Preclinical Study Design Considerations

Don’t be a bias denier

Anton Bespalov, MD, DMedSci
Partnership for Assessment and Accreditation of Scientific Practice
Heidelberg, Germany

Thomas Hudzik, PhD
ALA+ BioPharma Consulting

Disclosures

Anton Bespalov is Co-founder and managing partner at PAASP GmbH, a Shareholder at PAASP US LLC, Co-founder and CSO / managing director at EXCIVA GmbH

Thomas Hudzik is a consultant for pharma, NIDA, biomedical research institutions, World Anti-Doping

Outline

- Definition of a ‘good’ study design
- Blinding
- Randomization
- The power and peril of pre-specification of endpoints

Recommended (re)Reading

Why Most Published Research Findings Are False

John P. A. Ioannidis

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Elements of Good Study Design

- 'Good' Definition: data output
  - High validity, fidelity, replicability
- Achieved by study design that minimizes bias, maximizes rigor
  - Powering, blinding, randomization, use of appropriate controls, training, statistics, record-keeping, use of positive controls and comparators, pre-specification (endpoints, comparisons made, etc)

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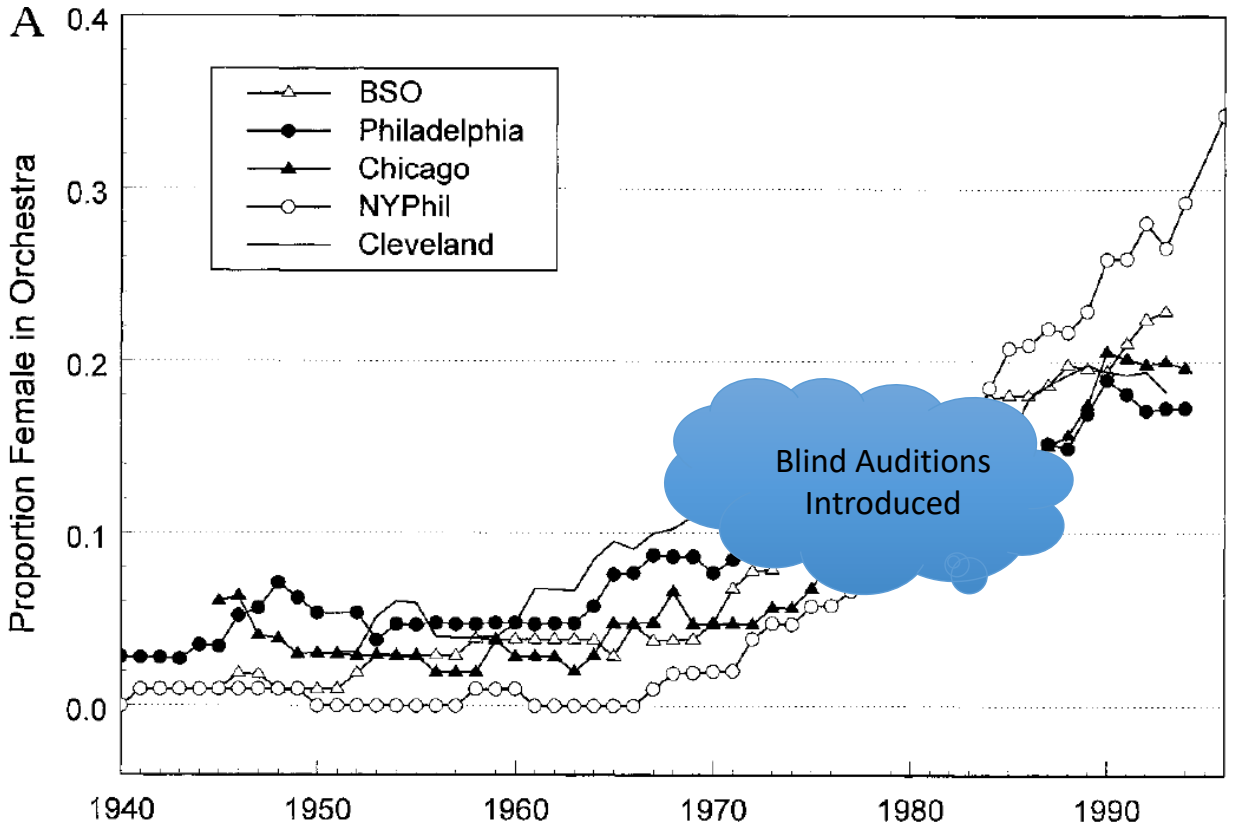
WHY BLIND?

