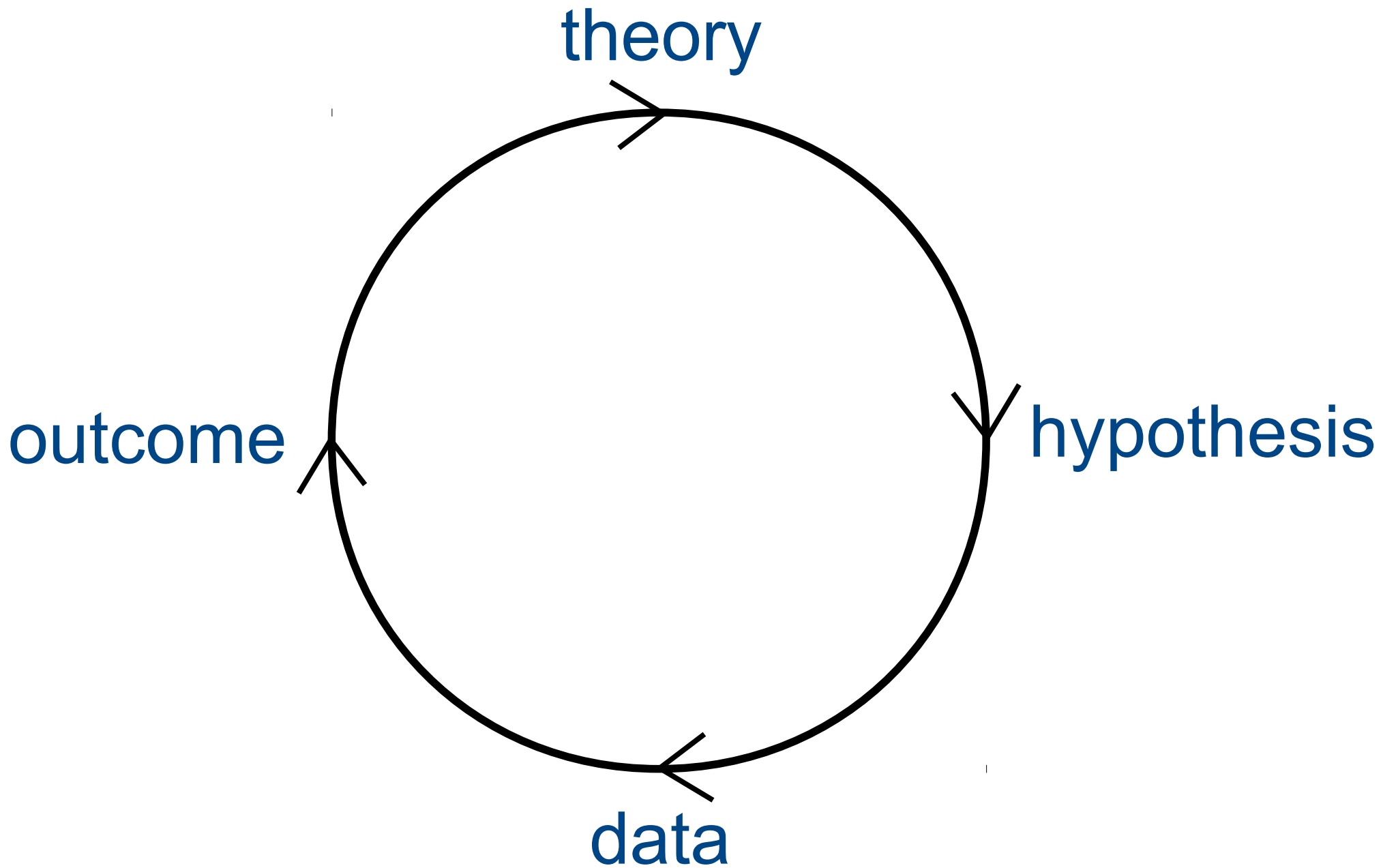
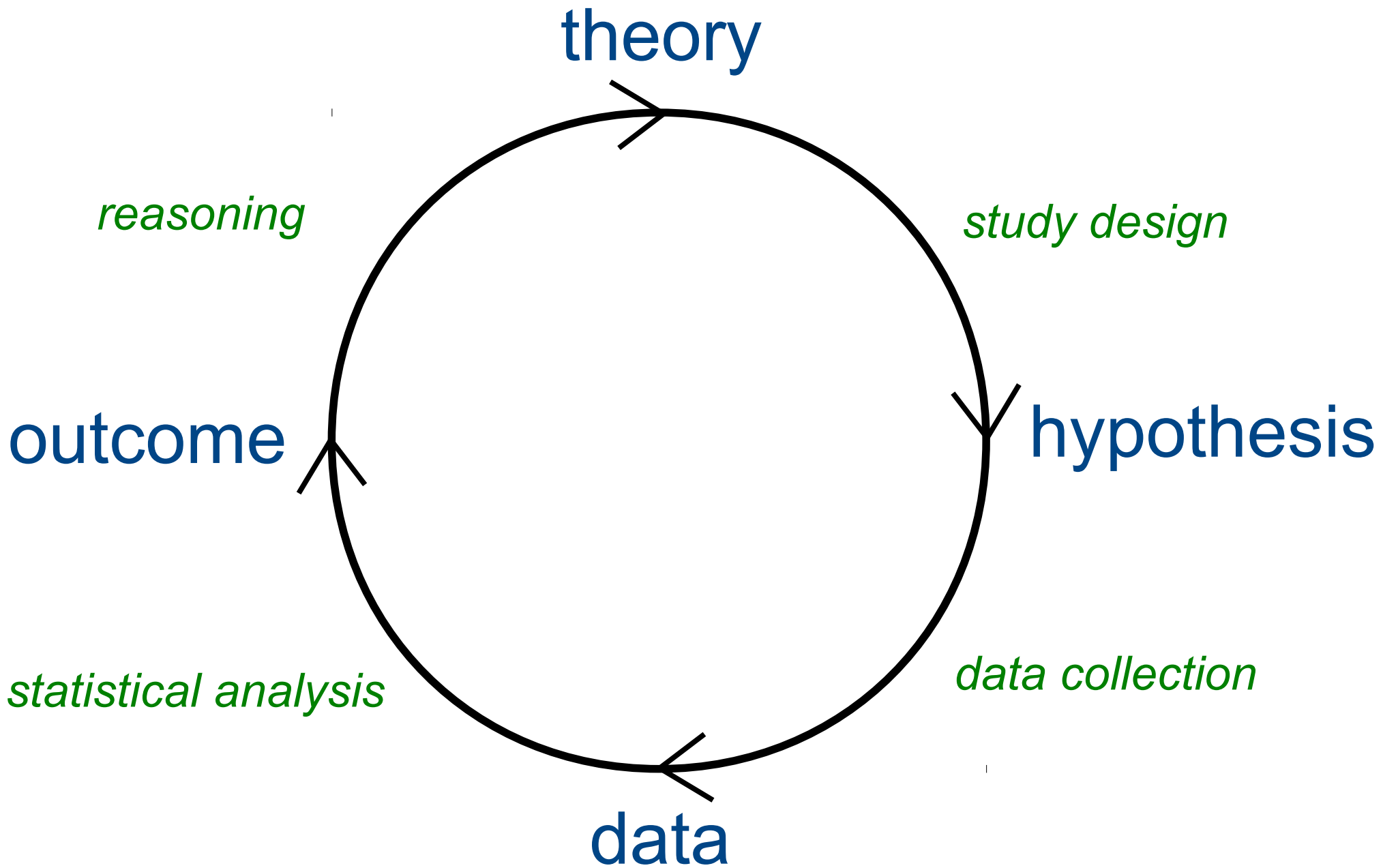


