatments:

- **Cyder, 1qt/day**
- **Elixir vitriol, 25 gutts, 3 times/day**
- **Vinegar, 2 tsp, 3 times/day**
- **Bigness of nutmeg 3 times/day**
- **orange (2) ; lemon (1) /day**

Control Treatment

- **Sea-water, ½ pt/day**

Follow-up: **6 days**

Outcome: **fit for duty**

Lind's Treaty on Scurvy, 1753

Kontrolirana klinična raziskava...
Prelomnice v zgodovini RCT

- 1747 Lind's Scurvy experiment
- 1800 Waterhouse's smallpox experiments
- 1863 Gull's use of Placebo Treatment
- 1923 Fisher's 1st application of randomization
- 1931 1st use of randomization (and blindness) in a clinical trial
- 1946 Nuremberg Code for Human Experimentation
- 1962 Hill AB Statistical Methods of Clinical and Preventive Medicine
- 1979 Society for Clinical Trials

From Curtis L Meinert. Clinical Trials, Oxford University Press 1986

Randomizacija

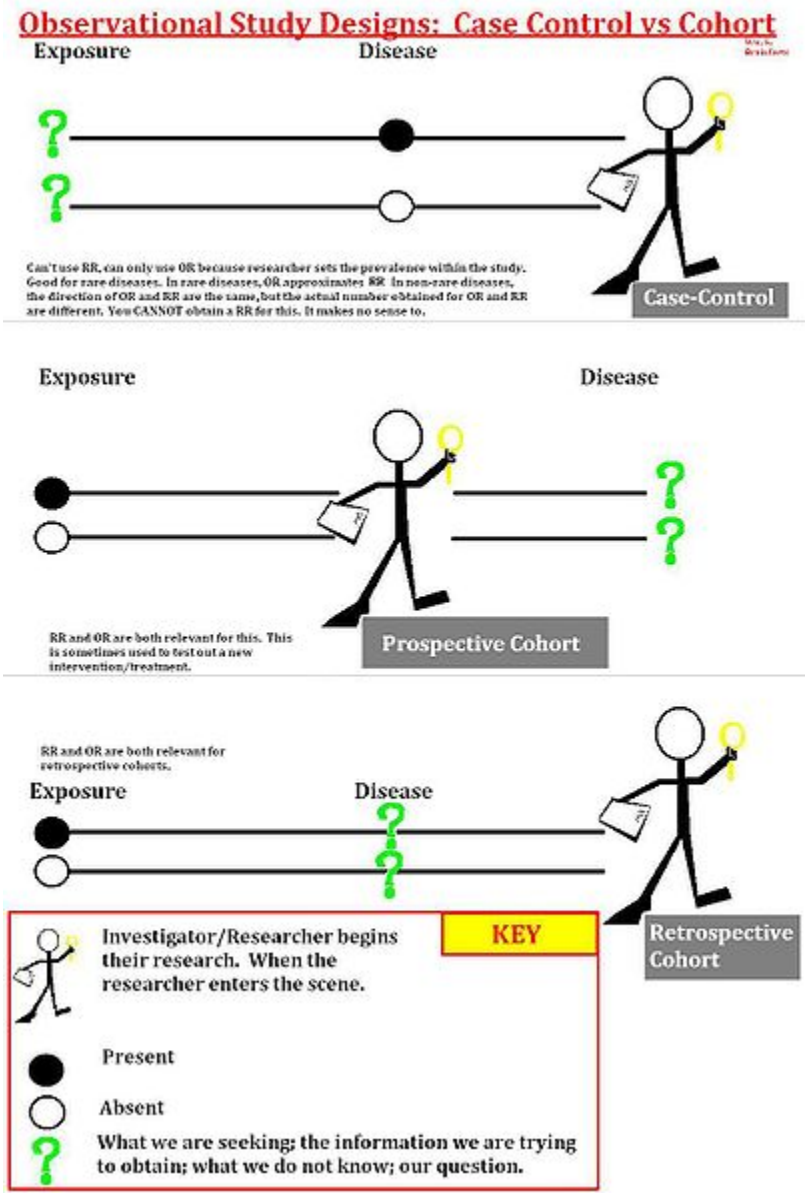
Randomizirana klinična raziskava

Terminologija

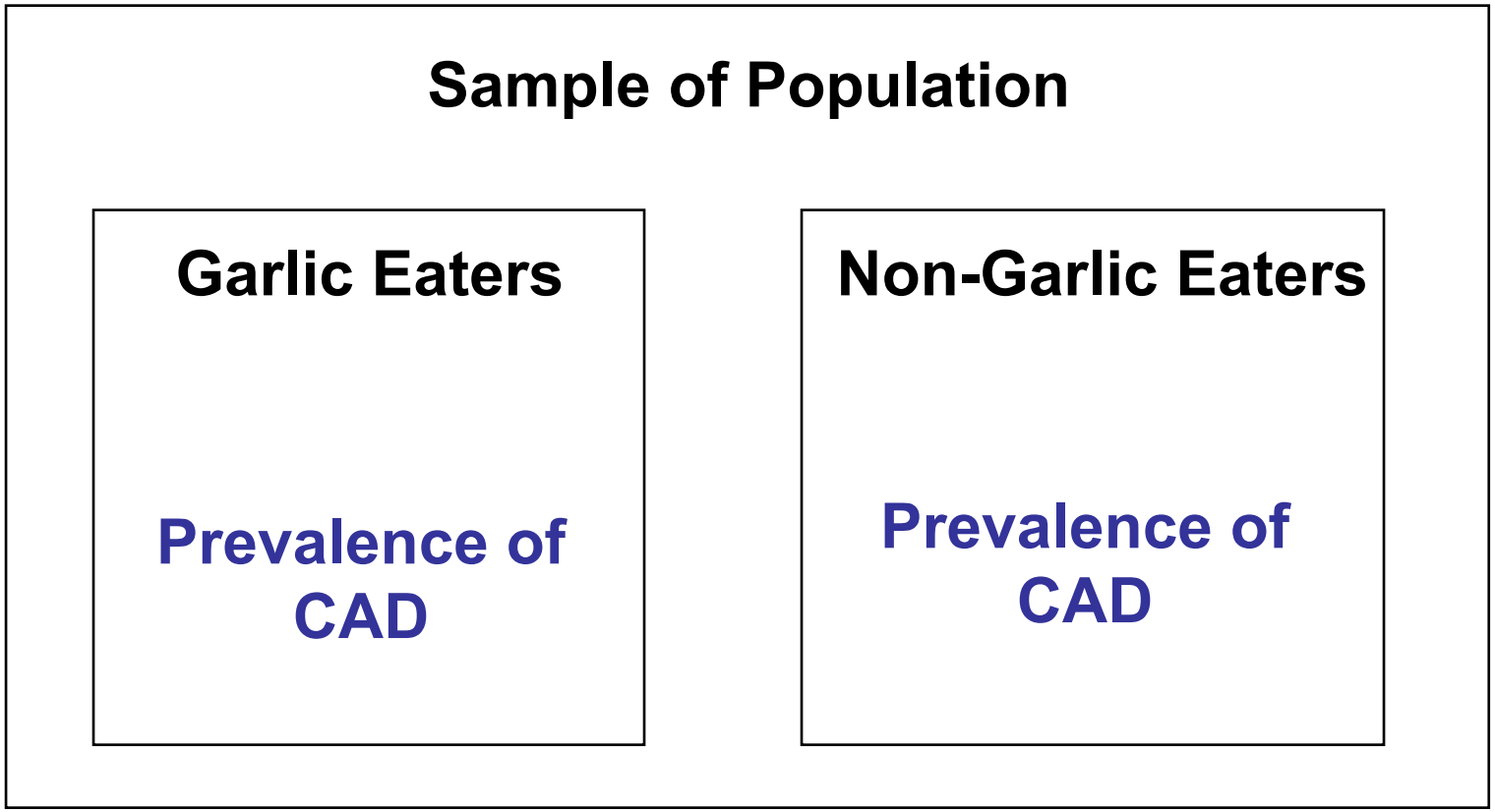
- **Clinical Trial:**
  - **An experiment testing medical (e.g. drug, surgical procedure, device or diagnostic test) treatments on human subjects**
    - **Experiment: a series of observations made under conditions controlled by the scientist**
    - **Prospective (≠ case-control study)**
    - **Comparative (≠ cohort study)**
    - **Involves human subjects**
  - **A research activity that involves administration of a "test treatment" to some "experimental unit" in order to evaluate that treatment**

Raziskave

- Deskriptivne
  - Poročila primerov (case reports)
  - Raziskava serije primerov (case series)
  - Populacijske raziskave (population studies)
- Analitične
  - Opazovalne
    - Presečne (cross-sectional)
    - Primer-kontrola (case-control)
    - Kohortne
  - Eksperimentalne
    - RCT



Presečna raziskava



Time Frame = Present

Randomizirana klinična raziskava
Terminologija

- **Randomization: the process of assigning patients to treatment using a random process (such as a table of random numbers)**

- **Randomized controlled clinical trial (or randomized clinical trial-RCT):**
  - **Clinical trial with at least one control treatment and one test treatment**
  - **In which the treatment administered are selected by a random process**

Zakaj randomizacija?

"The goal of randomization is to produce comparable groups in terms of general participant characteristics, such as age or gender, and other key factors that affect the probable course the disease would take. In this way, the two groups are as similar as possible at the start of the study. At the end of the study, if one group has a better outcome than the other, the investigators will be able to conclude with some confidence that one intervention is better than the other. "

Friedman et al. Fundamental of Clinical Trials, Mosby Press

Randomizacija

- Produce comparable groups: eliminate treatment selection bias
- Protect against both known and unknown confounders
- Best to establish causality
- Necessary to detect small but clinically important treatment differences

Kdaj?

