# INTRODUCTION TO
# Study design in clinical trials

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Research for a Life without Cancer

# Overview

- Causality: Three requirements

- The three pillars of interpretable comparisons
  Equality in structure
  Equality in observation
  Equality in analysis

- False Discovery Rates

# Causality

Does smoking cause lung cancer?

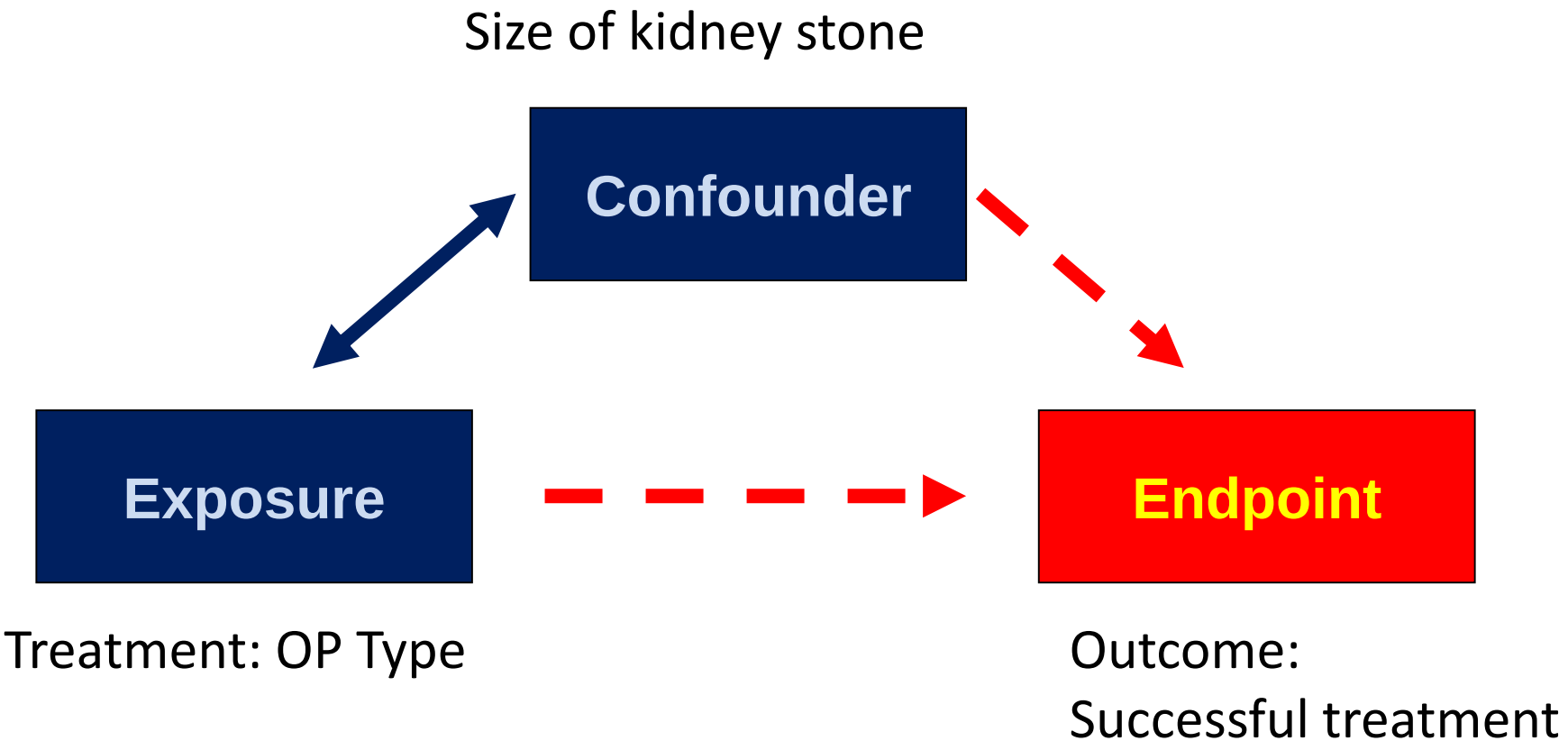
Do smokers get lung cancer more often?

Interpretation?

# Requirements for Causality

| | |
|---|---|
| Chronology: | exposure first, disease later |
| Change: | a change in exposure will change frequency of disease |
| No confounding: | the association between exposure and disease is not just a result of a confounding variable |

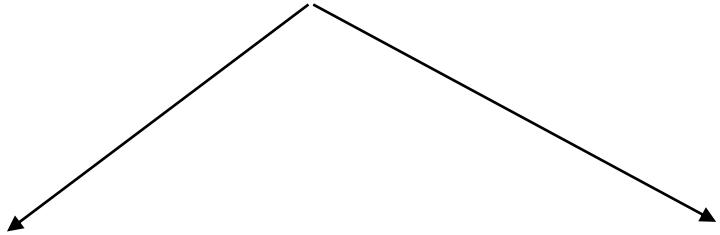
# Causality


Size of kidney stone
Confounder
Exposure
Endpoint
Treatment: OP Type
Outcome:
Successful treatment

# Confounding

Successful

| Kidney stone removal | yes | no | Σ |
|---|---|---|---|
| percutaneous | 289 (83%) | 61 (17%) | 350 |
| open | 273 (78%) | 77 (22%) | 350 |
| Σ | 562 (80%) | 138 (20%) | 700 |



| Stone < 2 cm | yes | no | Σ |
|---|---|---|---|
| percutaneous | 234 (87%) | 36 (13%) | 270 |
| open | 81 (93%) | 6 (7%) | 87 |
| Σ | 315 (88%) | 42 (12%) | 357 |

| Stone ≥ 2 cm | yes | no | |
|---|---|---|---|
| percutaneous | 55 (69%) | 25 (31%) | 80 |
| open | 192 (73%) | 71 (27%) | 263 |
| Σ | 247 (72%) | 96 (28%) | 343 |