From data to publication

Jonas Ranstam PhD





theory

study design

hypothesis

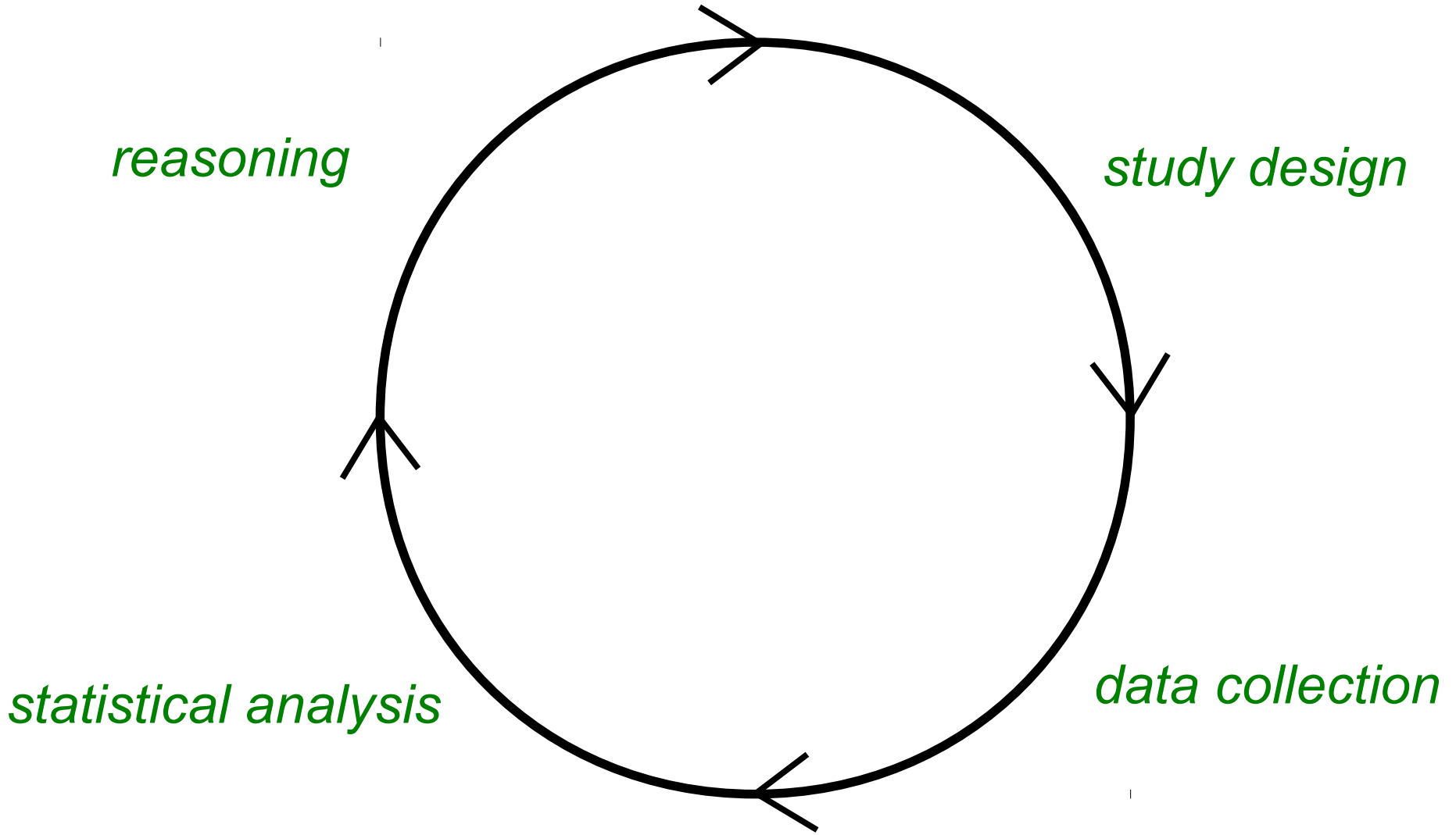
data collection

data

outcome

statistical analysis

reasoning



To discuss in this presentation

study design

- observation (case report, survey, epidemiological study)
- experiment (phantom, in vitro, in vivo, clinical trial)

data collection

- registration, monitoring, validation, documentation

statistical analysis

- data description, effect estimation, evaluation of bias and uncertainty

reasoning

- interpretation of outcome with respect to the limitations imposed by study design, data collection and statistical analysis

Design features (simplified)

Design

Characteristics

Experimental

Observational

Studied effects

beneficial

harmful

Sample size

small

large

Follow up

short

long

Internal validity

better

worse

Main outcome

efficacy

effectiveness

External validity

worse

better

Design features (simplified)

	Design	
Characteristics	Experimental	Observational
Data collection	from CRF to database	from ? to register
Statistical analysis	precision oriented	validity oriented
Reasoning	multiplicity, missing data, compliance, superiority, non-inferiority	confounding, selection and information bias, measurement errors

Data collection

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

4. **All clinical trials**, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of **good clinical practice**.

ICH-GCP

1.24 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights integrity and confidentiality of trial subjects are protected.

ICH-GCP

4.9 Records and Reports

The investigator should ensure the accuracy, completeness, legibility, and timeliness of all the data reported to the sponsor in the CRFs and all required reports.

ICH-GCP

5.5 Trial Management, Data Handling, and Record Keeping

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

(Audit trail: Documentation that allows reconstruction of the course of events)

ICH-GCP

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Obligation to Register Clinical Trials

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

Requirements for observational studies

ICMJE - Selection and Description of Participants

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population.

Requirements for observational studies

The STROBE statement

Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.

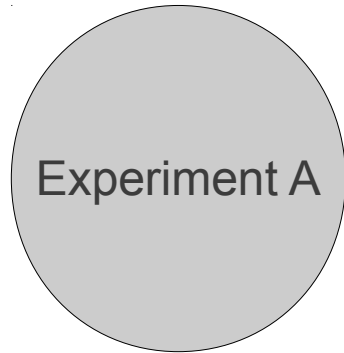
For each variable of interest, give sources of data and details of methods of assessment (measurement).

Statistical analysis and reasoning

Misunderstandings about statistical calculations

- They reveal otherwise unknown information about the studied population (sample)
- Their purpose is to find statistically significant differences or effects
- It is only interesting whether a difference has $p < 0.05$ or “ns”
- If a difference is not significant, it does not exist
- If a difference is significant, it is practically important
- It is important to test all differences, especially for evaluating the success of randomization (in clinical trials) and matching (in observational studies)
- Findings can only be published if they are statistically significant