www.curt-rice.com

Pervasive Attitude Prior to 1970: There is no place for women in orchestra



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21st C

Goldin & Rouse (2000) American Economic Review 90: 715

Blinding

Overestimation of treatment effect size
Increased false positive rate

META-RESEARCH ARTICLE

A qualitative study of the barriers to using blinding in in vivo experiments and suggestions for improvement

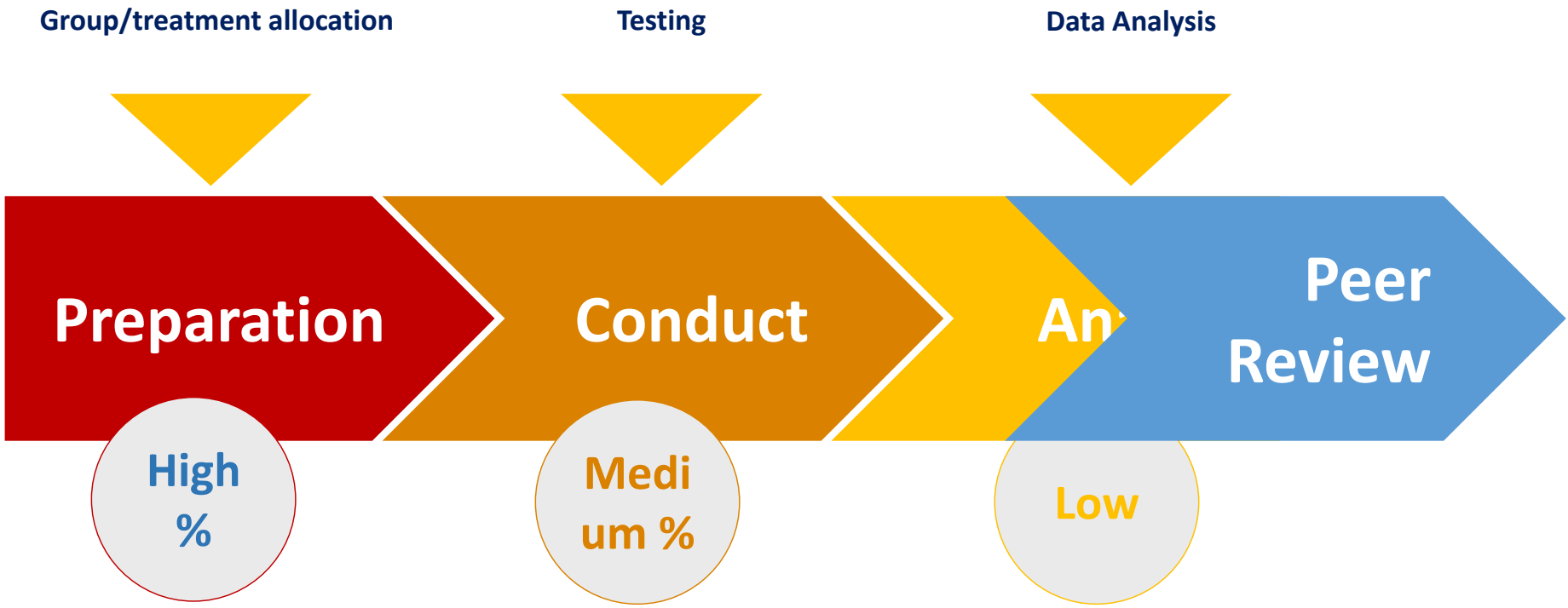
Natasha A. Karp[1]*, Esther J. Pearl[2], Emma J. Stringer[3], Chris Barkus[2], Jane Coates Ulrichsen[4], Nathalie Percie du Sert[2]