- Finding “window of opportunity”
  - Too early
    - Not enough “preliminary” evidence :biological plausibility, epidemiologic studies
    - Intervention not “mature” enough (e.g. surgical technique)
  - Too late: intervention already established in clinical practice
- Clinical Equipoise
- Changing Clinical Practice Guidelines

Faze kliničnega preskušanja

Faza 1

- First in humans
- Small, uncontrolled
- Healthy volunteers/failed conventional therapy
- Dose-escalation protocols
- Tolerability/toxicity study: Maximum Tolerated Dose (MTD)
- Dose-response models

Faza 2

- Test biologic activity/effect
- Estimate rates of adverse events
- Performed in patients with disease/condition of interest
- With or without comparison group
- Strict eligibility criteria

Faza 3

- Determine the effectiveness (overall benefit/risk-cost assessment) of new therapies relative to standard therapy
- Large sample size
- Multicenter
- Superiority, equality, equivalence or non inferiority

Faza 4

- Long term surveillance studies (“post marketing”) for safety
- Look for rare side effects
- Often non randomized

Raziskovanje

- George Box

Ciklični postopek
učenja (INDUKCIJA)
in
potrjevanja (DEDUKCIJA)

Klinični razvoj zdravila

- 1. cikel
  - Faza 1: zdravi prostovoljci; Kakšen je najustreznejši odmerek zdravila? (učenje)
  - Faza 2A: bolniki; izbran odmerek je potencialno sprejemljiv s stališča varnosti in učinkovitosti (potrjevanje)
- 2. cikel
  - Faza 2B: kako uporabljati zdravilo, da bo razmerje učinkovitost/varnost optimalno? (učenje)
  - Faza 3: izbran način uporabe je učinkovit in varen (potrjevanje)

Sheiner LB, Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997, 61: 275-91.

Učenje/potrjevanje

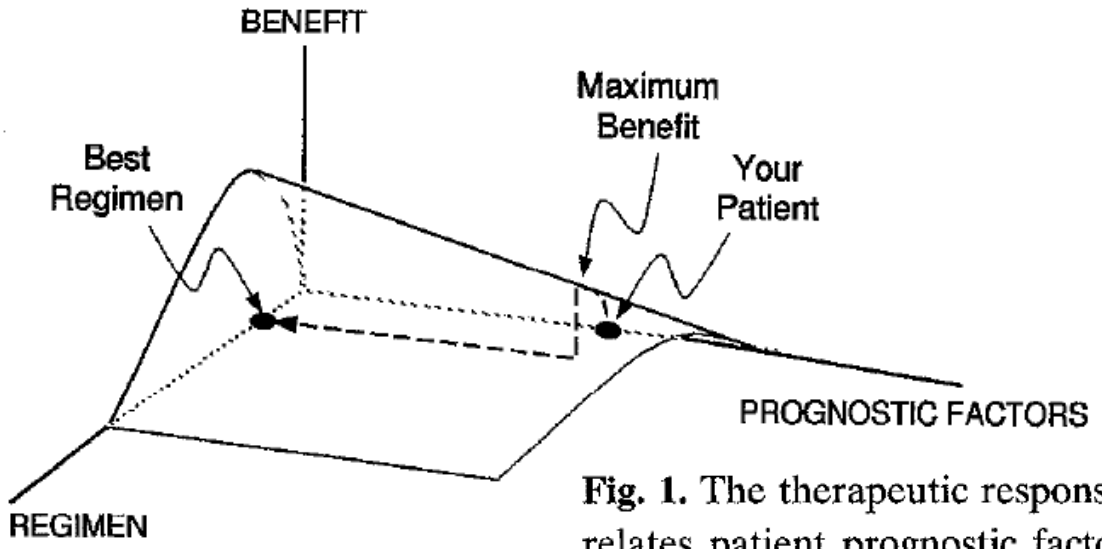


Fig. 1. The therapeutic response surface for a given drug relates patient prognostic factors (such as sex, age, and weight) and dose regimen (amount and timing) to benefit, the net utility of efficacy, and toxicity. A plane perpendicular to the prognostic axis at the value of "your" particular patient intersects the surface forming a curve (as shown). The optimal regimen for your patient is that corresponding to the maximum of this curve on the benefit axis (here, the value on the maximum benefit "ridge"). (Adapted from Sheiner. Clin Pharmacol Ther 1991;50:4-9. Used with permission.)