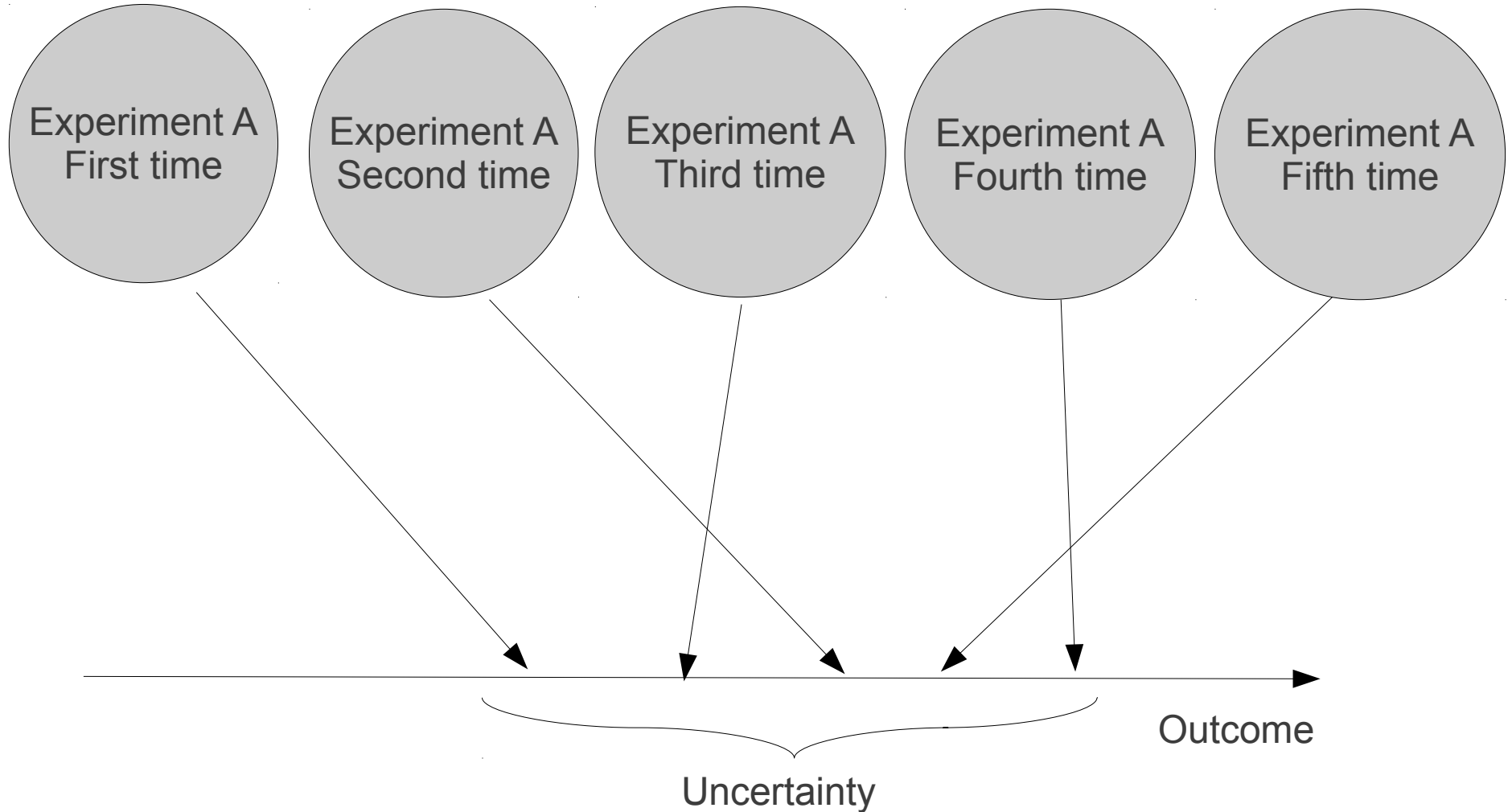
Sampling and measurement variability



What do we know about sampling and measurement variability when an experiment is performed only once?

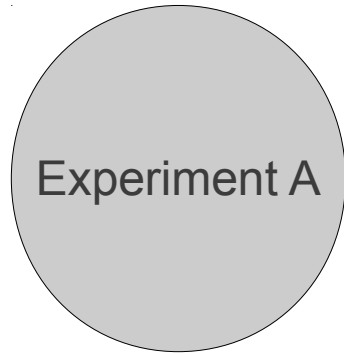
Outcome

Sampling and measurement variability



Had we replicated the experiment several times, the variation had been evident.

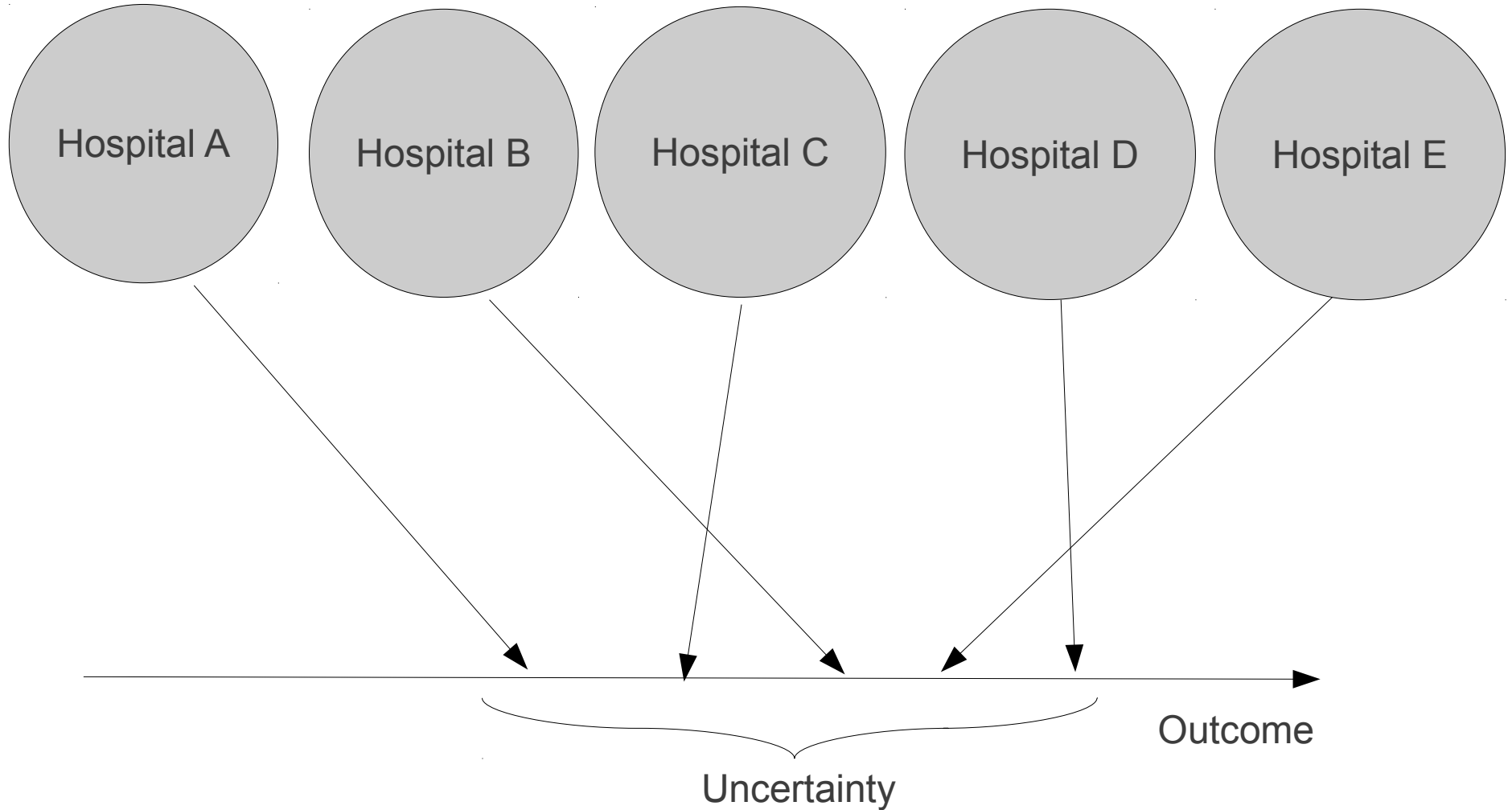
Sampling and measurement variability



With only one performance of the experiment, the uncertainty caused by sampling and measurement variation can be evaluated using statistical methodology.