1 Data Sciences & Quantitative Biology, Discovery Sciences, R&D, AstraZeneca, Cambridge, United Kingdom, 2 NC3Rs, London, United Kingdom, 3 Biomedical Services Unit, University of Birmingham, Birmingham, United Kingdom, 4 Early Oncology, AstraZeneca, Cambridge, United Kingdom

•https://doi.org/10.1371/journal.pbio.3001873

- Far less uptake than other design principals
  - Resource, culture, practical constraints as primary reasons
  - False belief that it doesn't improve studies
- Reported in only 12% of in vivo papers
- Of these, few provide details on methods of blinding, including which parts of experiment are blinded

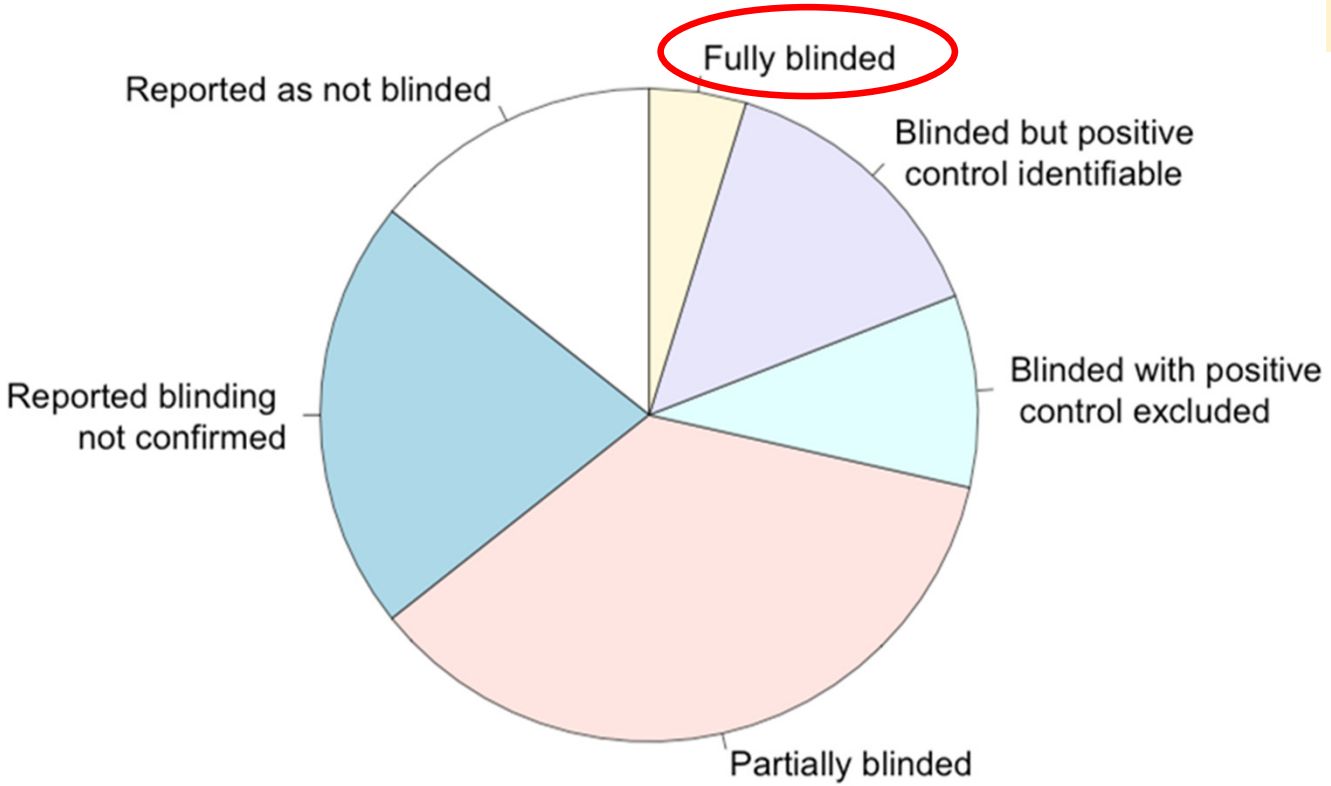
Blinding application by experimental stage



