ASSESSMENT OF MEDICAL INTERVENTIONS

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ASSESSMENT OF MEDICAL INTERVENTIONS

INTRODUCTION

- Guesses and Proofs
- Randomized Clinical Trials. An Introduction
- How To Start
- Study Conduct
- Ethics

PART I

GUESSES AND PROOFS

GUESSES

- We don't know the mechanism of disease
- We don't know the mechanism of action of drug
- We observe in practice that the drug treats the disease

GUESSES

- We know the mechanism of disease
- We know the mechanism of action of drug
- We believe that the drug treats the disease

GUESSES

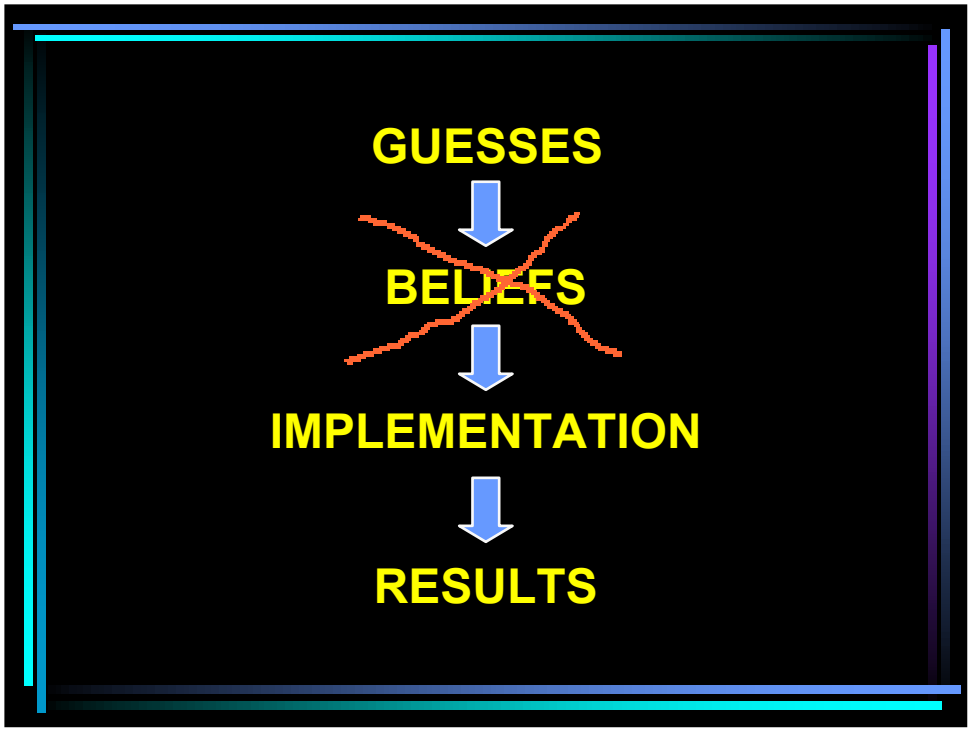
BELIEFS

IMPLEMENTATION

RESULTS

RESULTS:

- Diethylstilbestrol in pregnancy at risk to prevent threatened abortion: vaginal carcinoma in female offspring
- O_2 inhalation in premature newborns to treat hypoxia and prevent death: blindness
- Class I antiarrhythmics in AMI to prevent ventricular fibrillation and death: increase in mortality
- Etc.



GUESSES

EVIDENCE

IMPLEMENTATION

RESULTS

HOW TO COLLECT EVIDENCE?

- Before-after study
- Case-control study
- Non-randomized controlled study
- Randomized controlled study

BEFORE-AFTER STUDY

- We have a case
- We prescribe a drug
- We compare patient's condition before and after an intervention

CASE-CONTROL STUDY

- We have a group of cases
- We prescribe a drug in this group
- We have a matching group of controls (historical, or in the past)
- We compare patient's condition in the treated group with condition in the control group

NON-RANDOMIZED CONTROLLED STUDY

- We have a group of cases
- We voluntary divide it on treatment group and control group
- We compare patient's condition in the treatment group with condition in the control group

RANDOMIZED CONTROLLED STUDY

- We have a group of cases
- We randomly divide it on treatment group and control group
- We compare patient's condition in the treatment group with condition in the control group