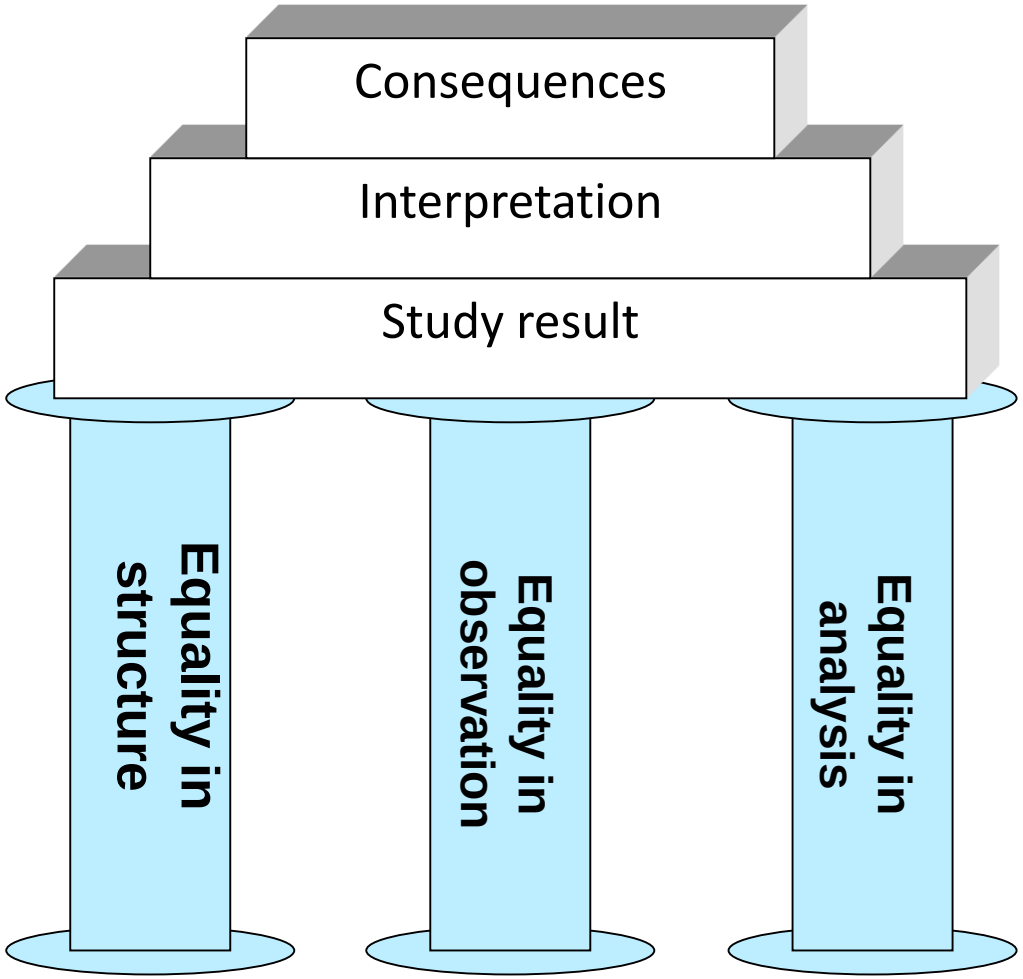
# Causality

**"The effect of any treatment for a given patient is the difference between what happened to the patient as a result of giving him the treatment and what would have happened had treatment been denied."**

„would have happened“ is not observable, instead we can compare groups of different patients