Sampling and measurement variability



Sampling and measurement variability must be taken into account when comparing different entities, otherwise the results cannot be meaningfully interpreted. Politicians and reporters do generally not understand this.

Observation vs. inference

For one particular observed sample

Central tendency: Mean, Median (statistic)

Dispersion: SD, Range

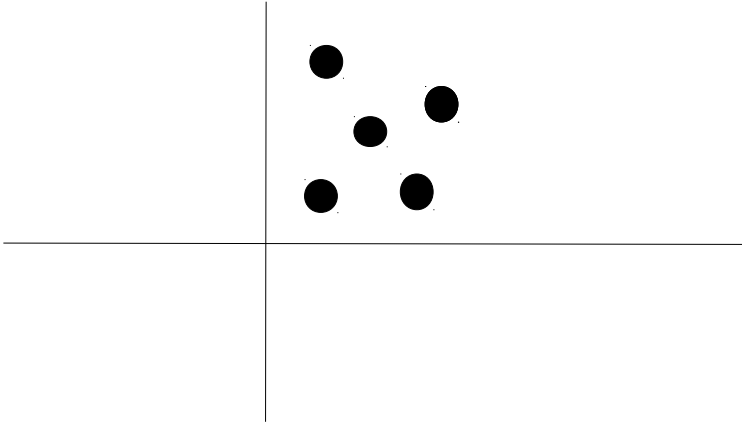
For the unobserved population of samples

Central tendency: Mean, Median (parameter)

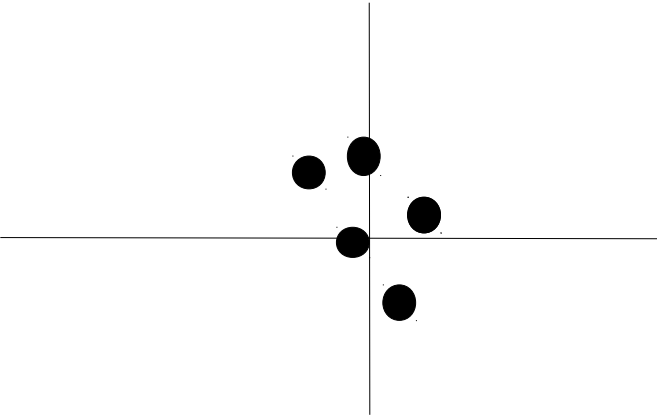
Uncertainty: SEM, confidence interval

Precision and validity of estimates

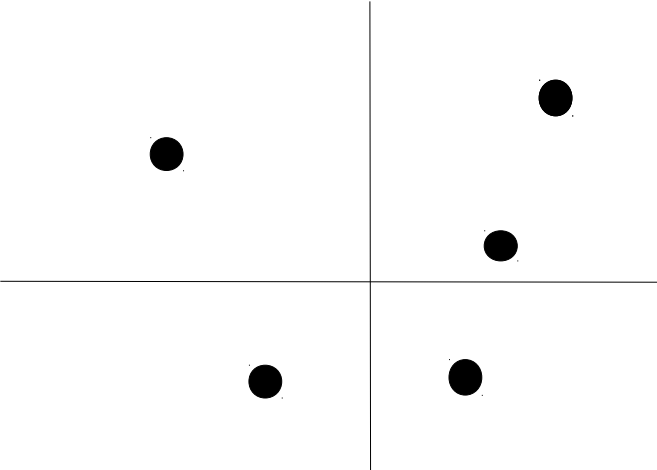
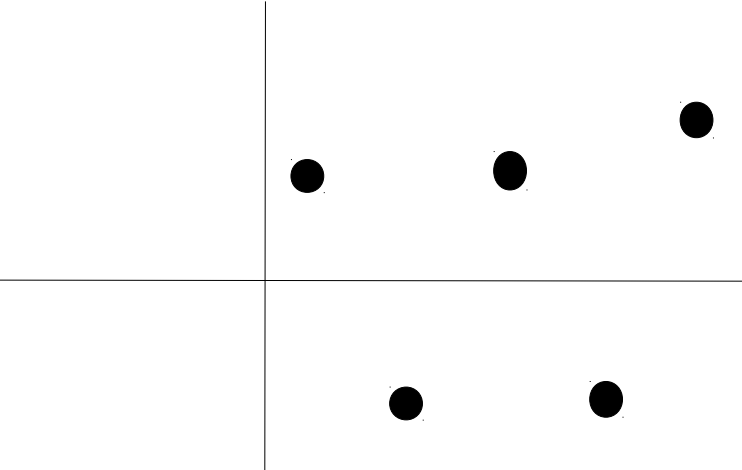
Lower validity



Higher validity



Higher precision



Lower precision

Precision and validity

Precision is often presented using a 95% confidence interval.

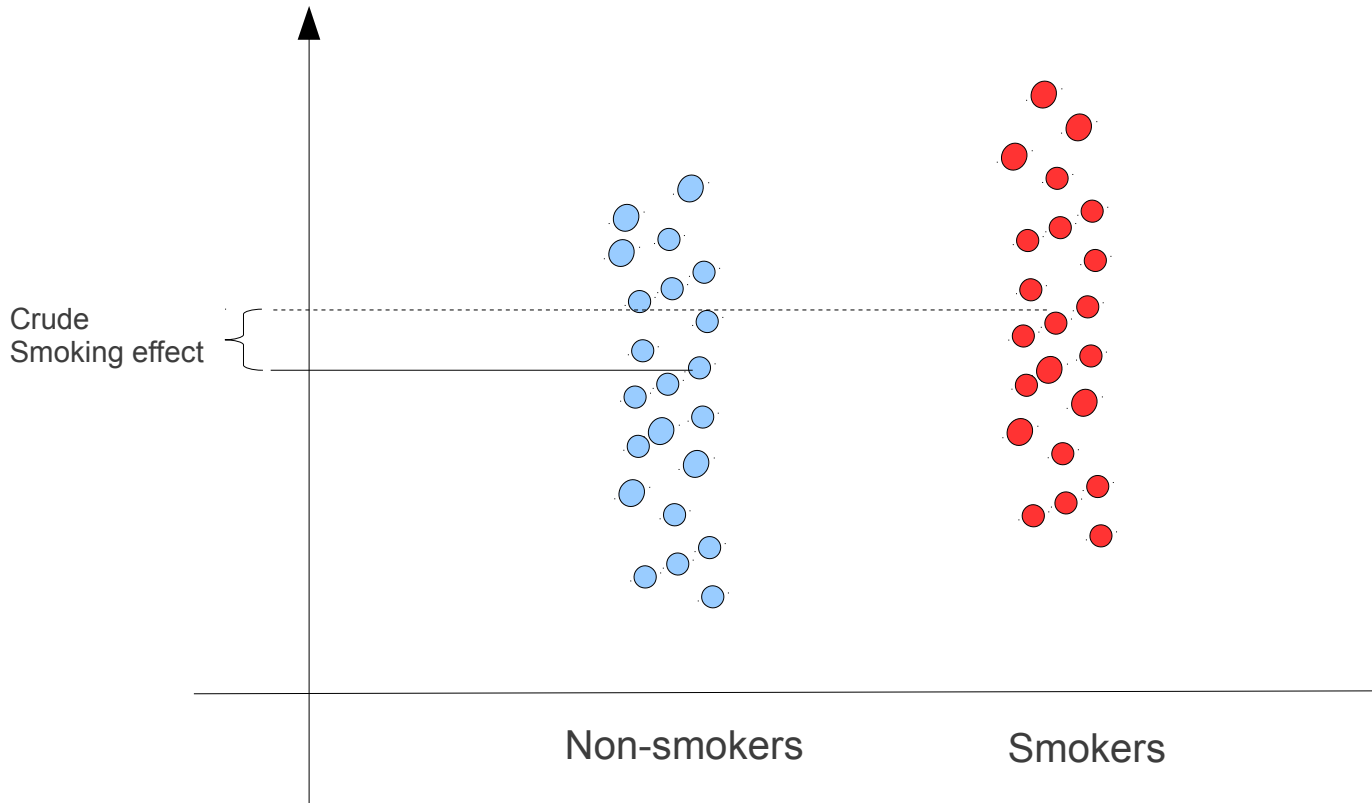
Like the p-value this is an estimate of the uncertainty related to sampling and measurement variability.