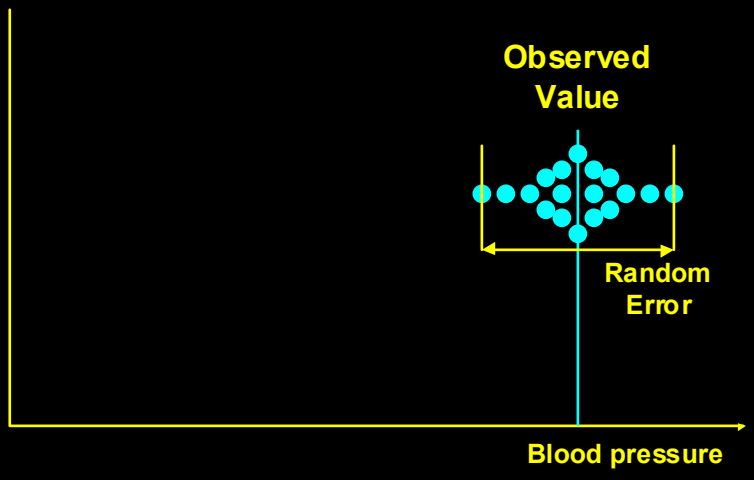
CLINICAL STUDIES

- Before-after study
- Case-control study
- Non-randomized controlled study

} Let us guess

- Randomized controlled study — Provide an evidence

BIAS



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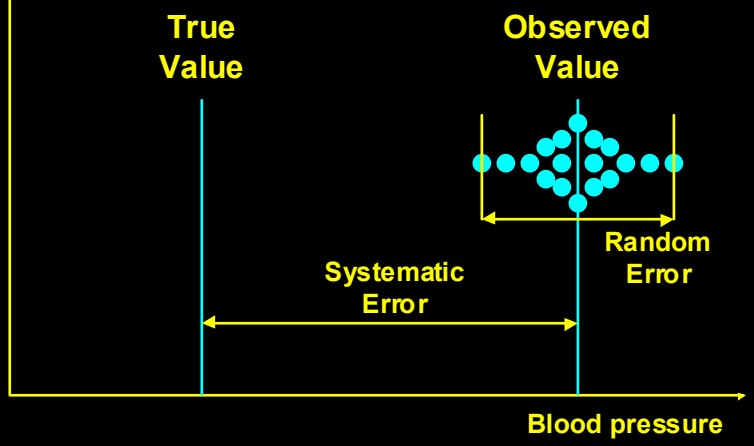


BIAS

- Selection bias
- Measurement bias
- Confounding bias

SELECTION BIAS

- Selection “at will”
- Voluntary allocation of patients to experimental and control treatment
- Selection based on condition
- Selection based on consent
- Selection based on compliance

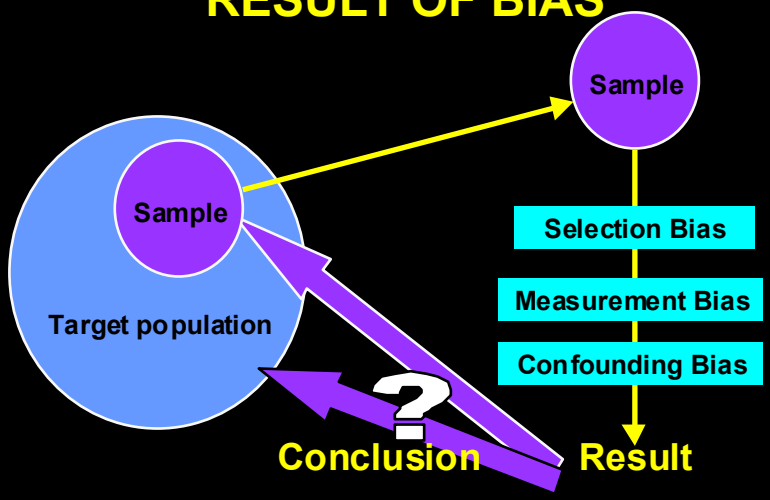
MEASUREMENT BIAS

- Different measurements in different groups
- Different precision of measurement in different groups

CONFOUNDING BIAS

- Two (or more) factors work together, but we control only one
- Some factors are unknown, but may affect the result