Evaluation only through time-parallel **comparison**

# 3 Pillars of Interpretable Comparisons



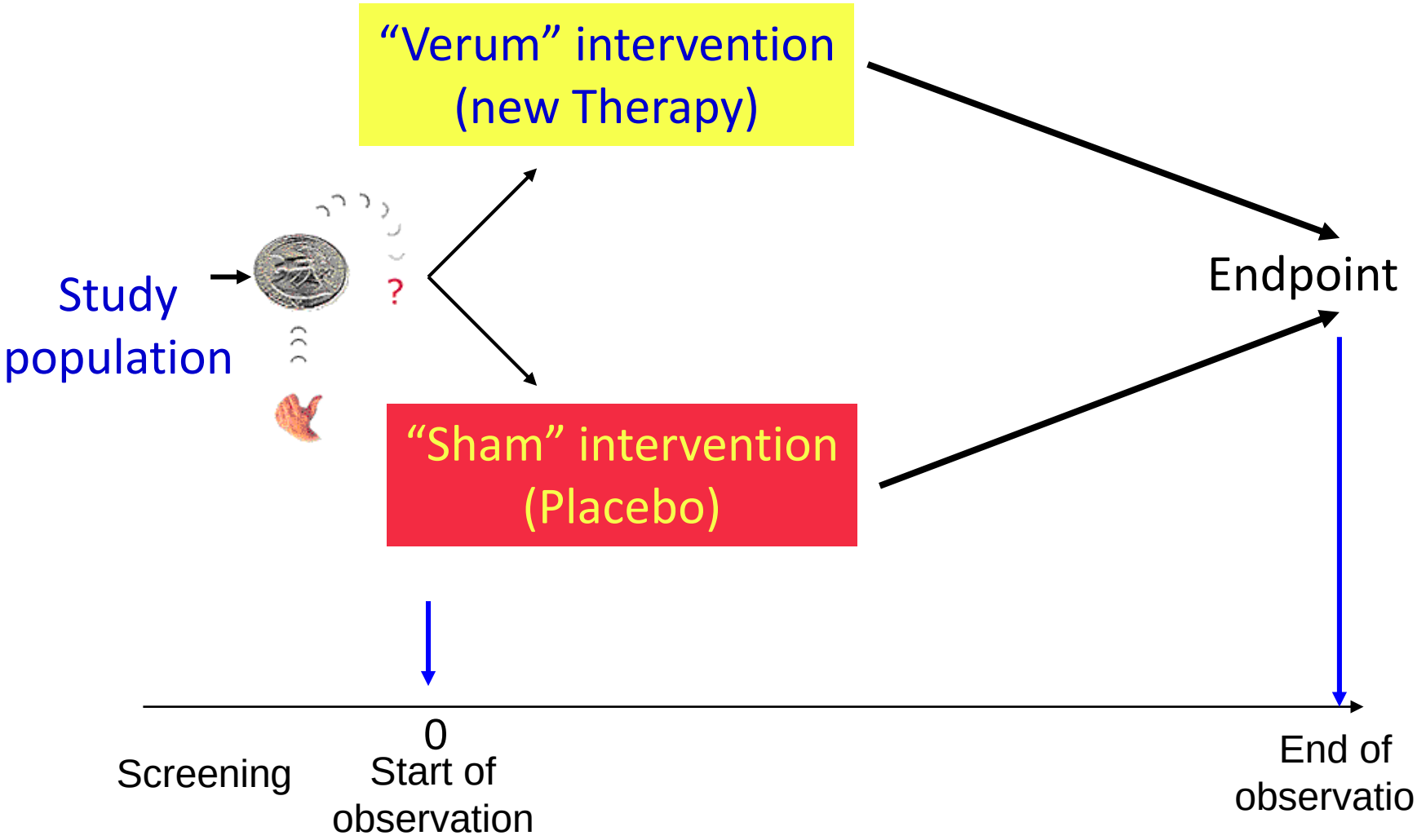

(randomised) (blinded) (intention to treat)

# 3 Pillars of Interpretable Comparisons

Equality in structure

☞ **Randomisation**

# Randomised trial



# Randomisation Plan

| Pat.-Nr. | Unbalanced | Balanced (1 Block à 16) | Balanced (2 Blocks à 8) | |
|---|---|---|---|---|
| 1 | B | A | A | Block 1 |
| 2 | B | B | A | |
| 3 | B | B | B | |
| 4 | A | A | A | |
| 5 | A | A | A | |
| 6 | B | B | B | |
| 7 | A | B | B | |
| 8 | B | B | B | |
| 9 | B | A | B | Block 2 |
| 10 | B | A | A | |
| 11 | A | A | A | |
| 12 | B | B | A | |
| 13 | A | B | B | |
| 14 | A | A | B | |
| 15 | B | A | A | |
| 16 | B | B | B | |

# 3 Pillars of Interpretable Comparisons

Equality in structure

☞ **Randomisation**

- stratified randomisation (for small sample sizes und major prognostic factors)
- cluster randomisation (z.B. doctors offices, hospitals, regions)
  **Important:** Has to be included in the analysis!
- external randomisation, especially in unblinded trials
  "Concealment" ( of the randomisation result)

  → e.g. by telephone randomisation

# Pseudo-randomised Trials

Alternating allocation

e.g. by last name, year of birth, day of inclusion, etc.

⇒**Selection might be different for the groups**

**Not random!**

⇒**Concealment might be violated**

**Not random!**

# Interpretation of Inclusion Criteria

Oxytocin for birth facilitation vs. amniotomy

„randomised study“
(even / uneven day of birth of mother)

| Bishop score | Even (Oxytocin) | Uneven (Amniotomy) |
|---|---|---|
| ≤ 3 | 28 | 7 |
| 4 or 5 | 56 | 58 |
| ≥ 6 | 29 | 45 |
| | 110 | 113 |

Bakos et al. (1987): Acta Obstet Gynecol Scand, 534

# Concealment

Randomization is important

Unpredictable randomization is more important!

(„concealment“)

# Empirical Evidence of Bias*

Randomisation plan:

