Evidence Based Dentistry

Controlled clinical trials - interventions

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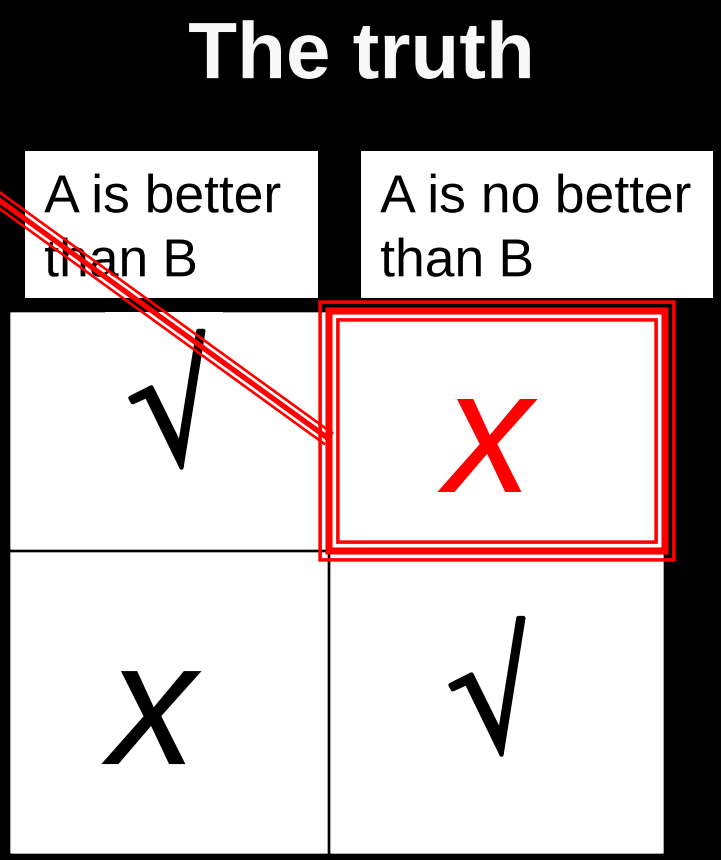
What can you show with a trial?

What the trial shows	The truth: A is better than B	The truth: A is no better than B
A is better than B	√	X
A is no better than B	X	√

What can you show with a trial?