RESULT OF BIAS



EVIDENCE

Randomized controlled study

Non-randomized controlled study

Case-control study

Before-after study

GUESS

RANDOMIZED CONTROLLED STUDY

=

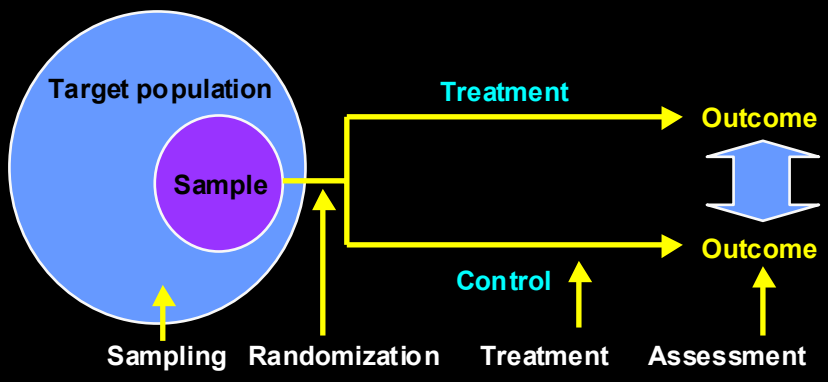
CLINICAL TRIAL

PART II

RANDOMIZED CONTROLLED TRIALS

An Introduction

CLINICAL TRIAL



SAMPLING

To form a subset of subjects which reflects the target population

- Selection (inclusion) criteria
- Exclusion criteria

RANDOMIZATION

To exclude influence of human will and make experimental and control groups identical

- Simple randomization
- Block randomization
- Systematic randomization

TREATMENT
(choose of control)

- No intervention
- Observation
- Conventional treatment
- Active control
- Placebo

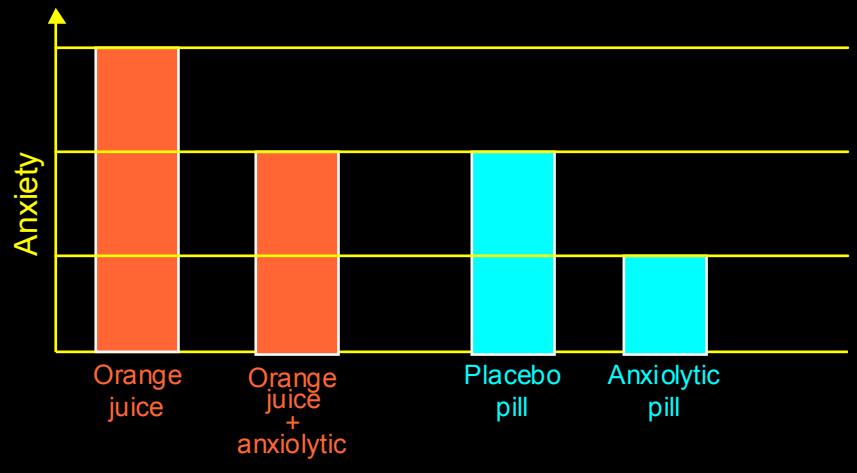
NON-SPECIFIC EFFECTS OF TREATMENT

- Natural course of the disease
- Hawthorne effect
- Regression to the mean
- Placebo effect

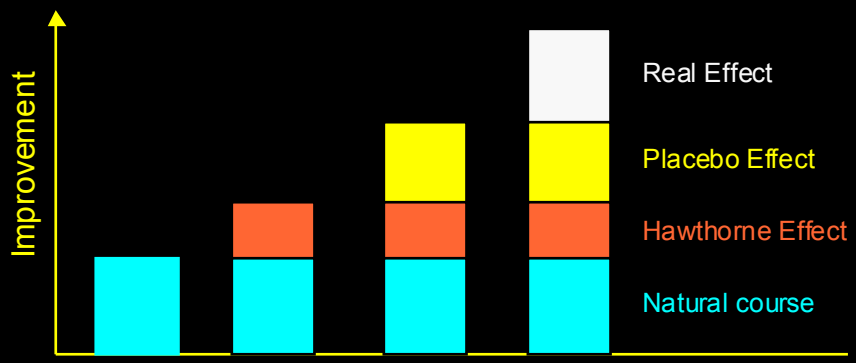
PLACEBO EFFECT

- Pt thinks there is No Treatment, and there is No Treatment
- Pt thinks there is No Treatment, but there is a Treatment
- Pt thinks there is a Treatment, but there is actually No Treatment
- Pt thinks there is a Treatment, and there is actually a Treatment