Adequate Concealment

(Therapy-) Effect=1.00

Description unclear

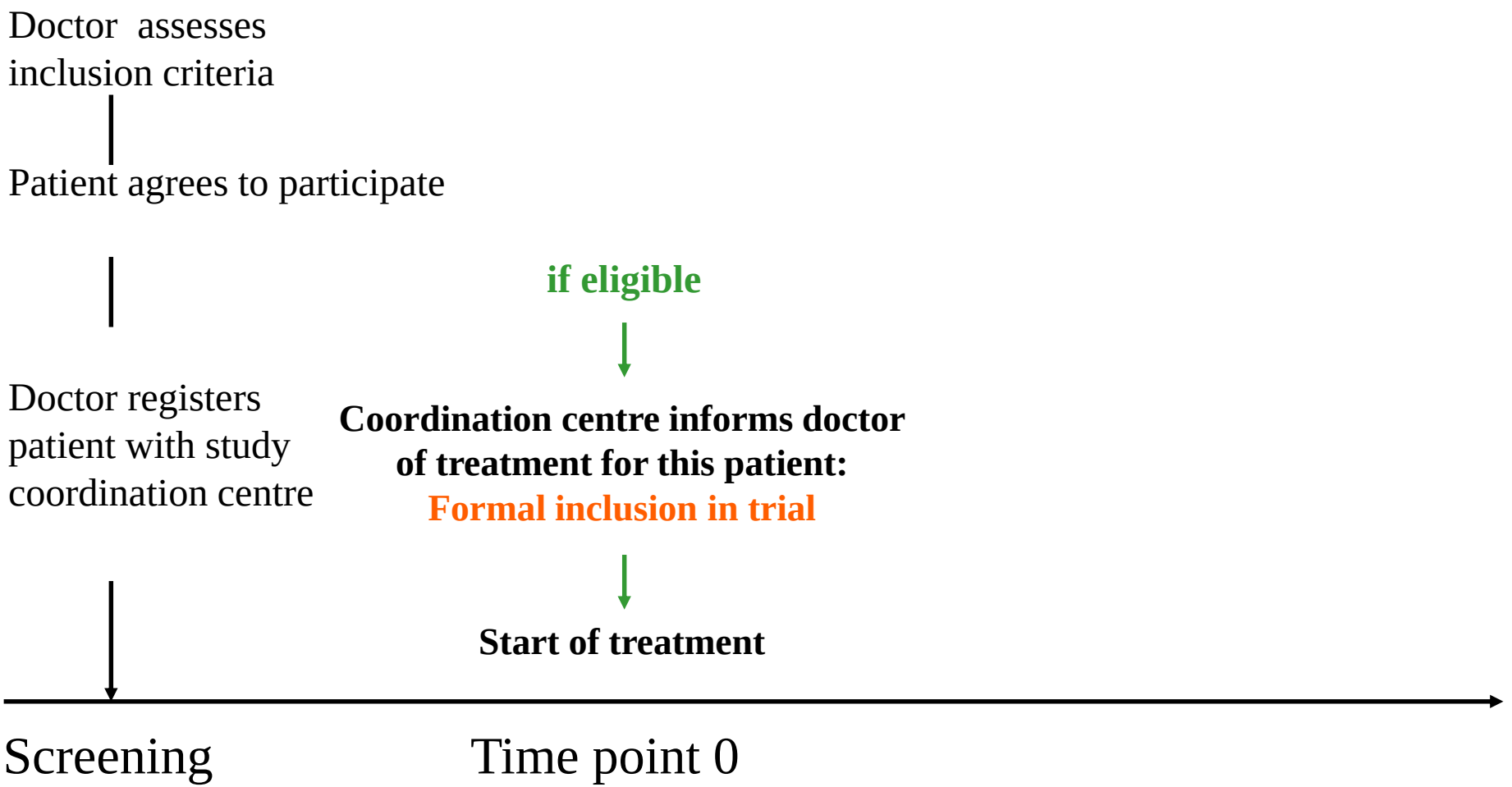
Effect=1.33

Inadequate Concealment

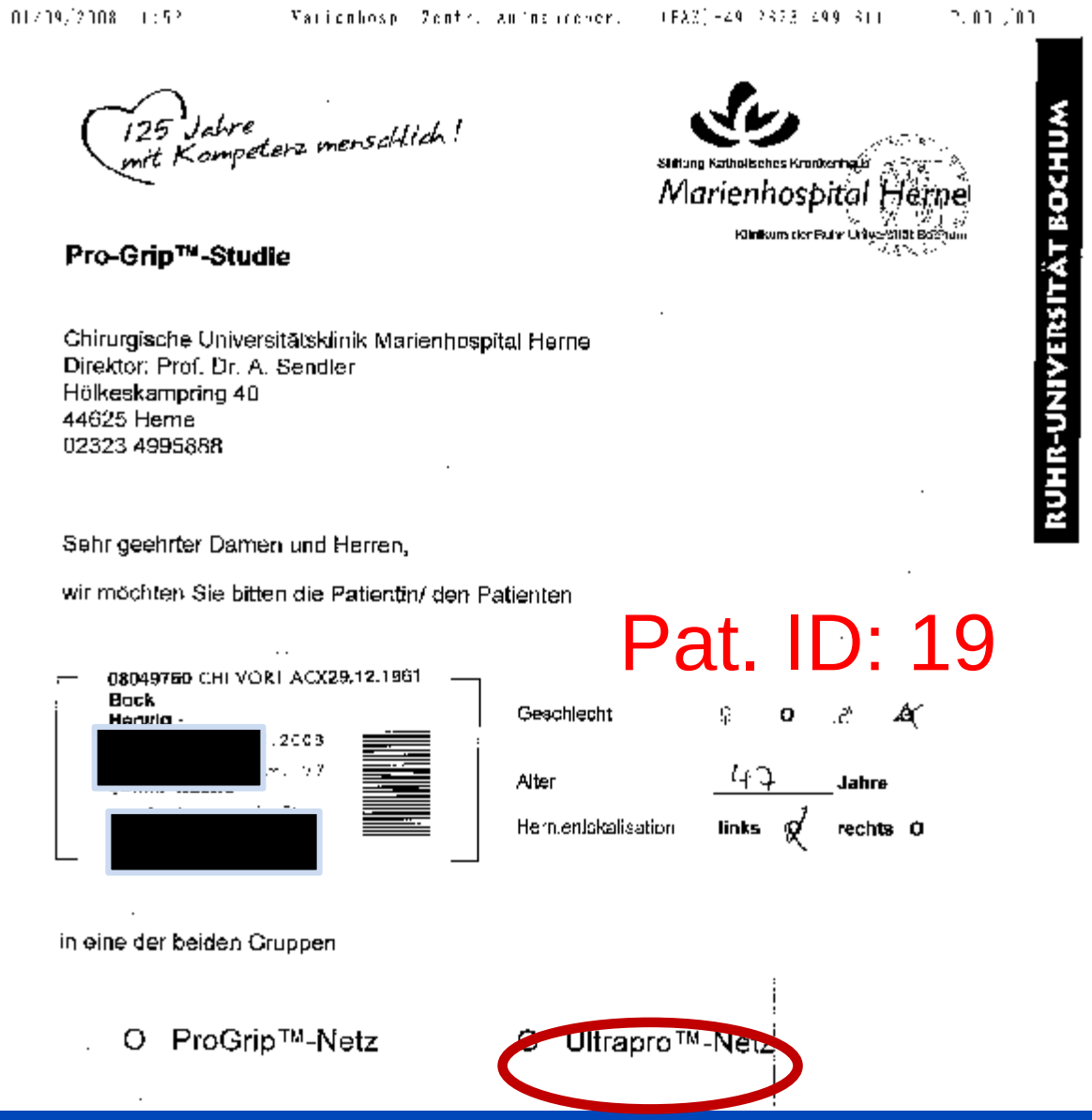
Effect=1.41

*Schulz KF et al; JAMA 1995; 273: 408-12

# Achieving Concealment



# Achieving Concealment



125 Jahre mit Kompetenz menschlich!

Stiftung Katholisches Krankenhaus
Marienhospital Herne
Klinikum der Ruhr-Universität Bochum

RUHR-UNIVERSITÄT BOCHUM

**Pro-Grip™-Studie**

Chirurgische Universitätsklinik Marienhospital Herne
Direktor: Prof. Dr. A. Sendler
Hölkeskampring 40
44625 Herne
02323 4995888