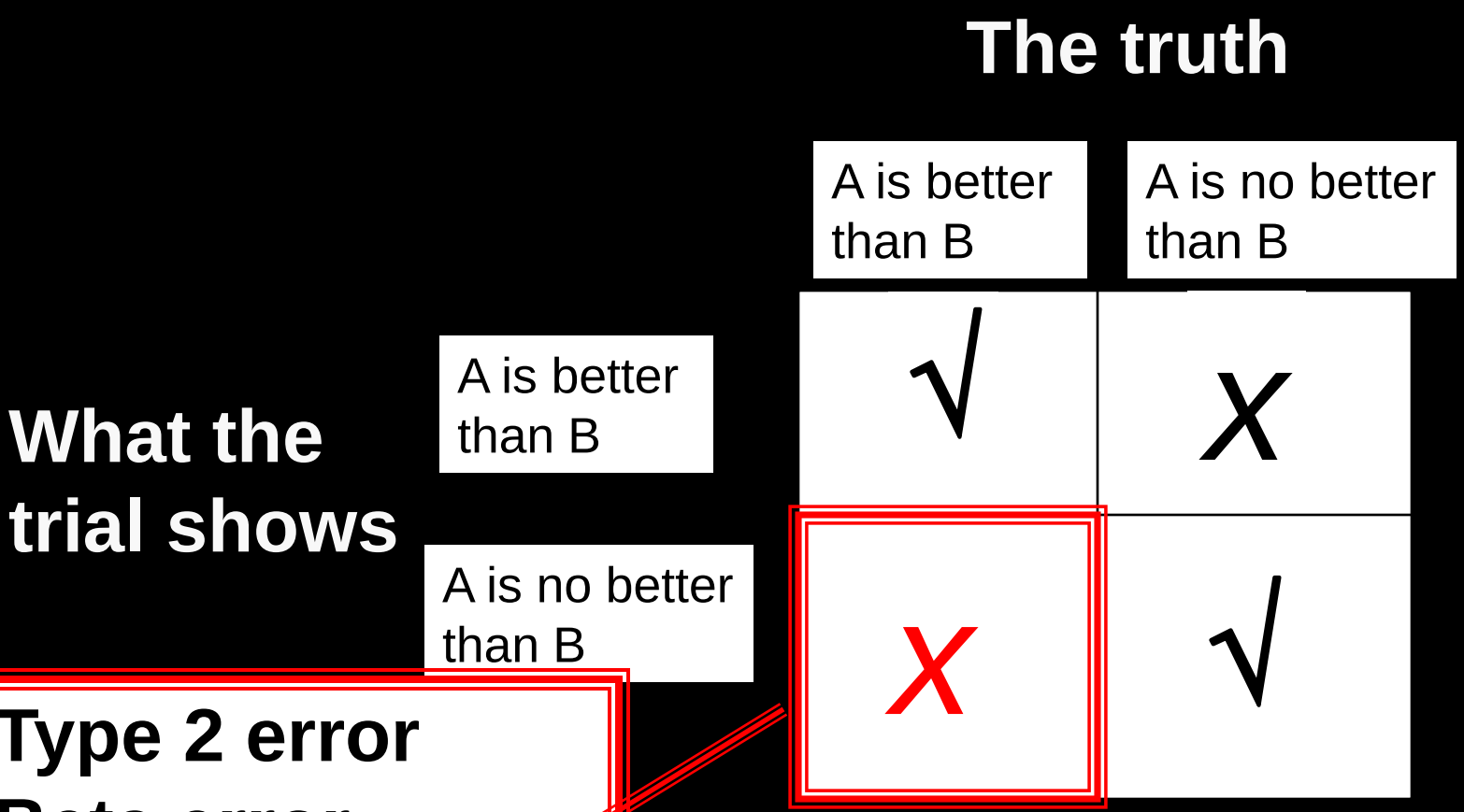
Type 1 error
Alfa error
Optimism error



Type 1 errors - fallacies of observed clinical success

- Spontaneous remission
- Placebo response
- Multiple variables in treatment
- Radical versus conservative treatment
- Over-treatment
- Long-term failure
- Side effects and sequelae of treatment

What can you show with a trial?



Type 2 errors - fallacies of observed clinical failures

- Wrong diagnosis
- Incorrect cause-effect correlations
- Multifactorial problems
- Lack of cooperation
- Improper execution of treatment
- Premature evaluation of treatment
- Limited success of treatment
- Psychological barriers to success

The easy approach to evaluate treatment effects

- Compare a single group of patients given the new treatment with a group previously treated with an alternative treatment.
- Usually such studies compare two consecutive series of patients in the same settings.

The easy approach is seriously flawed:

- Multiple examples in medicine where results from RCTs negates findings from clinical trials using inadequate study designs
- Controlled trials yield in general more optimistic results than randomised trials. (Altman DG. BMJ 1991;302:1481)
- Can never satisfactorily eliminate possible biases due to other factors (apart from treatment) that may have changed over time

The easy approach and risk of bias:

- If the clinician chooses which treatment to give each patient there will probably be differences in the clinical and demographic characteristics of the patients receiving the different treatments.
- Much the same will happen if patients choose their own treatment or if those who agree to have a treatment are compared with refusers.
- Similar problems when the different treatment groups are at different clinics or under different operators.
- Systematic differences will lead to an overestimate or underestimate of the difference between treatments.
- Bias can be avoided by using random allocation.

Strength of evidence of treatment effects

US Agency of Health Care Policy & Research, 1992

Ia. Meta-analysis of randomized controlled trials

Ib. At least one randomized controlled trial

IIa. At least one well-designed controlled study without randomization

IIb. At least one other quasi-experimental study

III. Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.