PLACEBO EFFECT



EFFECT OF TREATMENT



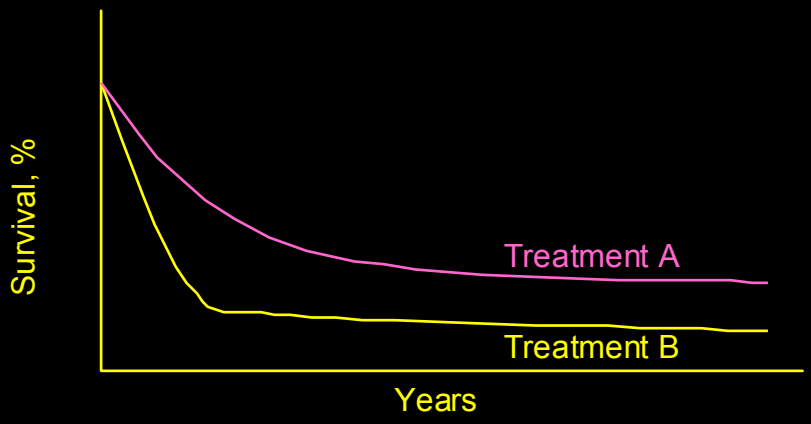
BLINDING

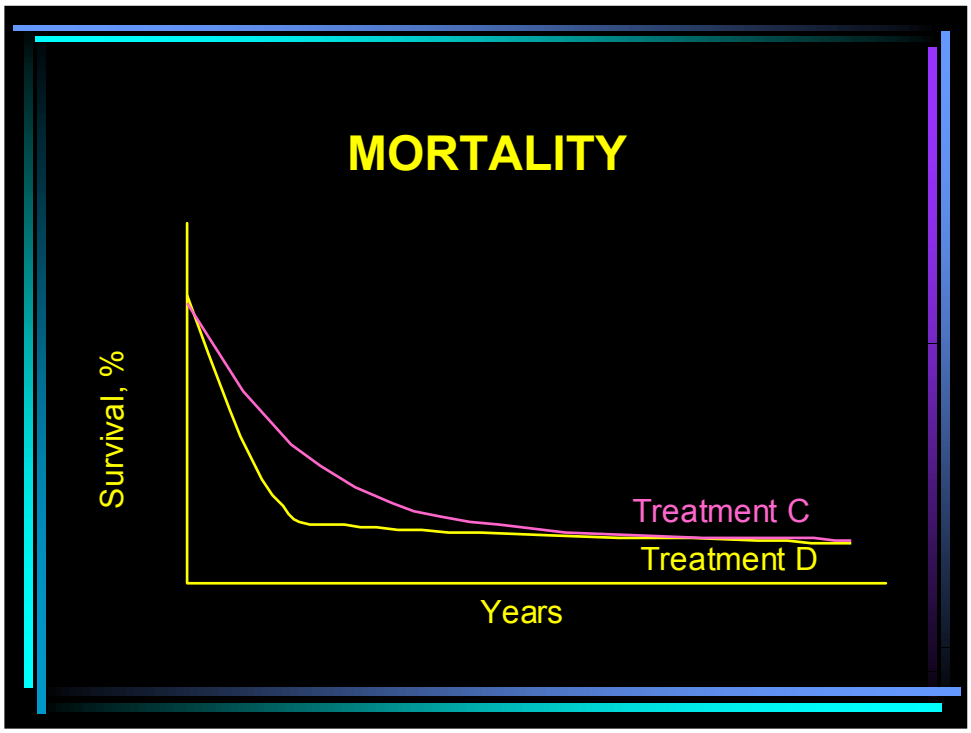
- To control non-specific effects of treatment
- Single: Patient does not know
- Double: Neither Patient, nor Doctor knows
- Triple: Patient, Doctor and Statistician do not know