Eksploratorni načrt
Potrditveni načrt

Načrt RCT

Vzporedni načrt

FREEDOM Design

Future REvascularization Evaluation in patients with Diabetes mellitus:
Optimal management of Multivessel disease

Eligibility: DM patients with MV-CAD eligible for stent or surgery
Exclude: Patients with acute STEMI, cardiogenic shock

Randomized 1:1

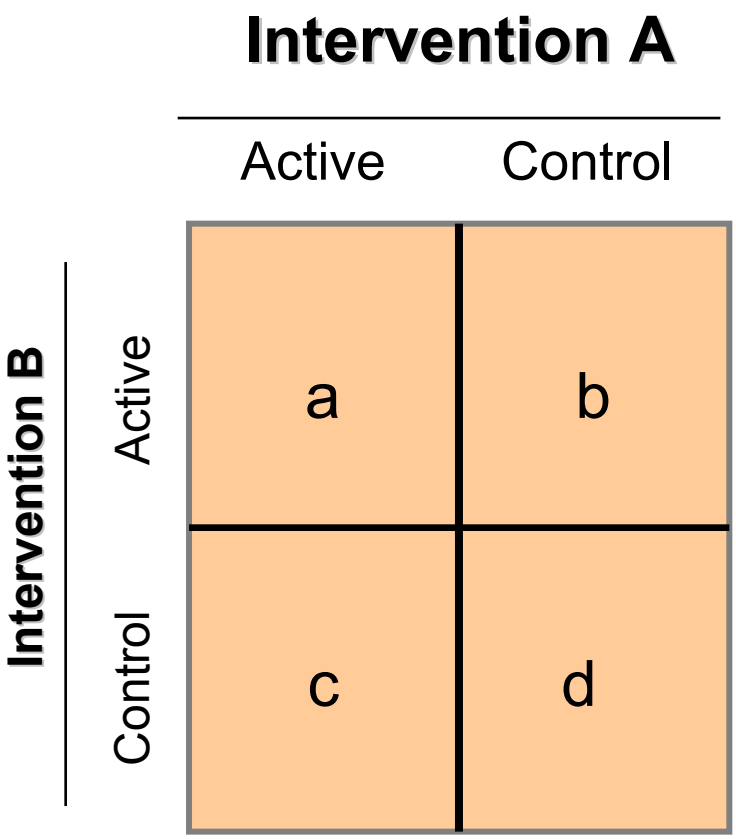
MV-stenting
With Drug-eluting stents
And abciximab

CABG
With or without CPB

Navzkrižni načrt

- Participant = own control
- Randomize: order of treatment for each patient (e.g. AB vs. BA)
- Advantages
  - Reduce variability → Reduce Sample Size
  - Detect difference in response in individual patient
- Disadvantages
  - Order of treatment should not matter
  - No carry over of effect → test for interaction

Faktorski načrt



Cells

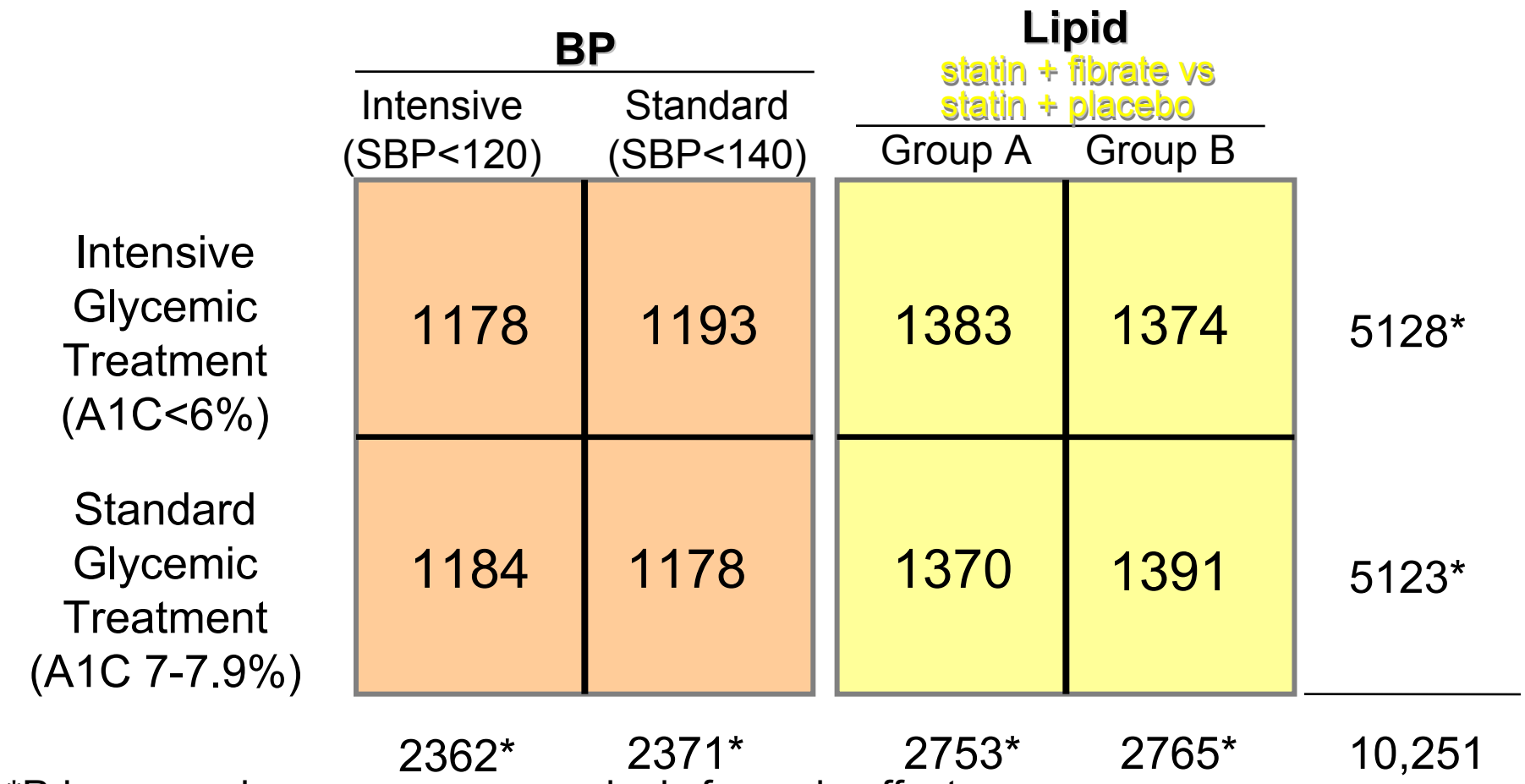
a= Active A + Active B
b= Control A + Active B
c= Active A + Control B
d= Control A + Control B

