Statistical analysis in clinical research

Today’ s contents

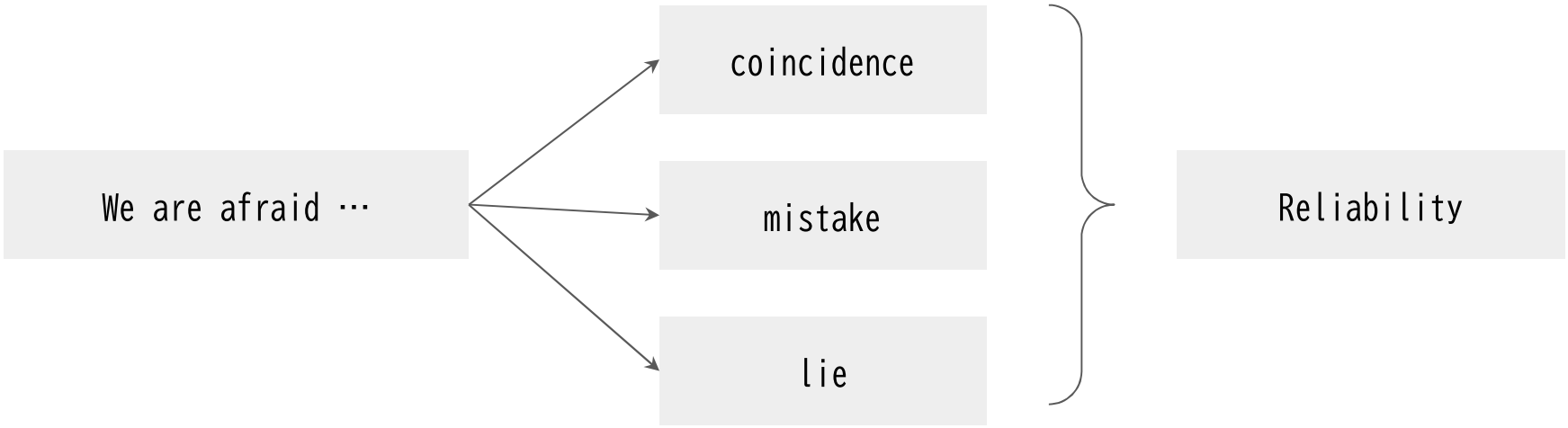
Introduction

Statistics in Clinical Research

Data Management in Clinical Research

Wrap up meeting

Why can not we believe it?