One should expect uniform application, but in principle, not so much

PAASP Survey on Blinding

84 experiments
12 academic labs
7 CROs
4 industry labs



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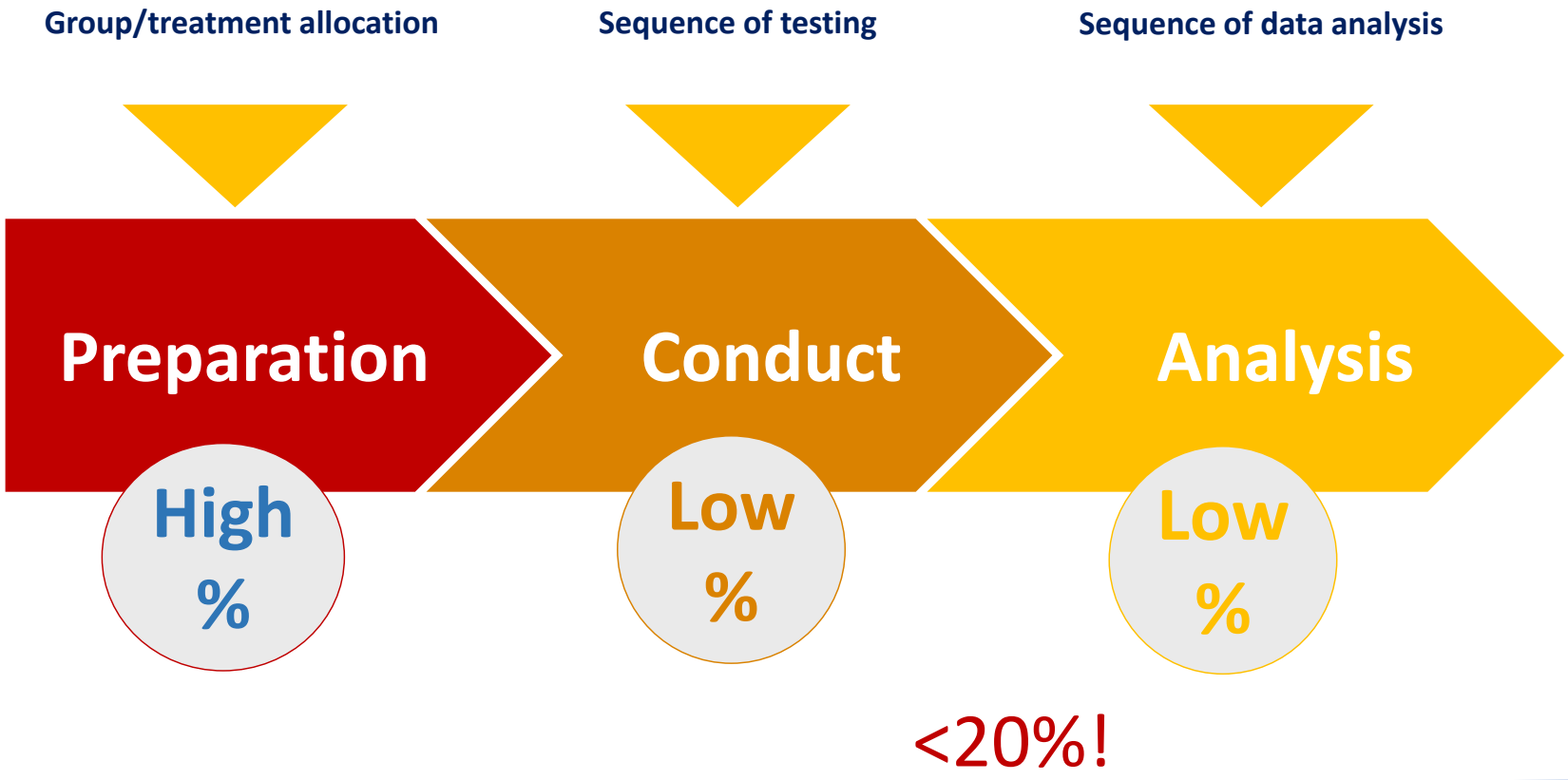
PAASP Survey on use of randomization