What about validity?

- Experiments are designed for validity (randomization, blinding, etc.)
- Observational studies are analyzed to reduce bias (validity errors).

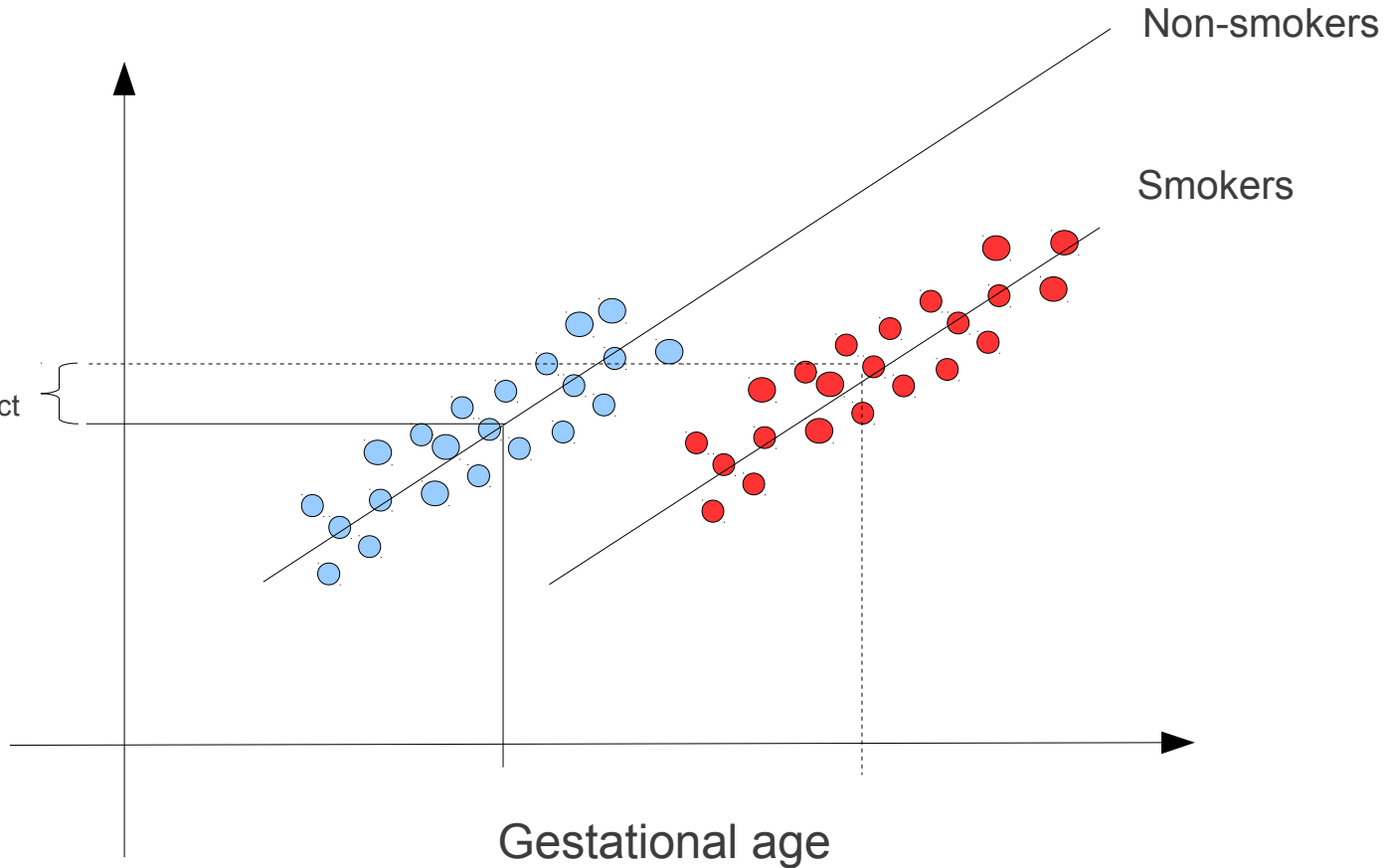
Confounding bias – crude estimate

Birth weight

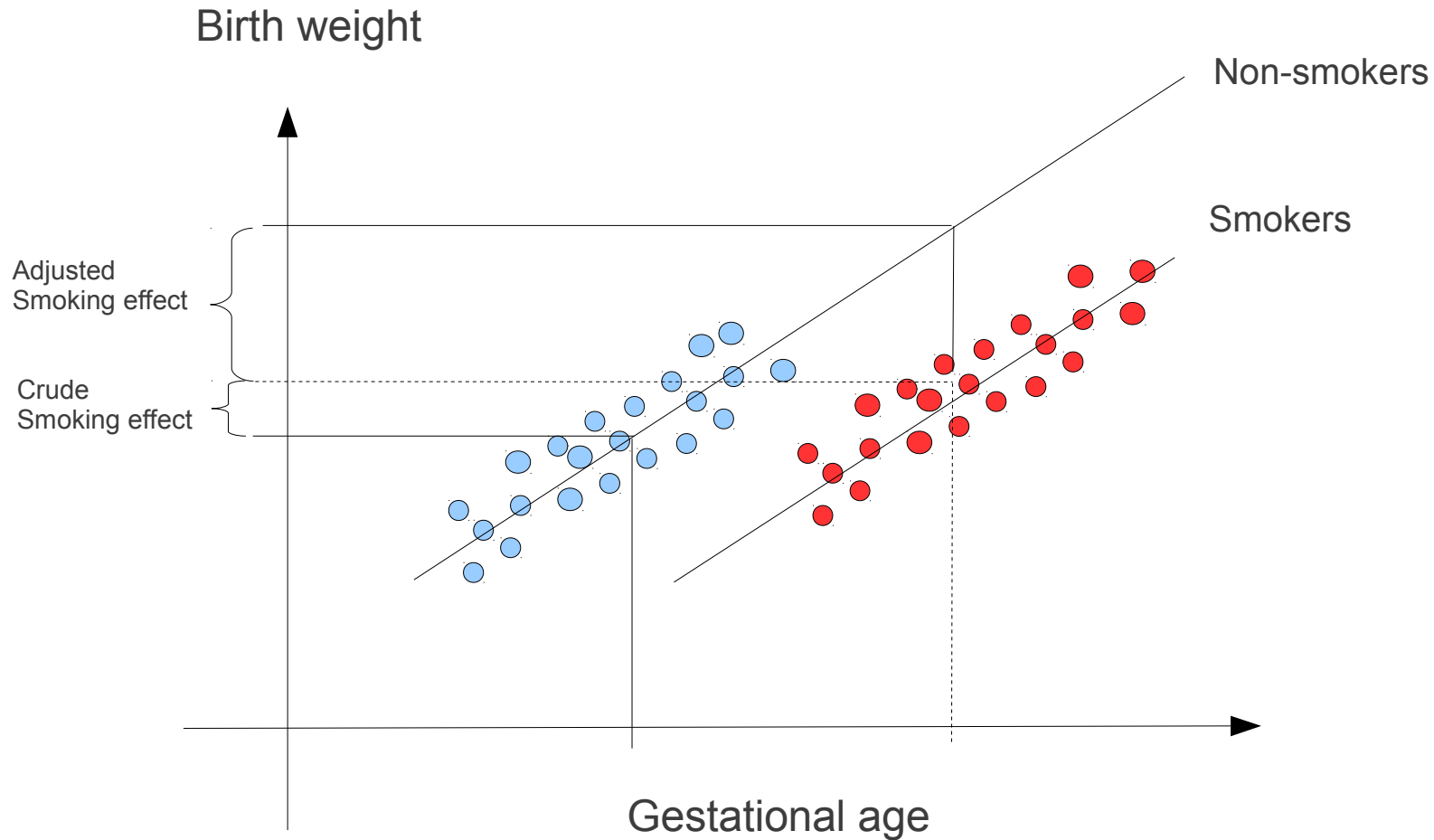


Confounding bias – crude estimate

Birth weight

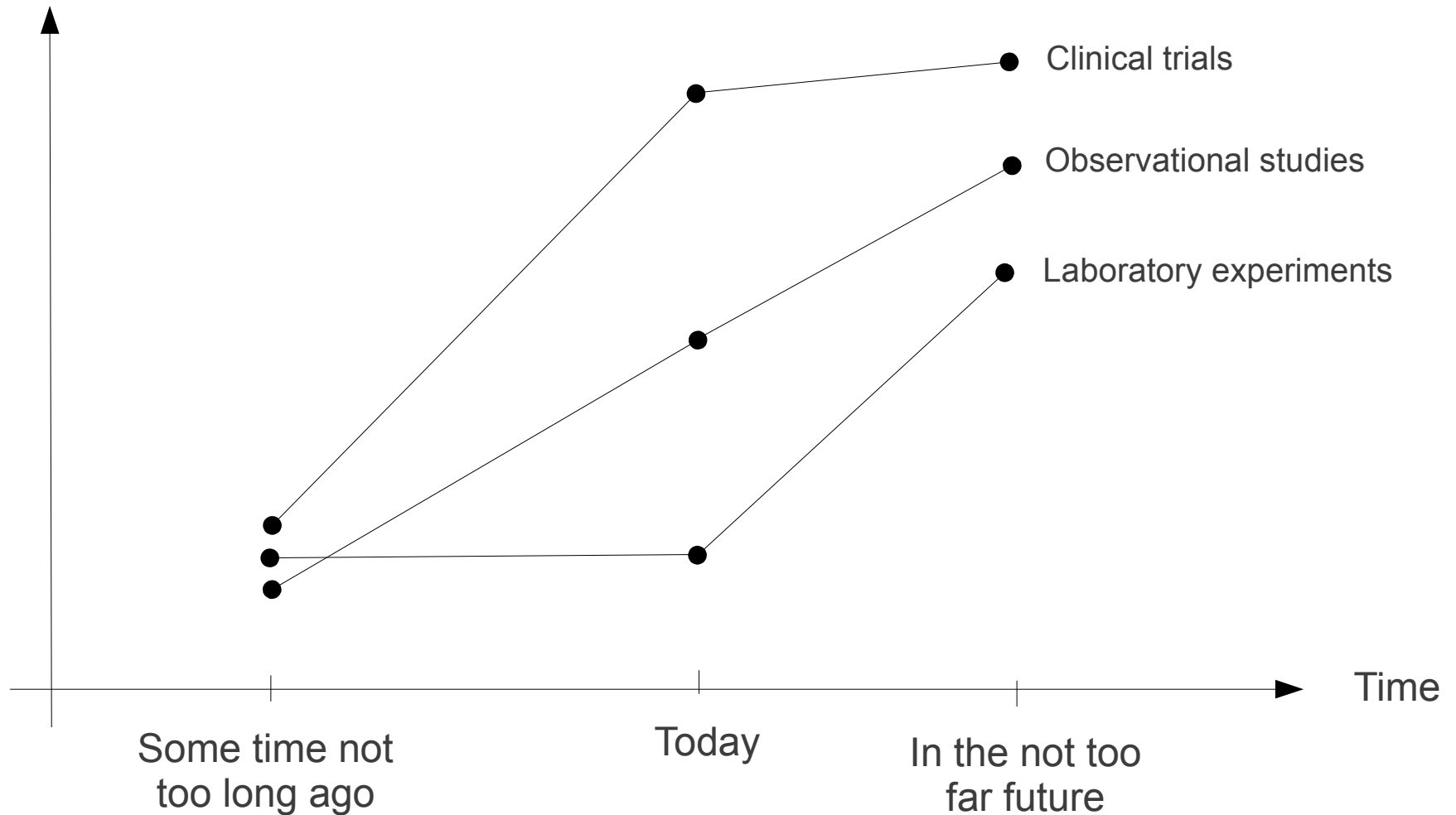


Confounding bias – adjusted estimate



Methodological development in different research areas

Level of proficiency



Recent developments in the analysis of observational studies

- Longitudinal analysis using random effects models
- Multilevel analysis
- Causality models
- The development of publication guidelines
- Debate on registration of epidemiological studies