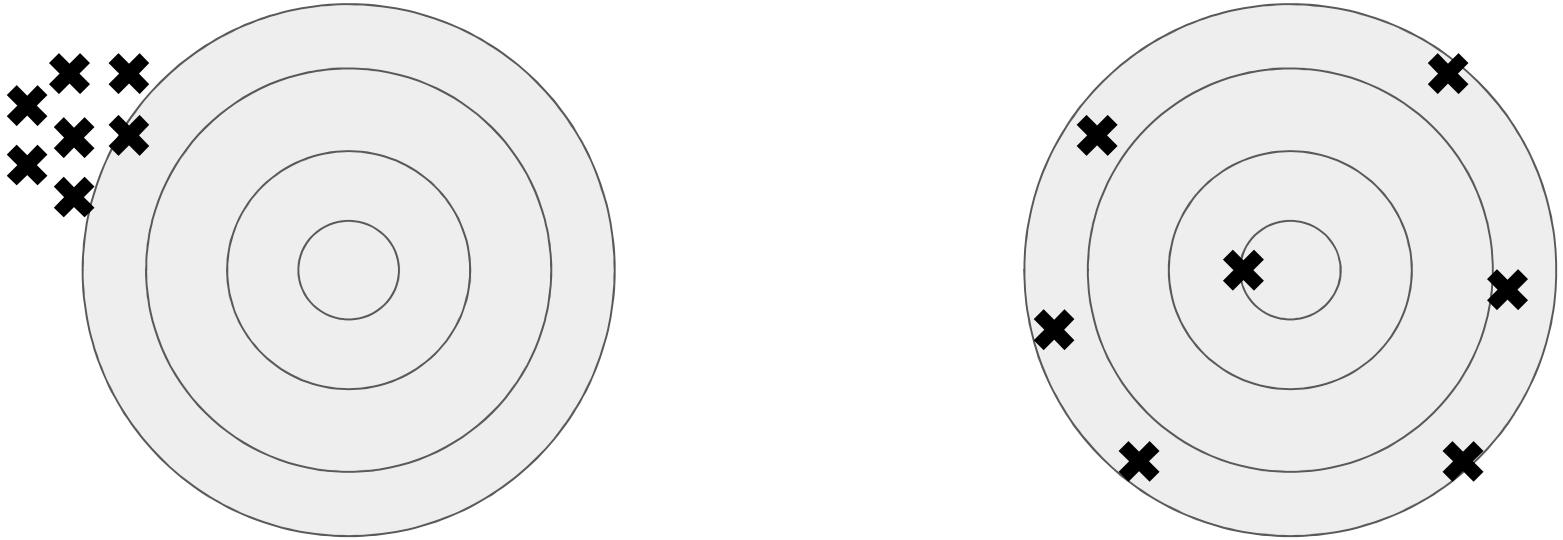


Our mission is to keep the Reliability of Clinical Research.
We call it “Quality of Clinical Research”.

Why do we need Statistics?

Standard regulation : ICH-E9 (STATISTICAL PRINCIPLES FOR CLINICAL TRIALS)

Which player is better?



We want to minimize Bias and Variability

ICH-E9

What is Bias?

The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as 'operational' bias. The other sources of bias listed above are referred to as 'statistical'.

- Cognitive bias
- Doctor
- Patient

- Regression fallacy
- Regression toward the mean
- Homeostasis

How can we avoid them?