- 30 CROs performing **GLP safety studies** contacted
  - 73% responded (22/30)
  - 45% (10/22) reported applying methods of randomization in all studies
  - 42% (5/12) will apply randomization only when requested by sponsors
  - 45% (10/22) will use a specialized tool to generate randomization sequence (although many, many freely available)

Procedures used for assignment of subjects to treatment groups (multiple answers)

Method	Used	Remark
Simple alternation	64% (9/14)	Not randomization
Matching	71% (10/14)	Not randomization
Latin square	29% (4/14)	Pseudo-randomization
Block design or	36% (5/14)	Ca-ching!
Simple randomization	7% (1/14)	Risk of unbalanced allocation w/ low N

Randomization application by experimental stage



<20%!

What if randomization is not done properly?

- You have to decide whether:
  - Can blinding still be applied?
  - Can the impact of stratification variables still be evaluated?
  - Is statistical power reduced and sample sizes need to be increased?
  - Is the statistical method chosen can still be applied?
- You have to be transparent about it

Pre-Specification of Endpoints

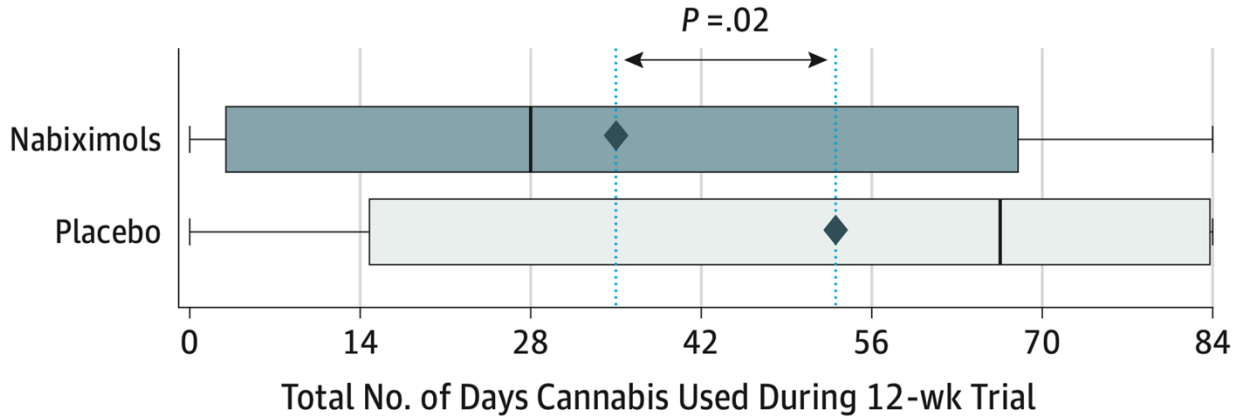
JAMA Internal Medicine | Original Investigation

Nabiximols for the Treatment of Cannabis Dependence
A Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE This study demonstrates that cannabinoid agonist treatment, in this case using nabiximols, in combination with psychosocial interventions is a safe approach for reducing cannabis use among individuals with cannabis dependence who are seeking treatment.

JAMA Intern Med. 2019;179(9):1242-1253

- **Primary End Point reported in the paper**:
  Frequency of cannabis use
  (Self-reported number of days using illicit cannabis during the 12-week period)



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  Reported

- **Primary Outcomes specified in the trial registry and protocol**

  A: Unsanctioned cannabis use will be quantified as 4-weekly point prevalence abstinence during the 12-week maintenance phase … *Unsanctioned cannabis use will also be reported as mean days used,* and percentage of positive urine drug screens.