Analysis of a 2 x 2 factorial RCT

Effect of A: ac vs. bd *
Effect of B: ab vs. cd *

*If no treatment interaction

Faktorski načrt



*Primary analyses compare marginals for main effects

ACCORD (Action to Control Cardiovascular Risk in Diabetes)

(ACCORD Study Group, Am J Cardiol 2007;99[suppl]:21i-33i)

Faktorski načrt

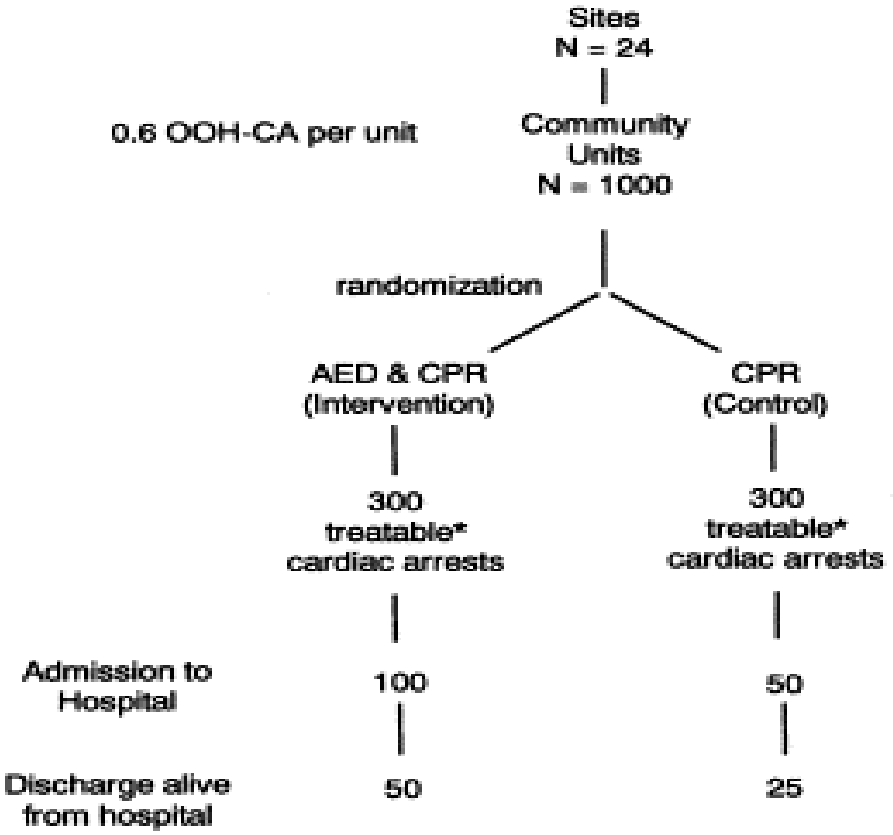
- **Advantage:**
  - Two trials for (almost) the price of one
  - Design is best if: two intervention have different mechanisms of actions or different outcomes (e.g. cancer for A and CV disease for B)

- **Disadvantages:**
  - Need to test for possibility of interaction (e.g. A differs based on the presence or absence of B)
  - Test for interaction not very powerful
  - Need to consider gain in cost vs. increased complexity, recruitment and adherence issues and potential for adverse events

Načrt z razvrščanjem skupin (Cluster Design)

- Cluster design= group randomization
- Group= schools, clinics, villages…
- Sample size: based on number of groups (not individuals)

Cluster Design: The Public Access Defibrillation (PAD) Trial



*Treatable arrests are considered to be those witnessed or discovered shortly after collapse.