IV. Expert committee reports or opinions and/or clinical experience of respected

EBM Working Group, McMaster University 1993

Systematic reviews and meta-analyses

RCT with definite results
RCT with non-definite results

Cohort studies
Case-control studies
Cross sectional studies

Case reports

Strength of evidence of treatment effects

Richards & Lawrence, Br Dent J 1995;175:270

1: at least 1 systematic review of multiple well designed randomised controlled trials (RCT)
2: at least 1 properly designed RCT of appropriate size and in an appropriate clinical setting
3: well-designed trials without randomisation, single group pre-post, cohort, time series or matched case controlled studies
4: well-designed experimental studies from more than one centre or research group

5: opinions of respected authorities based on clinical evidence, descriptive studies or reports of expert consensus

Sackett et al., Editorial. EBM 1995;1:4

(I-1) 2 or more well designed randomised controlled trials (RCT), meta-analyses, or systematic reviews.
(I-2) a RCT.

(II-1) a cohort study.
(II-2) a case controlled study.
(II-3) a dramatic uncontrolled experiment.

(III) respected authorities, expert committees (consensus) etc.

(IV) ...someone once told me

Strength of evidence of treatment effects

CEBM, 2001. (http://cebm.jr2.ox.ac.uk/docs/levels.html)

1a. Systematic review of RCTs (with homogeneity of RCTs)

1b. Individual RCT (with narrow confidence interval)

2a. Systematic review (with homogeneity) of cohort studies

2b. Individual cohort study (and low quality RCT; e.g.,<80% follow-up)

3a. Systematic review (with homogeneity) of case-control studies

3b. Individual case-control study

4. Case-series (and poor quality cohort and case-control studies)

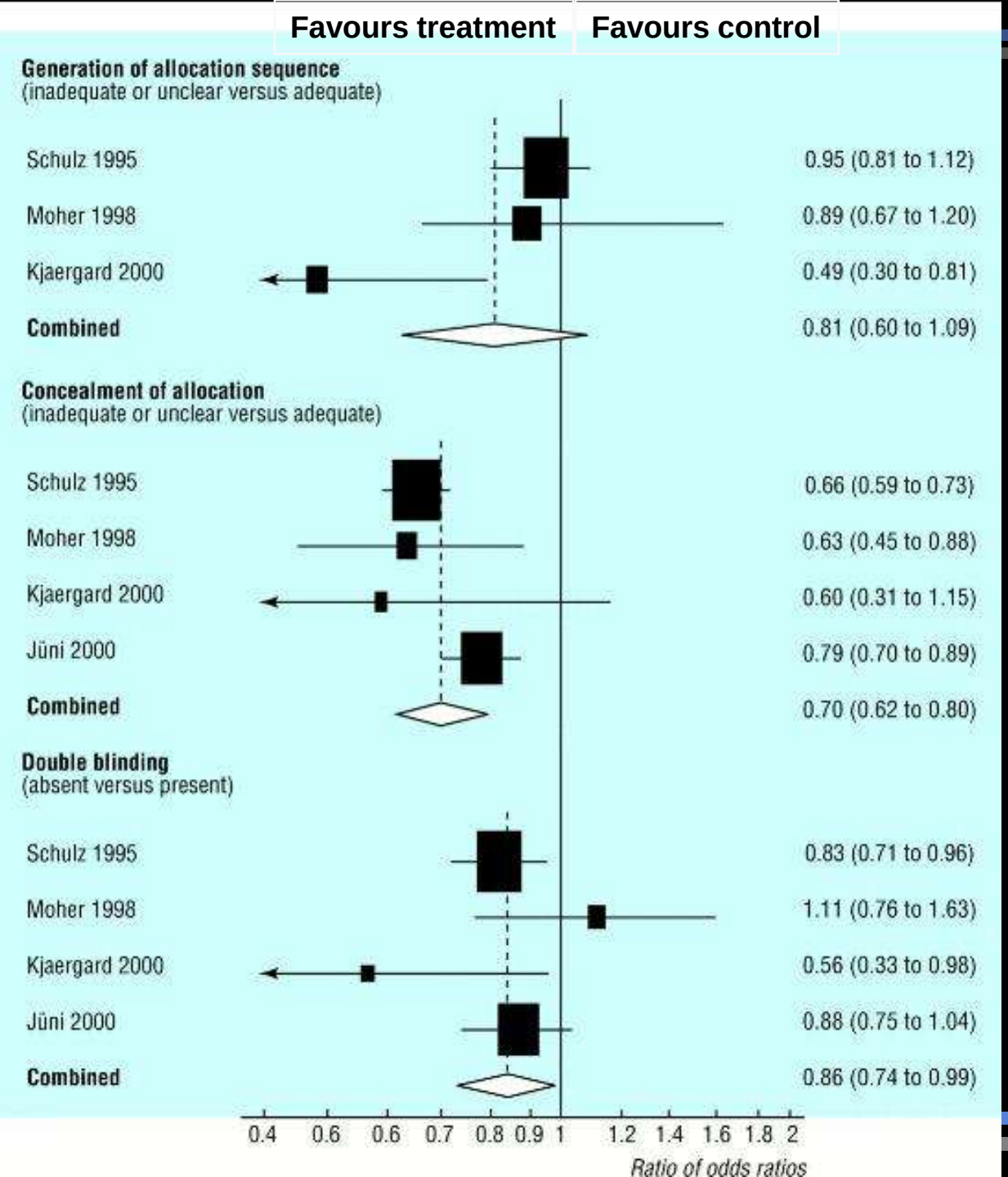
5. Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