The Design of Experiments

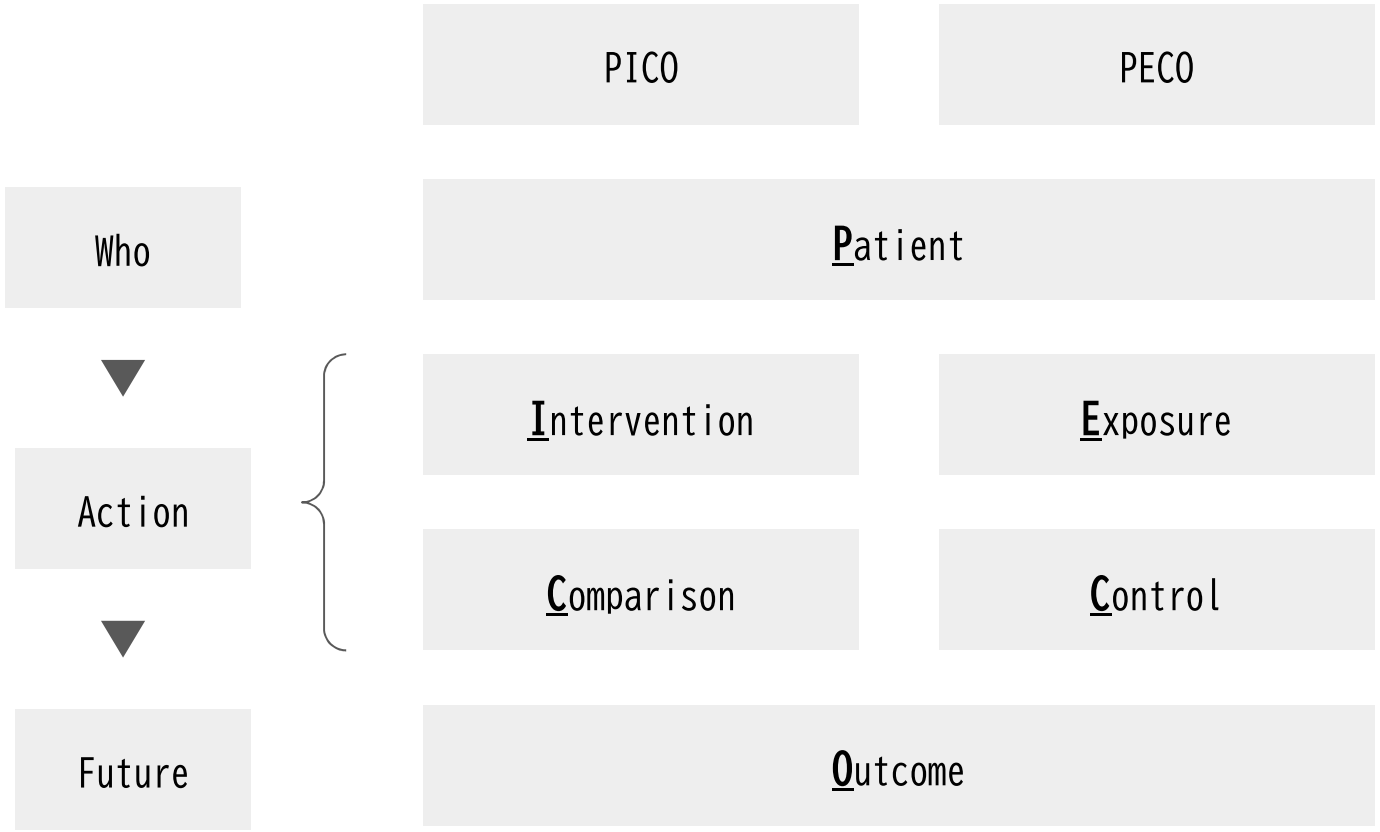
R. A. Fisher

Fisher's three principles

The Design of Experiments needs Story

Who	What kind of patient do you want to tell the result?
▼	
Action	What action will the patient take next?
▼	
Future	What kind of future will that action bring?

Clinical research has a similar format for thinking the stories



Patient : Who is the “real” target?

Protocol has “Inclusion and Exclusion Criteria”

They define the target of the clinical research … However …

Some investigators are a little confused

Inclusion criteria	Exclusion criteria
cancer patients less than equal 50 years old	cancer patients greater than 50 years old

What do you think?

Patient : Who is the “real” target?

Inclusion criteria	Exclusion criteria
cancer patients less than equal 50 years old	cancer patients greater than 50 years old

The purpose of this clinical research was to evaluate the efficacy of new medication

The end point was 5-year survival rate

Survival rate of 25 and 55 years old are different. This will cause of noise.

The investigator decided to exclude greater than 50 years old from this research

Patient : Who is the “real” target?

After this medication is launched, will it be administered to a 53-year-old cancer patient?

Inclusion criteria	Exclusion criteria
cancer patients	patients greater than 50 years old

“Inclusion Criteria” are the conditions of patient who is the target of the medication

“Exclusion Criteria” are the conditions for completing this study

Patient : dificult trade-off

Sensitivity

We want to conduct clinical research under conditions that facilitate the manifestation of effects as much as possible.

Mild

Young

Severe

Old

Complications

Generalisability

We want that other patients in the future will have the same effect as the results of this clinical research.

How can we avoid them?

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How can we avoid them?

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ICH-E9	2.3 Design Techniques to Avoid Bias

The most important design techniques for avoiding bias in clinical trials are blinding and randomisation, and these should be normal features of most controlled clinical trials intended to be included in a marketing application.

ICH-E9	2.3.1 Blinding

Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed.

ICH-E9	2.3.2 Randomisation

Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

Randomising subjects in blocks

Ex. block size = 4

A	A	P	P
A	P	A	P
A	P	P	A
P	A	A	P
P	A	P	A
P	P	A	A

A : Active group = 2
P : Placebo group = 2

Although unrestricted randomisation is an acceptable approach, some advantages can generally be gained by randomising subjects in blocks. This helps to increase the comparability of the treatment groups, particularly when subject characteristics may change over time, as a result, for example, of changes in recruitment policy.

Randomising subjects in blocks

Ex. block size = 4

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A	P	P	A
P	A	A	P
P	A	P	A
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A : Active group = 2
P : Placebo group = 2

Randomize


X Hospital


Y Hospital


Z Hospital

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P	A	P	A
P	P	A	A

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Randomize


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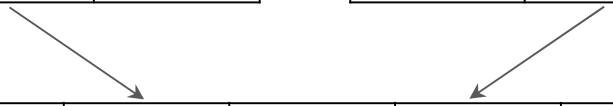
the treatment groups will be of nearly equal size.

one point advice : beware the “Simpson’ s paradox”

	Effective	In-effective	Total	Effective rate
Active group	60	40	100	60%
Placebo group	9	1	10	90%

	Effective	In-effective	Total	Effective rate
Active group	1	9	10	10%
Placebo group	30	70	100	30%



	Effective	In-effective	Total	Effective rate
Active group	61	49	110	55%
Placebo group	39	71	110	35%

We have to be careful about the imbalance between the groups

Design Configuration

Study design can help us reduce noise