Resuscitation. 2003 Feb;56(2):135-47

Enostaven načrt

- Needed to uncover smaller treatment effects

  That are important in common conditions

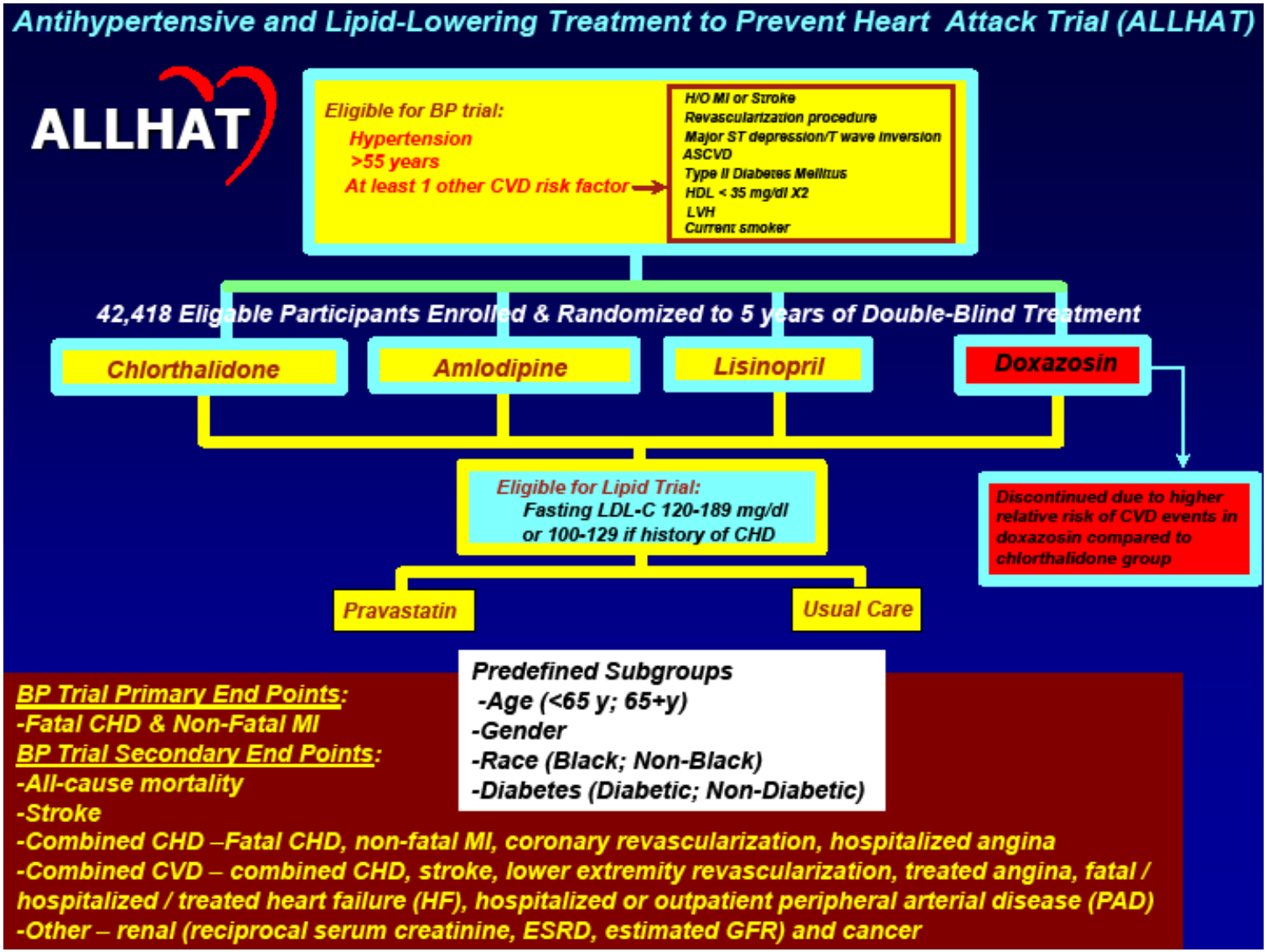
- Increase generalizability

  But limit data collection/subgroups and secondary analyses

- Decrease cost by simplifying design and management

  But need strong randomization procedures and reliable outcomes assessment

Primer


Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
ALLHAT
Eligible for BP trial:
Hypertension
>55 years
At least 1 other CVD risk factor
H/O MI or Stroke
Revascularization procedure
Major ST depression/T wave inversion
ASCVD
Type II Diabetes Mellitus
HDL < 35 mg/dl X2
LVH
Current smoker
42,418 Eligable Participants Enrolled & Randomized to 5 years of Double-Blind Treatment
Chlorthalidone
Amlodipine
Lisinopril
Doxazosin
Eligible for Lipid Trial:
Fasting LDL-C 120-189 mg/dl
or 100-129 if history of CHD
Discontinued due to higher relative risk of CVD events in doxazosin compared to chlorthalidone group
Pravastatin
Usual Care
Predefined Subgroups
-Age (<65 y; 65+y)
-Gender
-Race (Black; Non-Black)
-Diabetes (Diabetic; Non-Diabetic)
BP Trial Primary End Points:
-Fatal CHD & Non-Fatal MI
BP Trial Secondary End Points:
-All-cause mortality
-Stroke
-Combined CHD –Fatal CHD, non-fatal MI, coronary revascularization, hospitalized angina
-Combined CVD – combined CHD, stroke, lower extremity revascularization, treated angina, fatal / hospitalized / treated heart failure (HF), hospitalized or outpatient peripheral arterial disease (PAD)
-Other – renal (reciprocal serum creatinine, ESRD, estimated GFR) and cancer

Elementi RCT

Raziskovalni problem

(Kdo-Kaj-Kdaj)?

- Primary question tests the hypothesis
- Hypothesis must include:
  - *Population studied*
  - *Primary outcome of interest*
  - *Intervention studied*
  - *Period of observation*
- Objective: phrase the research question in concise, quantitative terms

Primarni in sekundarni namen

- Primary objective needs to be defined (determine sample size)
- Secondary objective needs to be:
  - *Defined a priori (avoid post hoc "fishing expedition")*
  - *Chosen parsimoniously (avoid false positive)*
- Primary vs. secondary:
  - *Question of greatest interest/relevance*
  - *Consider feasibility (e.g. mortality vs. morbidity)*

Izidi

- Quantitative measurement required by the objectives (= outcome, response variable)
- Event/condition the trial is designed to ameliorate, delay, prevent…
- Primary endpoint: need to be clearly and rigorously defined (*what is survival?)*
- Endpoints defined by type of measurement used:
  - **Discrete, dichotomous *(dead or alive?),* count**
  - **Continuous *(BP change),* ordered (*toxicity)***

Primarni izid

- Must answer the primary question
- Frequency of occurrence must be known in control (determine sample size)