Randomisation - rationale

- Main reason: prevent biases
- Random allocation means that all participants have the same chance of being assigned to each of the study groups
- Compare the outcomes of treatments given to groups of patients which do not differ in any systematic way

Randomisation - statistical theory

- Based on the idea of random sampling
- In a study with random allocation the differences between treatment groups behave like the differences between random samples from a single population
- We know how random samples are expected to behave and so can compare the observations with what we would expect if the treatments were equally effective



Effects of inadequate study design on results

Jüni et al.Methodological quality of controlled trials and effect estimates. BMJ 2001.

RCTs - a checklist

- Good randomisation procedures
- Patients blind to treatment
- Clinicians blind to treatment
- All participants followed up
- All participants analysed in the groups to which they were randomised (intention to treat)

Randomisation Procedures

- Alternate allocation
- Date of birth
- Day of study
- Flip Coin
- Record numbers
- Roll of dice
- Computer generated random numbers
- Random number tables

Allocation is not determined by the investigators, the clinicians, or the study participants.

Blinding

Blinding

• Participants don’t know what healthcare intervention they are getting

Double blinding

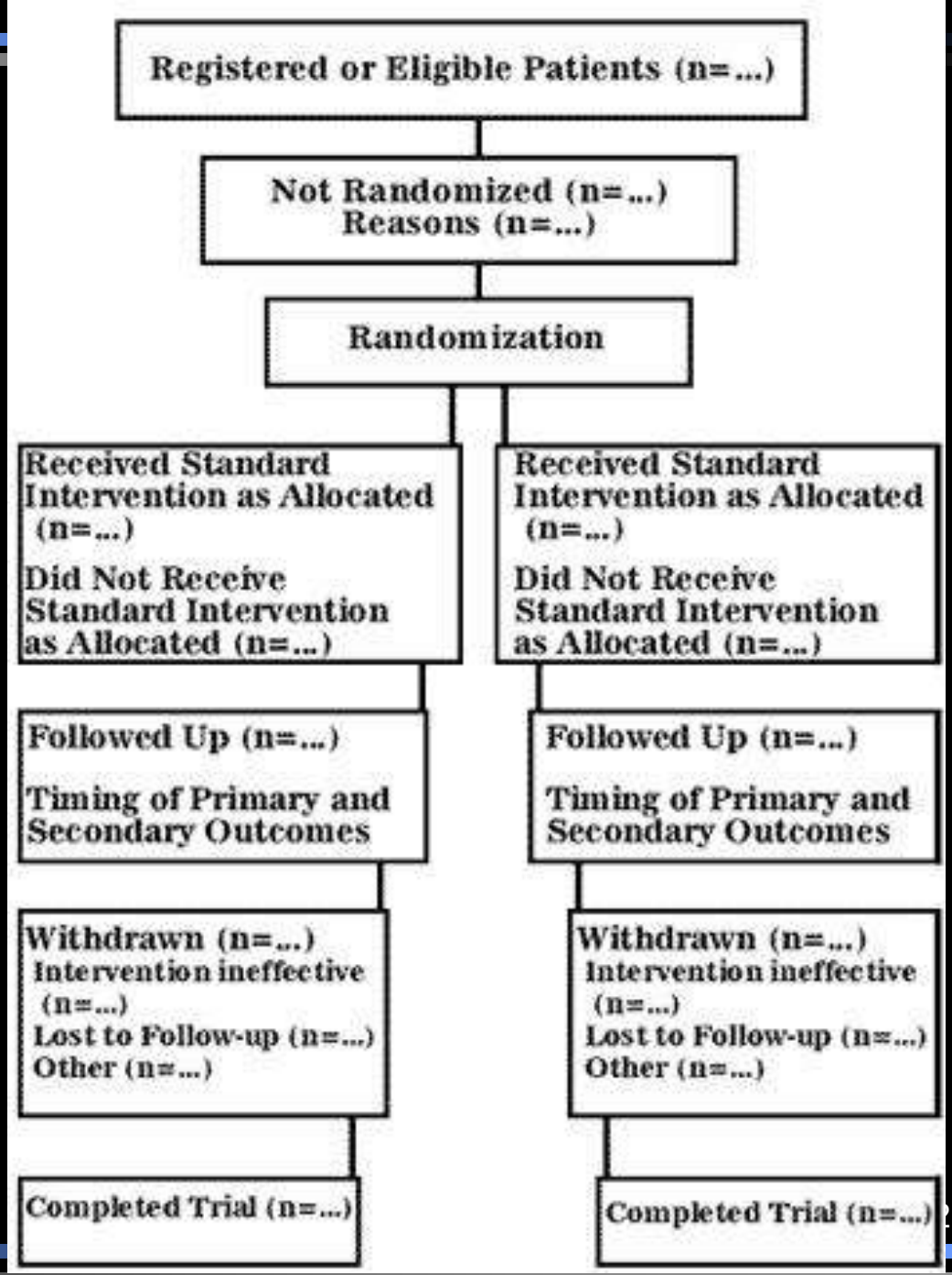
• Those giving the healthcare don’t know what the participant is receiving (i.e. doctors, healthcare professionals)