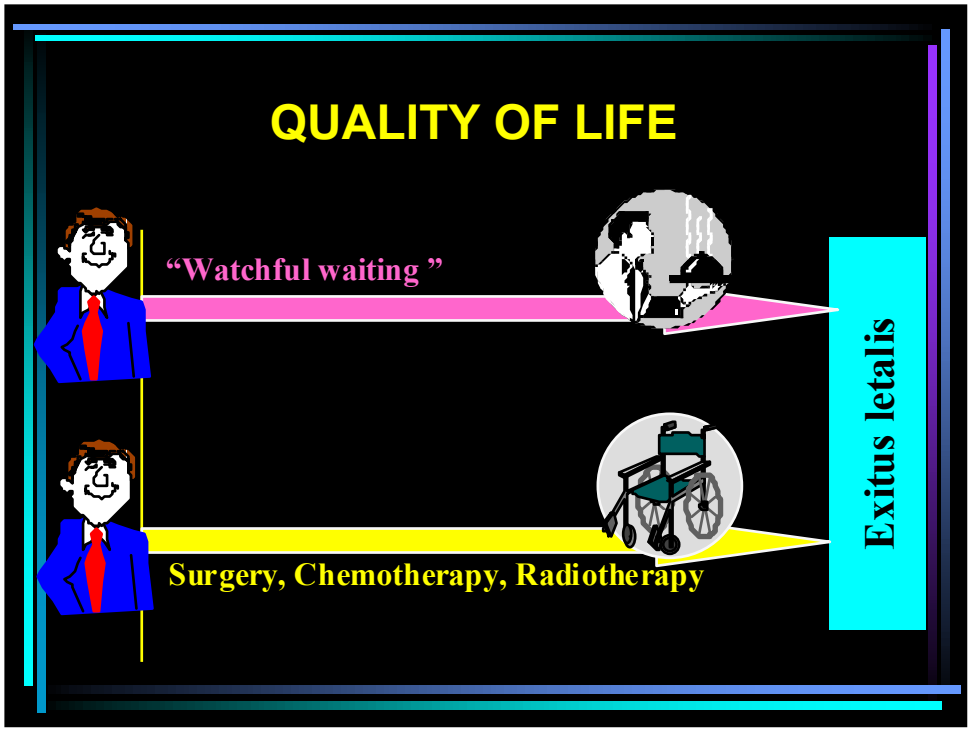
ASSESSMENT OF OUTCOMES

- Surrogate outcomes
  - Biological parameters
- True outcomes
  - Mortality
  - Quality of Life

MORTALITY




MORTALITY
Survival, %
Treatment C
Treatment D
Years


QUALITY OF LIFE
"Watchful waiting "
Surgery, Chemotherapy, Radiotherapy
Exitus letalis

QUALITY OF LIFE

- Questionnaires
- Visual-analog scales
- Time trade-off
- Standard gambling

QUALITY OF LIFE

- Q-TWIST: QOL-Time Spent Without Symptoms and Toxicity

  QAS: Quality-Assessed Survival

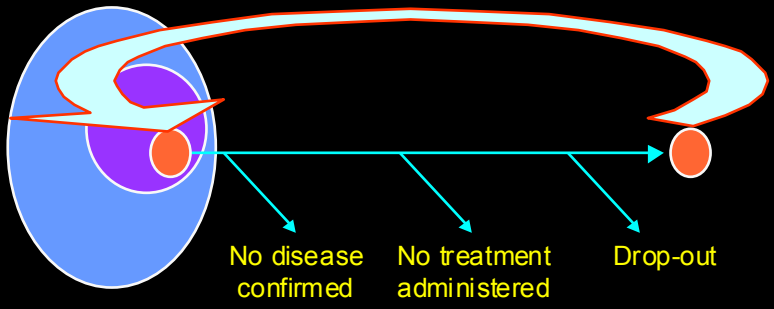
  QTIME: Quality Survival Time

  QALY: Quality-Adjusted Life Years

HOW TO ASSESS OUTCOMES

- **Intention-to-treat (ITT) analysis**
  if we assess the treatment strategy
- **Per-treatment analysis**
  if we assess the effect of drug

PER-TREATMENT ANALYSIS



HOW TO PRESENT OUTCOMES

- Relative Risk Reduction (RRR) is the percent reduction in events in the treated group event rate (EER) compared to the control group event rate (CER):

$$RRR = (CER - EER) / CER * 100$$

HOW TO PRESENT OUTCOMES

- Absolute Risk Reduction (ARR) is the difference in the event rate between control group (CER) and treated group (EER):

$$ARR = CER - EER$$

HOW TO PRESENT OUTCOMES

- The Number Needed to Treat (NNT) is the number of patients you need to treat to prevent one additional bad outcome (death, stroke, etc.):