Sehr geehrter Damen und Herren,

wir möchten Sie bitten die Patientin/ den Patienten

Pat. ID: 19

08049760 CHI VORI ACX29.12.1961
Bock
[redacted]

Geschlecht ♀ O ♂ X

Alter 47 Jahre

Hernienlokalisation links X rechts O

in eine der beiden Gruppen

O ProGrip™-Netz O Ultrapro™-Netz

# Three Pillars of Interpretable Comparisons

Equality in structure

- ☞ **Randomisation**
- ☞ in unblinded trials: by telephone/fax (Concealment)

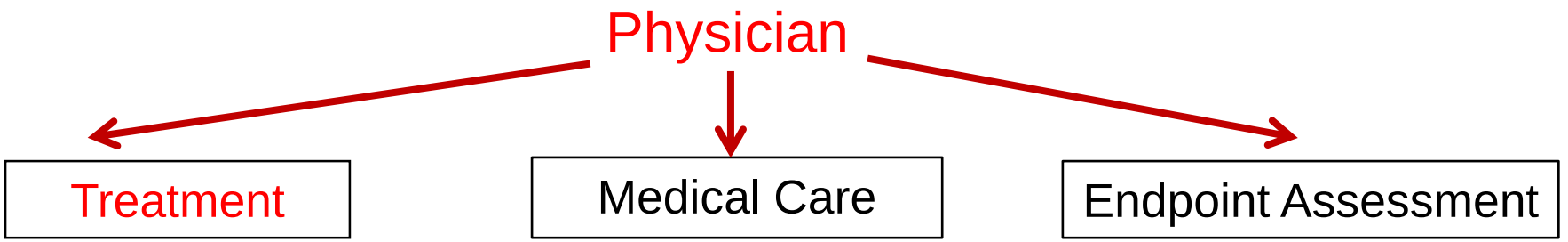
Equality in observation

- ☞ **Double blinded**
- ☞ blinded assessment of study endpoint especially important

# Blinding

**As comprehensive as possible**

| | |
|---|---|
| Double-blind | Physician and patient blinded<br>**possible mainly in drug studies** |
| Single-blind | Patient blinded, treating physician unblinded, physicians responsible for medical care and endpoint assessment blinded<br>**possible in most cases** |
| Single-blind | Patient unblinded, treating physician unblinded, physicians responsible for medical care and endpoint assessment blinded<br>**(almost) always possible** |
| Open | all participants unblinded |



# Empirical Evidence of Bias*

Blinding:

Double blind

(Therapy-) Effect=1.00

Not double blind

Effect=1.17

*Schulz KF et al; JAMA 1995; 273: 408-12

# Three Pillars of Interpretable Comparisons

Equality in structure

- **Randomisation**
- in unblinded trials: by telephone/fax (Concealment)

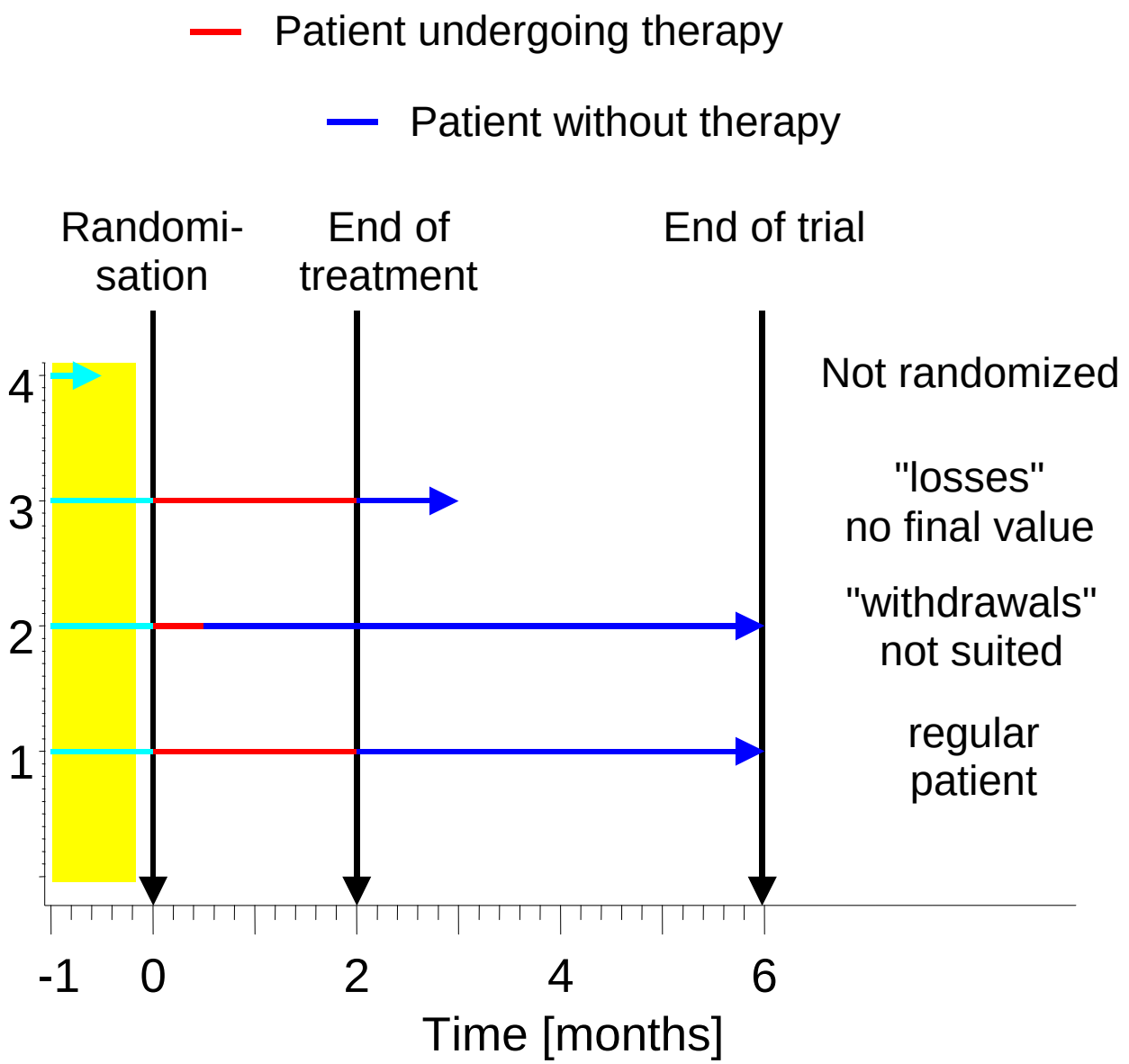
Equality in observation

- **Double blinded**
- blinded assessment of study endpoint especially important
- Double dummy