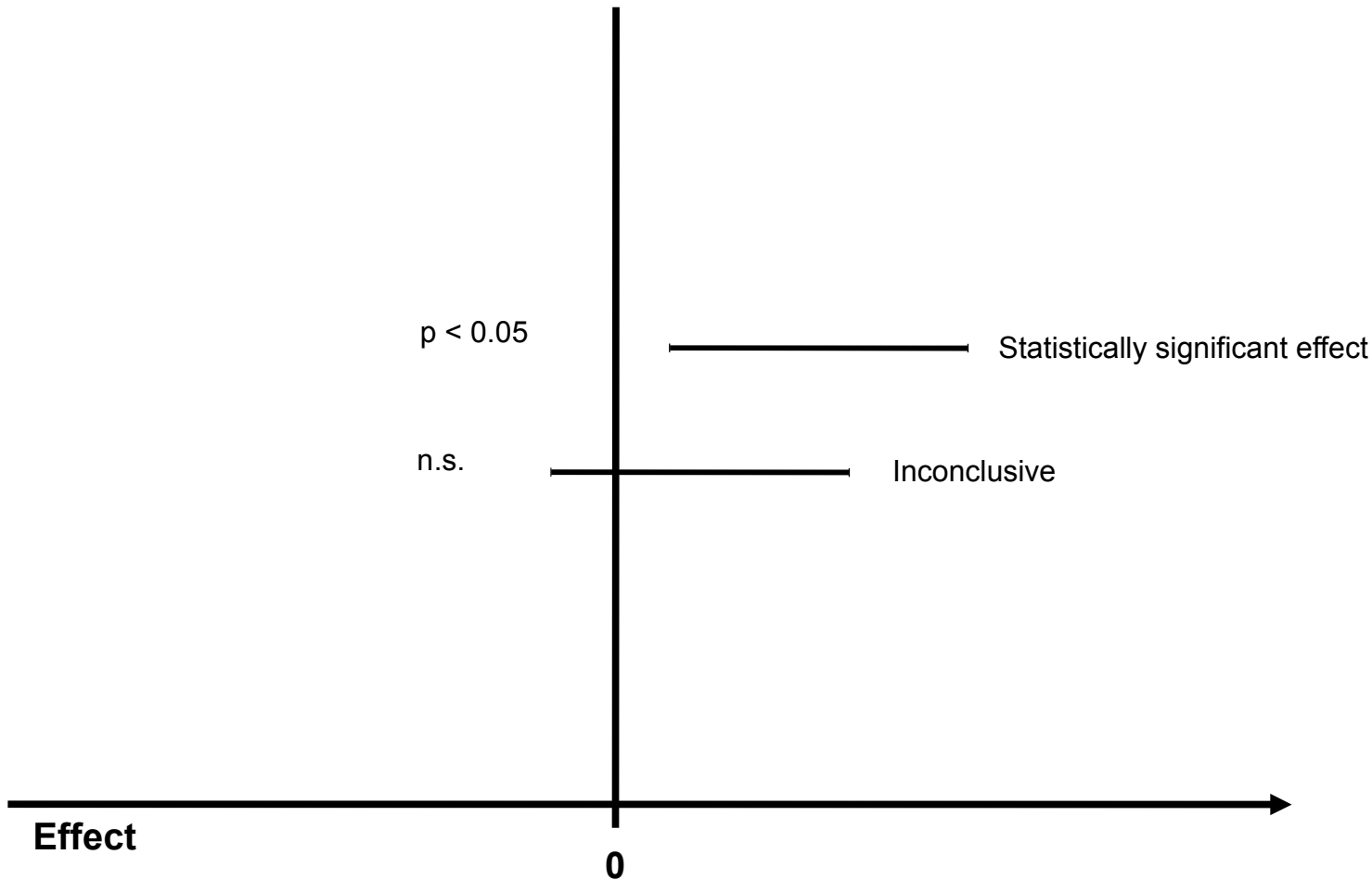
Recent developments in clinical trials

- Random effects models for analysis of FAS
- Closed test procedure strategies for handling multiplicity issues
- Development of superiority, equivalence, and non-inferiority trial designs
- The development of ICH guidelines for design and analysis
- The development of publication guidelines
- Registration of trials in a public register

P-value and confidence interval

Information in p-values
[2 possibilities]

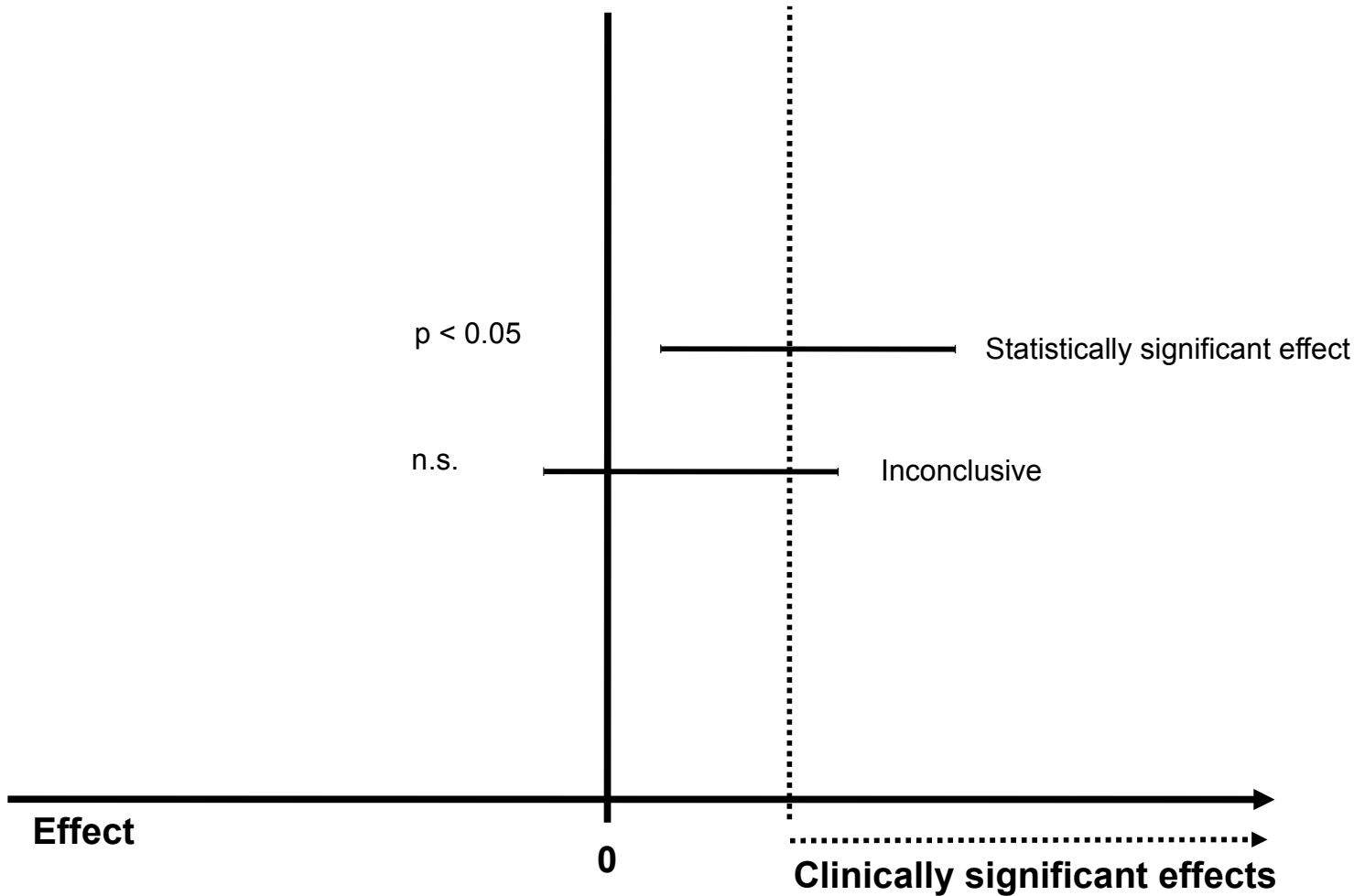
Information in confidence intervals
[2 possibilities]



P-value and confidence interval

Information in p-values
[2 possibilities]