NNT = 1/ARR

OR

NNT = 1/(CER – EER)

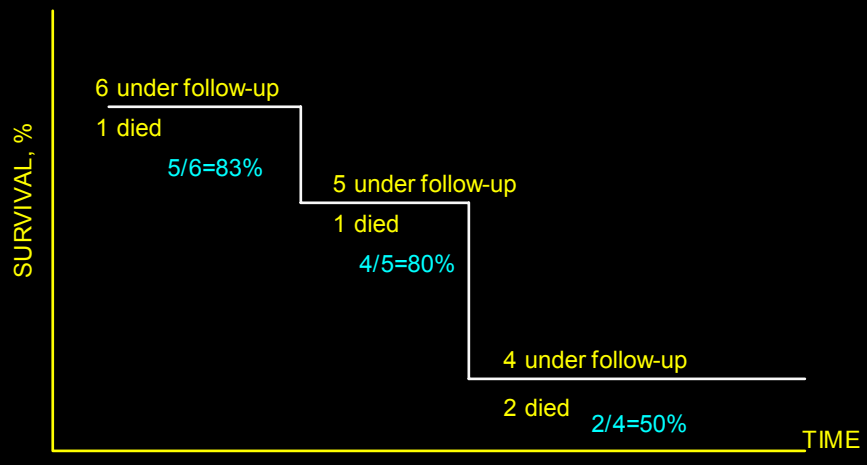
HOW TO PRESENT OUTCOMES

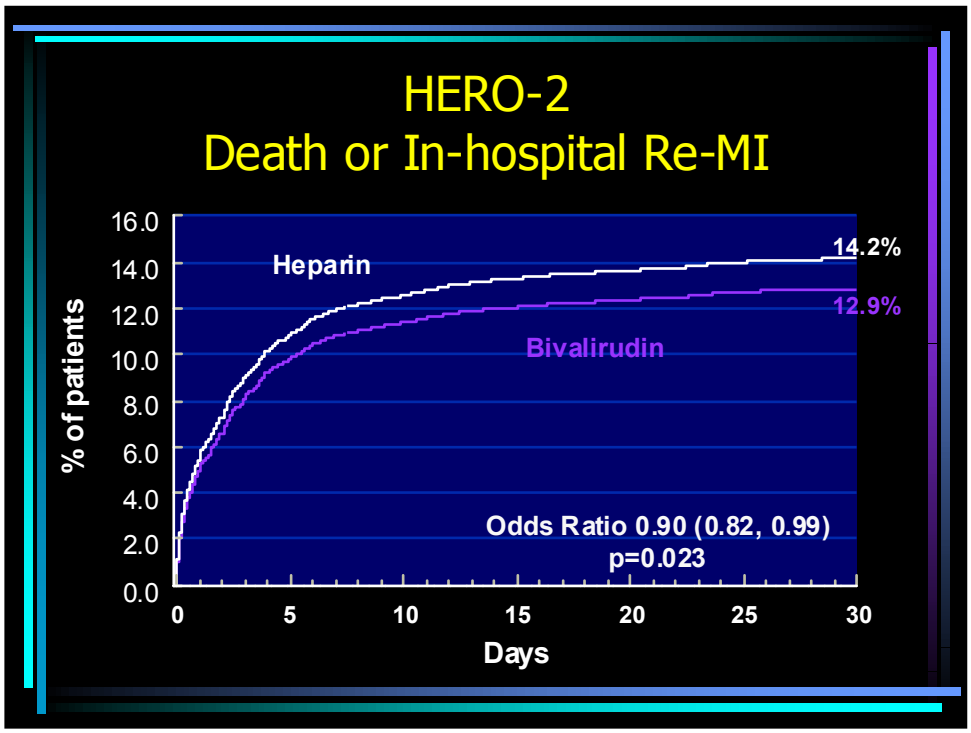
CER	EER	RRR	ARR	NNT
0.096	0.028	71%	0.068	14,7 (15)
0.96	0.28	71%	0.68	1.47 (2)
0.0096	0.0028	71%	0.0068	147

HERO-2 STUDY OUTCOMES

Outcome	CER	EER	RRR	ARR	NNT
Death	10.9%	10.8%	0.99%	0.001	1000
Death or re-MI	14.2%	12.9%	9%	0.013	76.9 (77)

SURVIVAL CURVES (KAPLAN-MEYER)