Loss to follow-up

It is important to ensure that all those that are randomized into the trial are followed up to the trials conclusion

Reporting:

CONSORT



Intention to treat analysis

Analysing people, at the end of the trial, in the groups to which they were randomized, even if they did not receive the intended intervention.

CONSORT STATEMENT

strength in science, sound ethics

Improving the Quality of Reporting of Randomized Controlled Trials

Colin Begg, PhD; Mildred Cho, PhD; Susan Eastwood, ELS(D); Richard Horton, MB; David Moher, MSc; Ingram Olkin, PhD; Roy Pitkin, MD; Drummond Rennie, MD; Kenneth F. Schulz, PhD; David Simel, MD; Donna F. Stroup, PhD

TRANSLATIONS AND PDF FORMATS

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- The Statement Checklist (8 K)
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- The Statement Comments Section(10 K)
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Foreign Language Translations of CONSORT:

- FRENCH
- GERMAN
- SPANISH
- JAPANESE (This site requires a browser configured for Japanese text)
- For hard copy versions of the CONSORT Statement in Dutch please contact us.

INTRODUCTION

Are the results of the trial valid?

1. Do the trial address a clearly focussed issue?

   i.e. focused in terms of the population studied, the intervention, the outcomes considered

2. Was the assignment of patients to the intervention randomised in a correct way?
3. Were all patients who entered the trial properly accounted for at its conclusion?
   - *was follow-up complete?*
   - *were patients analysed in the groups to which they were randomised?*

Are the results of the trial valid?

4. Were there any attempts to of blinding?
   patients? health workers? study personnel?

5. Were the groups similar at the trial start?
   In terms of other factors that might effect the outcome such as age, sex and social class

6. Aside from the experimental intervention - were the groups treated equally?

What are the results?

7 . How large was the effect of the intervention?

What outcomes are measured?

8. How precise was the estimate of the effect of intervention?

What are its confidence limits?

Will the results help my patients?

9. Can the results be applied to my patients?

   Do you think that the patients covered by the trial are similar enough to your population?

10. Were all clinically important outcomes considered?

    If not, does this affect the decision?

11. Are the benefits worth the harms and costs?

    Usually unlikely to be addressed by the trial.