Equality in analysis

- **Intention-to-treat-principle**: Every patient included in the trial (i.e. randomized) will be included in the analysis
- if necessary, missing values have to be replaced conservatively

# Equality in Analysis



# Exclusions from Analysis

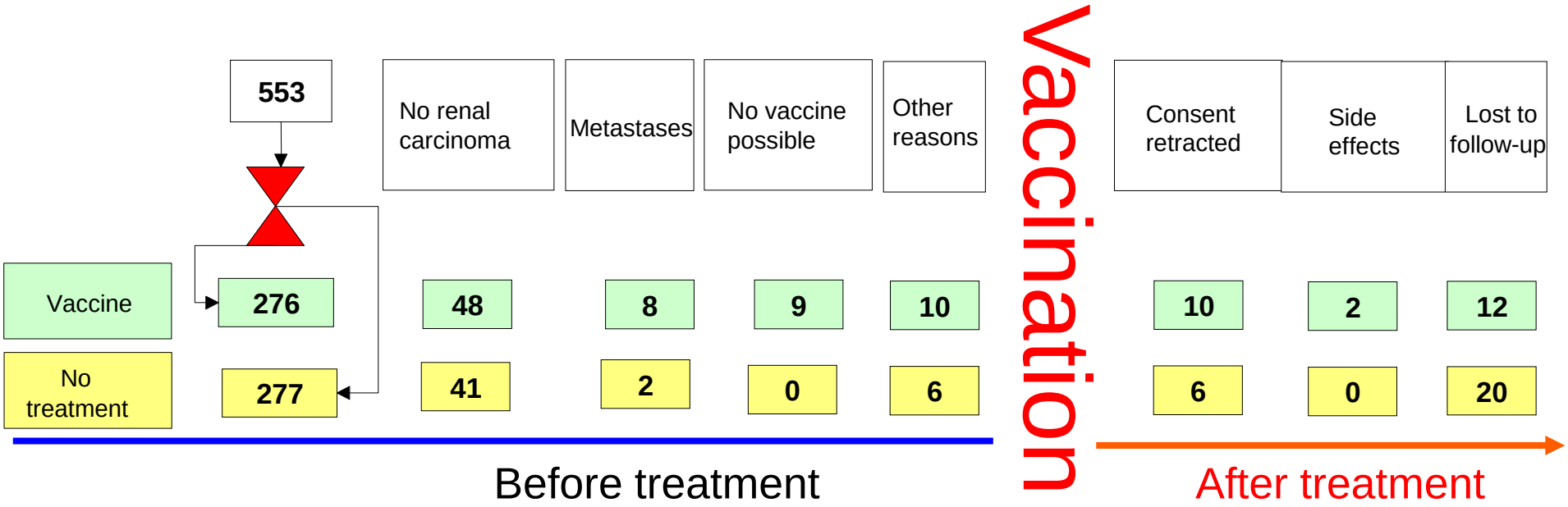
6-weeks-mortality of patients with infarction (β-Blockers)

| | Propranolol | Atenolol | Placebo |
|---|---|---|---|
| Regular treatment | 3.4% | 2.6% | 11.2% |
| Treatment stopped (side effects etc.) | 15.9% | 17.6% | 12.5% |
| All | 7.6% | 8.7% | 11.6% |

Wilcox RG et al.; BMJ: 280: 885-8 (1980)