WHAT DO WE ASSESS IN CLINICAL TRIALS

- **Effectiveness**

  Outcomes in a population receiving treatment in real conditions (Phase IV)

- **Efficacy**

  Outcomes in a highly selected study sample (Phase III)

- **Safety**

LIMITATIONS OF CLINICAL TRIALS

- Selection bias
  - ➢ Generalizability
- Artificial conditions of follow-up
  - ➢ Efficacy
- Drop-outs/Contamination
  - ➢ ITT analysis

GENERALIZABILITY

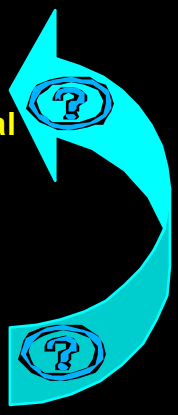
100% - TARGET POPULATION WITH CONDITION in a selected hospital

30% - Meet Inclusion/exclusion criteria

20% - Agreed to participate

15% - Complied with the protocol

12% - Completed the follow-up period



PART III

RANDOMIZED CONTROLLED TRIALS

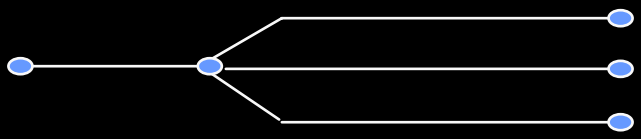
How To Start

PHASES OF CLINICAL TRIALS

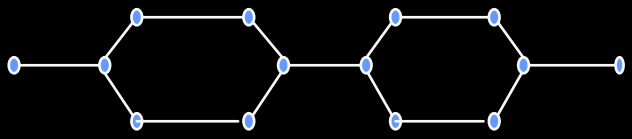
- Phase I: “First in men”, safety, pharmacokinetics (10-20 subjects)
- Phase II: Dose-finding, efficacy, safety (100-200 subjects)
- Phase III: Large-scale efficacy/safety (800-20.000 subjects)
- Phase IV: Postmarketing evaluation

DESIGN OF CLINICAL TRIALS

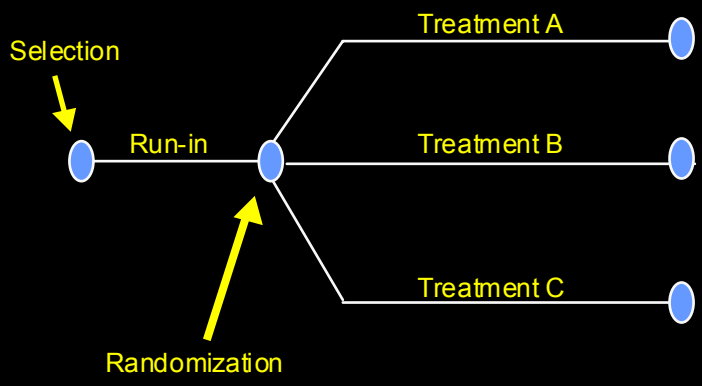
- Parallel design



- Cross-over design



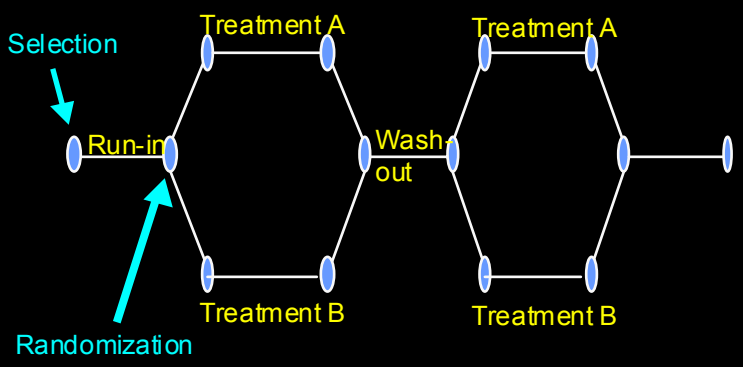
PARALLEL DESIGN



RUN-IN PERIOD

- Control of stability of the target condition
- Control of compliance
- Wash-out

CROSS-OVER DESIGN



PROTOCOL

- Define objectives end end-points
- Establish selection criteria
- Choose treatment design
- Calculate sample size
- Describe statistical analysis

OBJECTIVES

- Superiority studies: One treatment is better than another
- Non-inferiority studies: One treatment is not worse than another