- Must be able to estimate treatment effect: clinical relevance (*minimum desired effect to change practice?)*
- Must be assessed/evaluable in all participants
- Can be measured accurately/reliably/objectively
  - Blinded randomization
  - Blinded assessment (*soft end point?*)
- All patients must be evaluated (no post randomization exclusion/no lost to follow up)

Združevanje izidov

- Decrease sample size
- One (first?) event per participant
- Need to be clinically meaningful, may be biologically related (*non fatal myocardial infarction and CHD death*)
- Many potential problems:
  - Hierarchy of importance (e.g. death > MI > revascularization)
  - Rare vs. common event
  - Same biological pathway? If not: components may go in opposite directions!
- Method of analysis: often event-time (need exposition/follow up time and censoring info for each participant)

Nadomestni kazalniki izidov

- Endpoint that is measured *in lieu* of a more definitive, meaningful (clinical) endpoint (= surrogate marker, intermediate EP)
- Used when definitive endpoint trial would be too long or costly. Surrogate endpoint trial generally smaller because:
  - Continuous measurements
  - More frequent events
  - Measure subclinical disease
- And if:
  - Accurate and reliable measurement
  - Acceptable to the participants (*invasive?)* and investigators (*cost, ease of use?)*

Nadomestni kazalniki

Disease	Definitive Endpoint	Surrogate Endpoint
Cardiovascular disease	Myocardial infarction	Cholesterol level
	CHD	Carotid IMT
	Heart Failure	BNP
	Stroke	Blood pressure
Cancer	Mortality	Tumor size reduction
Prostate Cancer	Disease progression	PSA
HIV Infection	AIDS/Death	CD4+ count
Glaucoma	Vision Loss	Intraocular pressure

Nadomestni kazalnik

- Change in surrogate strongly correlated with change in clinical outcome (but: correlation ≠ causality)
- Surrogate is in the biological pathway of the disease (but: there may be > 1pathway)
- Strong statistical association
- Short latency (↑surrogate followed by rapid onset of disease)
- Responsive to treatment (but: effect on disease often not predicted by effect on surrogate)

There is NO surrogate for safety!

Populacija

- Subset of population with disease/condition of interest
- Patients enrolled = subset of study population defined by the eligibility criteria
- Inclusion criteria: Define “at risk” population
  - Less inclusive (= more homogeneous population): potential for benefit increase
    - but need to understand mechanism of action of intervention
    - Cannot generalize to other “subgroups”
  - More inclusive (= more heterogeneous population):
    - Increase generalizability
    - But may dilute effect of intervention (increase sample size)
  - Select group more likely to benefit from intervention
    - Higher risk: increase number of events, decrease sample size
    - But: are results applicable to lower risk?