„pragmatic“ approach → close to practical situation

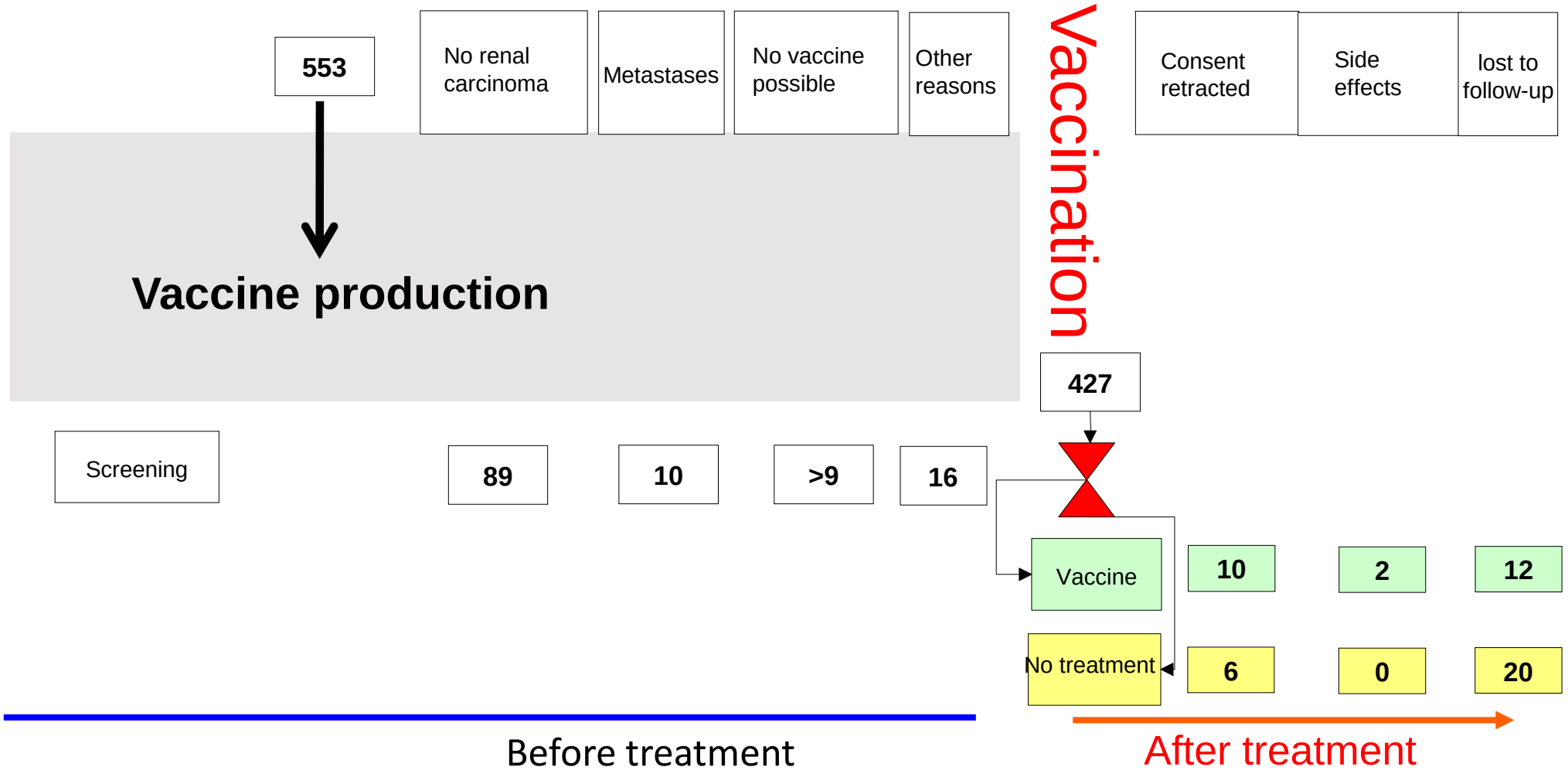
# Exclusion of Patients*




| Group | randomised | excluded | completed |
|---|---|---|---|
| Vaccine | 276 | 99 (35,9%) | 177 |
| Control | 277 | 75 (27,1%) | 202 |
| Total | 553 | 174 (31,5%) | 349 |

*Jocham D et al. (2004): Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. Lancet, 363 (9409): 594-599.

# Late randomisation avoids patient losses



# Three Pillars of Interpretable Comparisons

Equality in structure

☞ **Randomisation**

- external randomisation in unblinded trials
- best via telephone/fax

Equality in observation

☞ **Double-blinded**

- double-dummy-technique
- blinded (external) assessment of endpoints
- endpoint not dependent on observer

„Equality in analysis"

☞ **Intention-to-treat**

- all randomized patients in the trial are analyzed in the group they were randomized to
- missing values are replaced to disfavor the new treatment (conservative replacement)

# Levels of Evidence

Ia At least one systematic review based on high quality randomized controlled trials (**R**andomised **C**ontrolled **T**rials, RCT's)

Ib At least one high quality randomised controlled trial (RCT) of sufficient sample size

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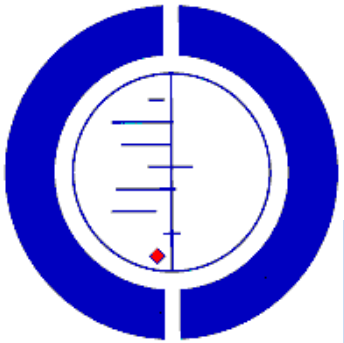
IIa High quality controlled clinical trials without randomisation (e.g. cohort trials)

IIb Other quasi-experimental trials

III Uncontrolled / non-experimental trials

IV Expert opinions

# Cochrane Collaboration



THE COCHRANE LIBRARY

www.cochrane.de

- Network of working groups (Cochrane Review Groups)

→ Creates and updates systematic reviews according to a detailed standard

- Cochrane Library

→ - **C**ochrane Controlled **C**linical **T**rial **R**egister (CCTR, about 680 000 Entries)

- **C**ochrane **D**atabase of **S**ystematic **R**eviews (CDSR , about 5000 complete, 2.000 protocols)