END-POINTS

- True end-points
- Surrogate end-points
- Efficacy end-points
- Safety end-points
- Primary end-points
- Secondary end-points

SELECTION CRITERIA

- Inclusion criteria
- Exclusion criteria

SAMPLE SIZE

- Nature of data (discrete, continuous)
- Alfa-risk (Type I Error, P_α)
- Beta-risk (Type II Error, P_β) and statistical power ($1 - P_\beta$)
- Effect size
- Objective (superiority, non-inferiority)
- Frequency of outcome in control group

STATISTICS

- Choose statistical model/test
- Define Type I and II Errors, and Statistical Power
- Identify effect size
- Describe all comparisons (groups, subgroups)

RANDOMIZATION

- Sealed envelopes
- Fax
- Interactive Voice Response System (IVRS)
- Internet

DATA COLLECTION

Paper CRF or e-CRF (direct data capture)

- Patient's ID
- Clinical/biological data
- Use of study drug
- Compliance
- Adverse events

PART IV

RANDOMIZED CONTROLLED TRIALS

Study Conduct

PARTIES INVOLVED

- Project management
- Monitoring
- Data management
- Statistics
- Reporting
- Other

PROJECT MANAGEMENT

- Budget (who?)
- Quality (what?)
- Schedule (when?)

PROJECT MANAGEMENT

- Goals
- Planning
- Organizing and staffing
- Directing and leading
- Controlling
- Reporting

MONITORING

- Selection of investigators and sites
- Site visits and meetings
- Adverse events reporting
- Data collection (CRF)
- Data verification (source against CRF)
- Query resolution

DATA MANAGEMENT

- Database design
- Double data entry with third person verification
- Generation of queries
- Data cleaning
- Data security
- Data transfer

STATISTICS

- Statistical model and software
- Interim analysis (DSMB)
- Primary end-point analysis
- Secondary end-point analysis
- Subgroup analysis

REPORTING

- Interim efficacy/safety reporting (DSMB)
- Presentation to the public
- Presentation to the authorities
- Marketing approval application

OTHER IMPORTANT ISSUES

- Regulatory
- Study drug
- Logistics
- IT
- Budget

REGULATORY ISSUES

- IND (US)
- CFR21(US)
- ICH GCP (US+ EU+Japan)
- National regulations
- Inspections

STUDY DRUG

- Manufacturing
- Distribution
- Keeping and controlling
- Re-collection
- Destruction

LOGISTICS

- Circulation of papers
- Circulation of the study drug
- Customs
- Traveling
- Meetings

INFORMATION TECHNOLOGY

- Local networks
- Global networks
- Secure info exchange
- Teleconferencing
- Backup

BUDGET

- Management costs
- Production costs
- Monitoring costs
- Data management cost
- Statistics costs
- Communication costs
- Regulatory costs
- Investigator's grants
- Other costs

PART V

RANDOMIZED CONTROLLED TRIALS

Ethics

ETHICS

- Nuremberg Code - 1949
- International Code of Medical Ethics of WMA - 1949
- Declaration of Helsinki - 1964
- Belmont Report - 1979
- ICH GCP - 1996

THE NUREMBERG CODE

from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.

Nuremberg, October 1946–April 1949

PERMISSIBLE MEDICAL EXPERIMENTS

INTERNATIONAL CODE OF MEDICAL ETHICS OF THE WORLD MEDICAL ASSOCIATION

Adopted by the Third General Assembly of the World Medical Association at London in October 1949.

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

- Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the
- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

THE BELMONT REPORT

Ethical Principles and Guidelines for the Protection of Human Subjects of Research The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

ETHICS

- IRB and Independent Ethics Committees
- Written Informed Consent
- Primacy of patient's rights, integrity and well-being

ICH GCP

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL EQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

GOOD CLINICAL PRACTICE

ICH GCP

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

ICH GCP

- GLOSSARY
- THE PRINCIPLES OF ICH GCP
- INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE (IRB/IEC)
- INVESTIGATOR
- SPONSOR
- CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)
- INVESTIGATOR'S BROCHURE
- ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

ASSESSMENT OF MEDICAL INTERVENTIONS

SUMMARY

- Hypothesis and evidence
- An introduction to clinical trials
- How to start a trial
- How to conduct a study
- Ethical considerations

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