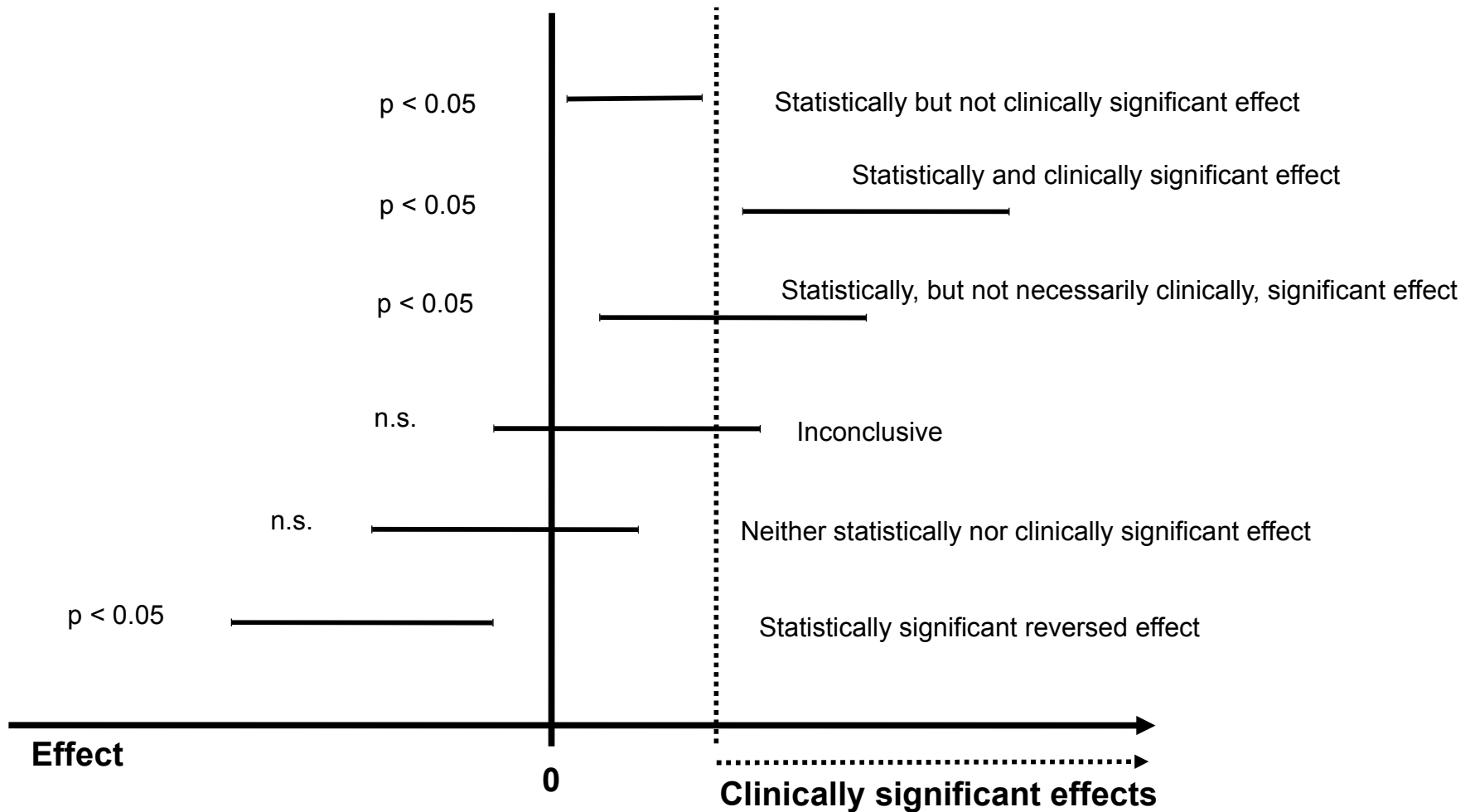
Information in confidence intervals
[2 possibilities]



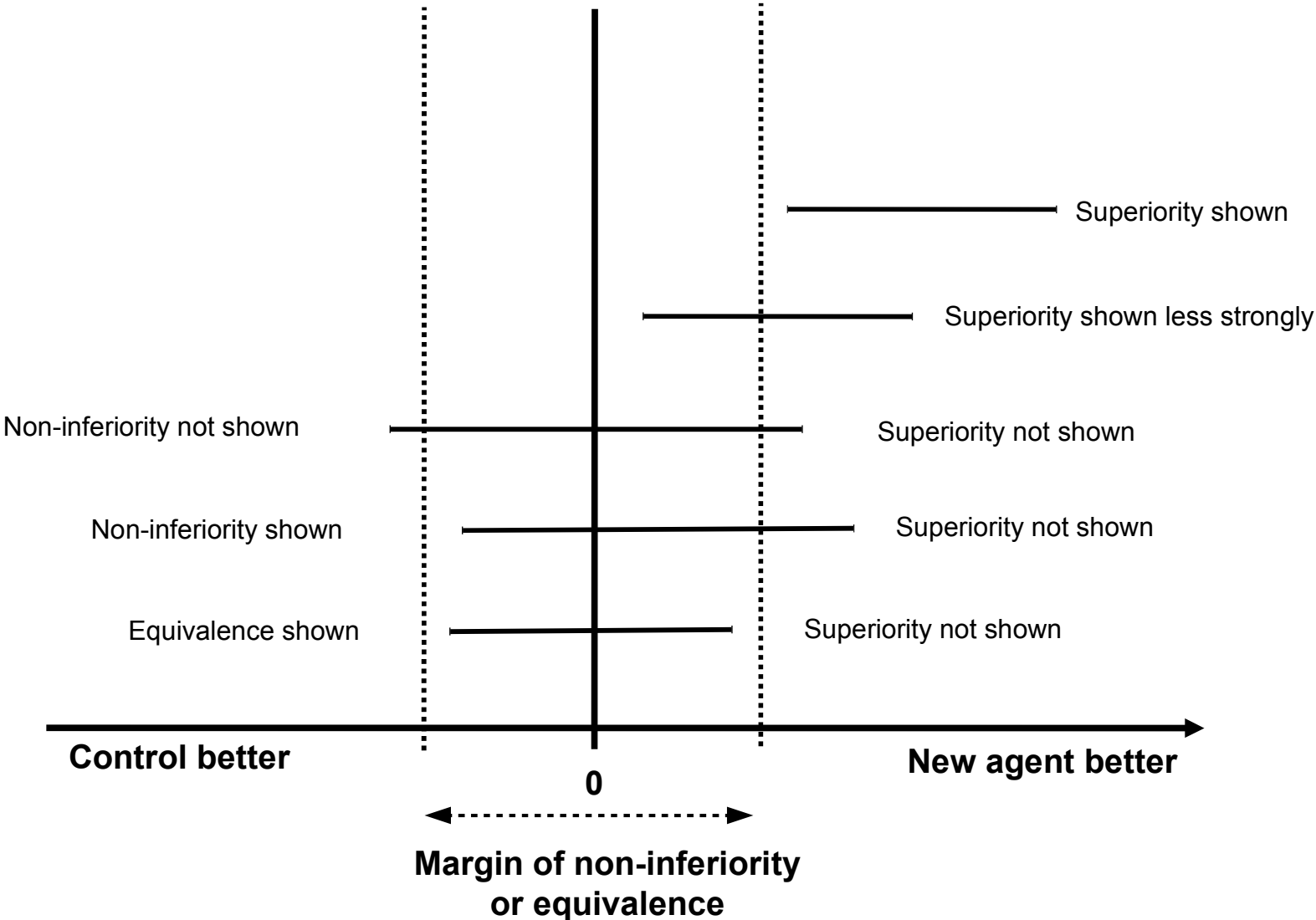
P-value and confidence interval

Information in p-values
[2 possibilities]

Information in confidence intervals
[6 possibilities]



Superiority, non-inferiority and equivalence



Statistical analysis of clinical trials

- ICH E9 Statistical Principles for Clinical Trials
- CPMP Points to consider on multiplicity issues in clinical trials
- CPMP Points to consider on adjustment for baseline covariates
- CPMP Points to consider on missing data
- CPMP Point to consider on switching between superiority and non-inferiority

Recent developments in the analysis of laboratory experiments

- Bioinformatics (FDR, etc.)
- The (slow) development of publication guidelines

Manuscript preparation guidelines

See <http://www.equator-network.org/>

Clinical trials

- CONSORT statement (several)

Laboratory experiments (primarily in vivo)

- ARRIVE statement

Observational studies

- STROBE statement