# False Discovery Rates (FDR)

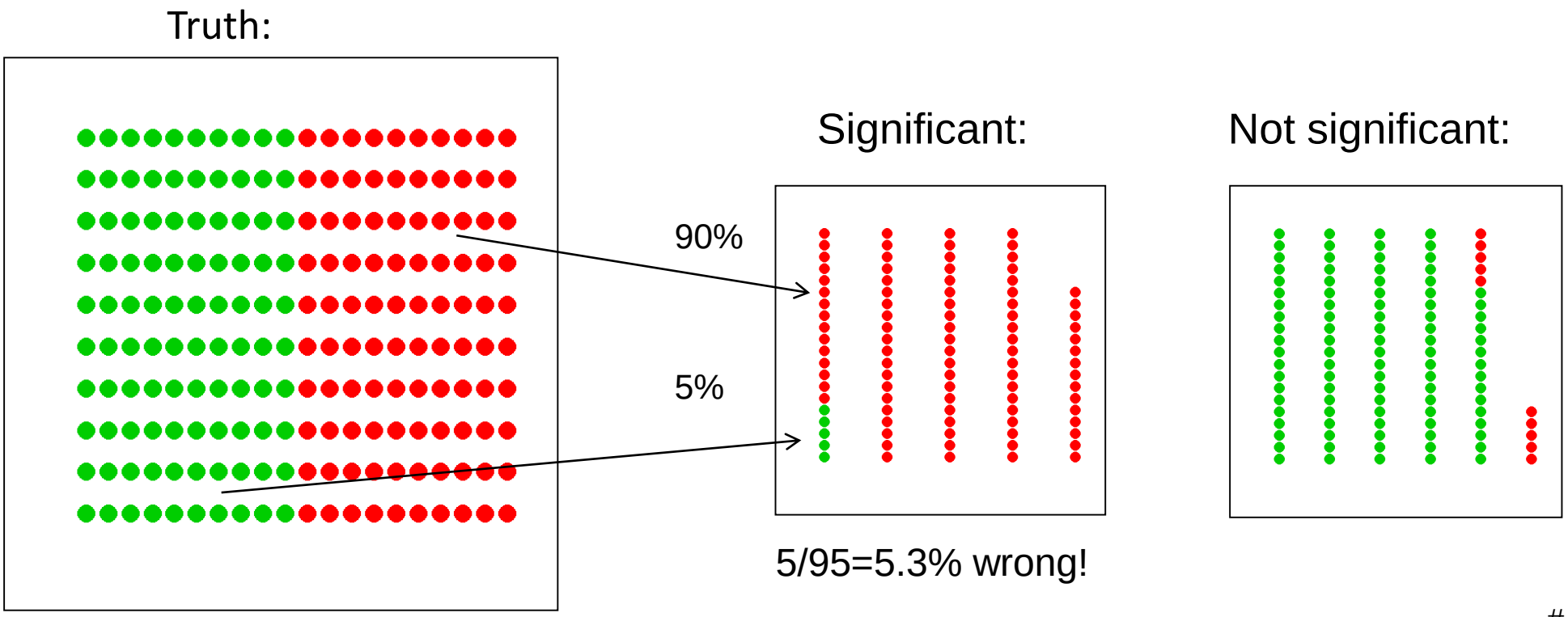
New discoveries are published daily. How many of these are actually true?

For a single trial the false positive rate is 5%. Does this answer the question?

# False Discovery Rates (FDR)

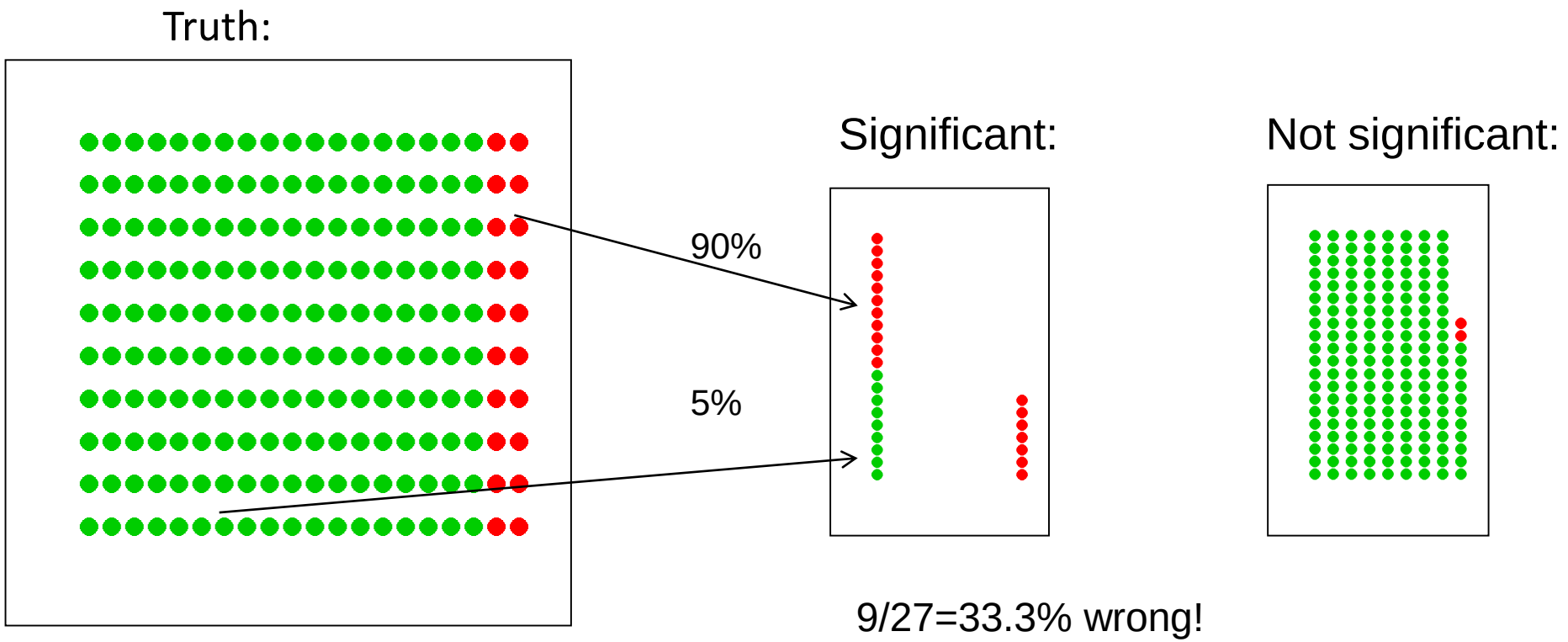
## Example:

Assume 200 trials are conducted, each with power=90% and alpha=5%. In 100 of these the null hypothesis is actually true:



# False Discovery Rates (FDR)

Now assume the null hypothesis is actually true in 180 of the 200 trials:



# False Discovery Rates (FDR)

Trials about „unlikely“ hypotheses result in many false discoveries.

Important in trials about risk factors and genetic/epigenetic markers.

Probability for truth of hypotheses depends on the a-priori probability!

# False Discovery Rates (FDR)

Reality: Study by Ioannidis(2005)*

All first reports of discoveries in Top 3 medicine journals 1990-2003 were investigated

Comparison with results from later trials

16% of results were contradicted entirely, 16% showed much weaker effects.

=> FDR=16%

*Ioannidis,JPA (2005): *Contradicted and Initially Stronger Effects in Highly Cited Clinical Research*, JAMA 294 (2), p218-228

**Next lecture:**

## Multiple Testing

Tim Holland-Letz

December 16, 2020, 9:00 am