Populacija

- **Exclusion criteria:**
  - **Insure patient safety (risk/benefit in specific subgroups)**
  - **Assess competitive risk**
  - **Assess likelihood of adherence to protocol and intervention**

Eligibility criteria will be defined by goal of trial: efficacy vs. effectiveness trial?

- **Intention to treat**
- **As treated**

Homogenost in generalizacija

Homogeneity

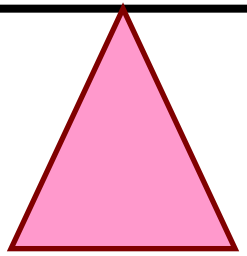
- **Divergent subgroup of patients (i.e., “atypical ” patients) can distort findings for the majority**
- **Restriction of population reduces “noise” and allows study to be done in a smaller sample size**

→ Restrict population to homogenous group

Generalizability

- **At the end of the study, it will be important to apply findings to the broad population of patients with the disease**
- **It is questionable to generalize the findings to those excluded from the study**

→ Have broad inclusion criteria “welcoming” all



From: Virgina Howard

Učinkovitost in zmogljivost

Defining the Study Population: Efficacy vs. effectiveness trial

Characteristic	Efficacy Trial	Effectiveness Trial
Goal	Test biological question	Assess "real life" effect of intervention
No participants	< 1,000	> 10,000
Cohort	Homogeneous	Heterogeneous
Data collection	Extensive	Limited
Focus of inference	Internal validity	Generalizability
Eligibility criteria	Strict	Broad

From: Steven Piantadosi. Clinical Trials. A Methodologic Perspective. John Wiley & Sons, Inc 1997

Protokol raziskave

- Abstract
- I. STUDY HYPOTHESIS
- II. INTRODUCTION AND BACKGROUND
- III. OBJECTIVES OF THE STUDY
  - A. Primary objective
  - B. Secondary objective
- IV. STUDY ENDPOINTS
  - A. Primary Endpoint
  - B. Secondary Endpoints
- V. STUDY DESIGN
- VI. PATIENT SELECTION
  - A. Inclusion criteria
  - B. Exclusion Criteria
- VII. INFORMED CONSENT PROCEDURE

Protokol

- VIII. RANDOMIZATION PROCEDURE
- IX. ADMINISTRATION OF STUDY DRUG
- X. DATA MANAGEMENT, QUALITY ASSURANCE & MONITORING PROCEDURES
  - A. Data collection and management
  - B. Monitoring reports
    - 1. Executive Committee
    - 2. Steering Committee
    - 3. Data and Safety Monitoring Board
  - C. Quality Assurance
- XI. STATISTICAL ANALYSES
  - A. Primary endpoint
  - B. Sample size and power
  - C. Subgroup and secondary analyses
  - D. Interim analyses

Protokol

- XII. STUDY ORGANIZATION
  - A. National Heart, Lung, and Blood Institute
  - B. Steering Committee
  - C. Clinical Trial Center
  - D. Data and Safety Monitoring Board
- XIII. SUBSTUDIES AND ANCILLARY STUDIES
  - A. Introduction
  - B. Ancillary studies
  - C. Databank studies
  - D. Application review process
  - E. Data storage and analysis

Protokol

- XIV. PUBLICATION POLICY
  - A. Data analysis and release of results
  - B. Review process
  - C. Primary outcome papers, abstracts and presentations
- XV. CLOSEOUT PROCEDURES
  - A. Interim
  - B. Reporting of Study Results
- XVI. REFERENCES

Appendices

-Mode Informed Consent

-Conflict of Interest Policies

Etični vidiki

Etični vidiki kliničnega preskušanja

- Special ethical concerns because treatment is determined by chance
- The arms of the clinical trial must be in clinical equipoise
- Principle of nonmaleficence, withholding proven treatment from control group
- Periodic analysis of interim data by independent Data and Safety Monitoring Board

Informirani pristanek

- Purpose of the trial
- Nature of the trial
- Procedures of the trial
- Risks and potential benefits and alternatives to participating
- Procedures to maintain confidentiality
- Assurances and contact information

Informirani pristanek

- Withdrawal
  - Participant is free to withdraw at any time
- New findings
  - Obligation to tell participant of any significant new findings that may affect his/her willingness to continue
- Potential for coercion

Informirani pristanek

- Human Subjects Research Protection
  - http://www.hhs.gov/ohrp/
  - Training: http://phrp.nihtraining.com/users/login.php
- Registry of clinical Trials and Background:
  - http://clinicaltrials.gov/
- Regulations and Ethical Guidelines: http://ohsr.od.nih.gov/guidelines/index.html
  - 45 CFR 46 Protection Of Human Subjects
  - Guidelines for Conduct of Research Involving Human Subjects at NIH (Gray Booklet) (pdf file)
  - The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research
  - Nuremberg Code Directives for Human Experimentation
  - World Medical Association Declaration Of Helsinki
- NIH bioethics Resources: http://bioethics.od.nih.gov/index.html