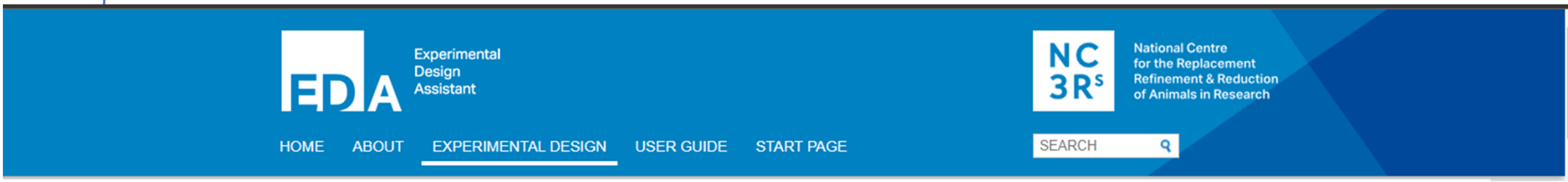
  B: Treatment retention (days in protocol treatment)

  Not reported
  Reported
  Not reported
  Reported
  (no treatment effect)

Summary

- We can do a much better job of minimizing bias in our studies
- Blinding and randomizing across all study stages is an initial hassle, but vital in generating repeatable study outcomes
  - GSK and AZ have mandated and enforced rigor for all internal and external in-vivo studies, which has facilitated application in all study types
    - 2024 publication on the ‘what and how’

Free-to-use resources for testing rigor



equator network

Enhancing the QUAlity and Transparency Of health Research

NIH
National Institutes of Health

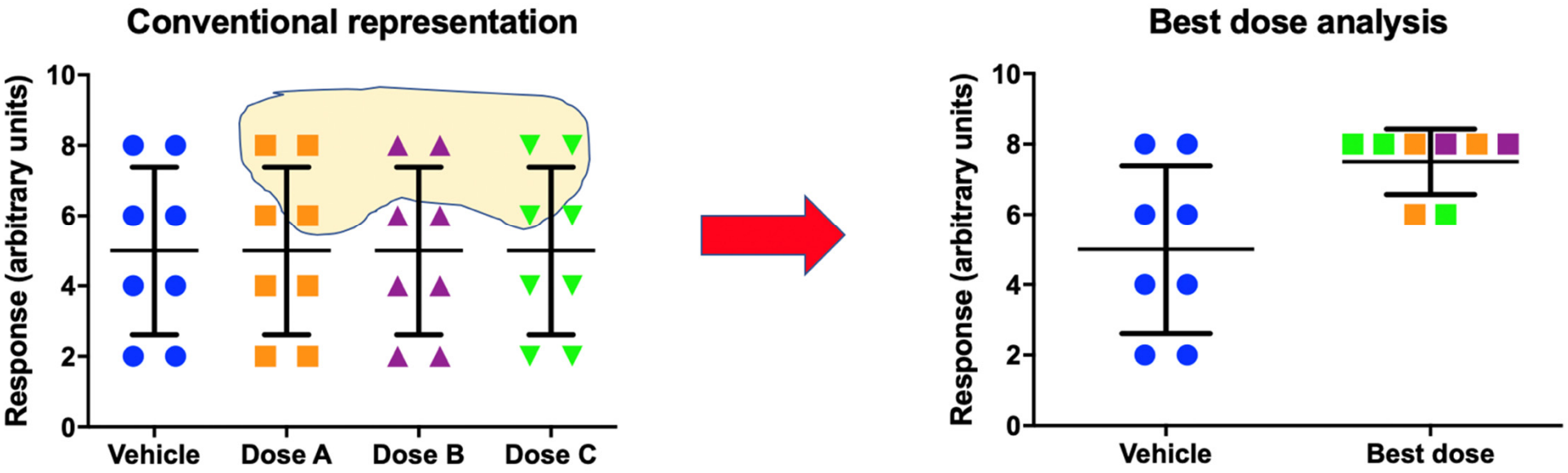
Extras

Heads I win, tails you lose

Scenario	Positive control worked	Positive control failed
My drug worked		???
My drug failed		

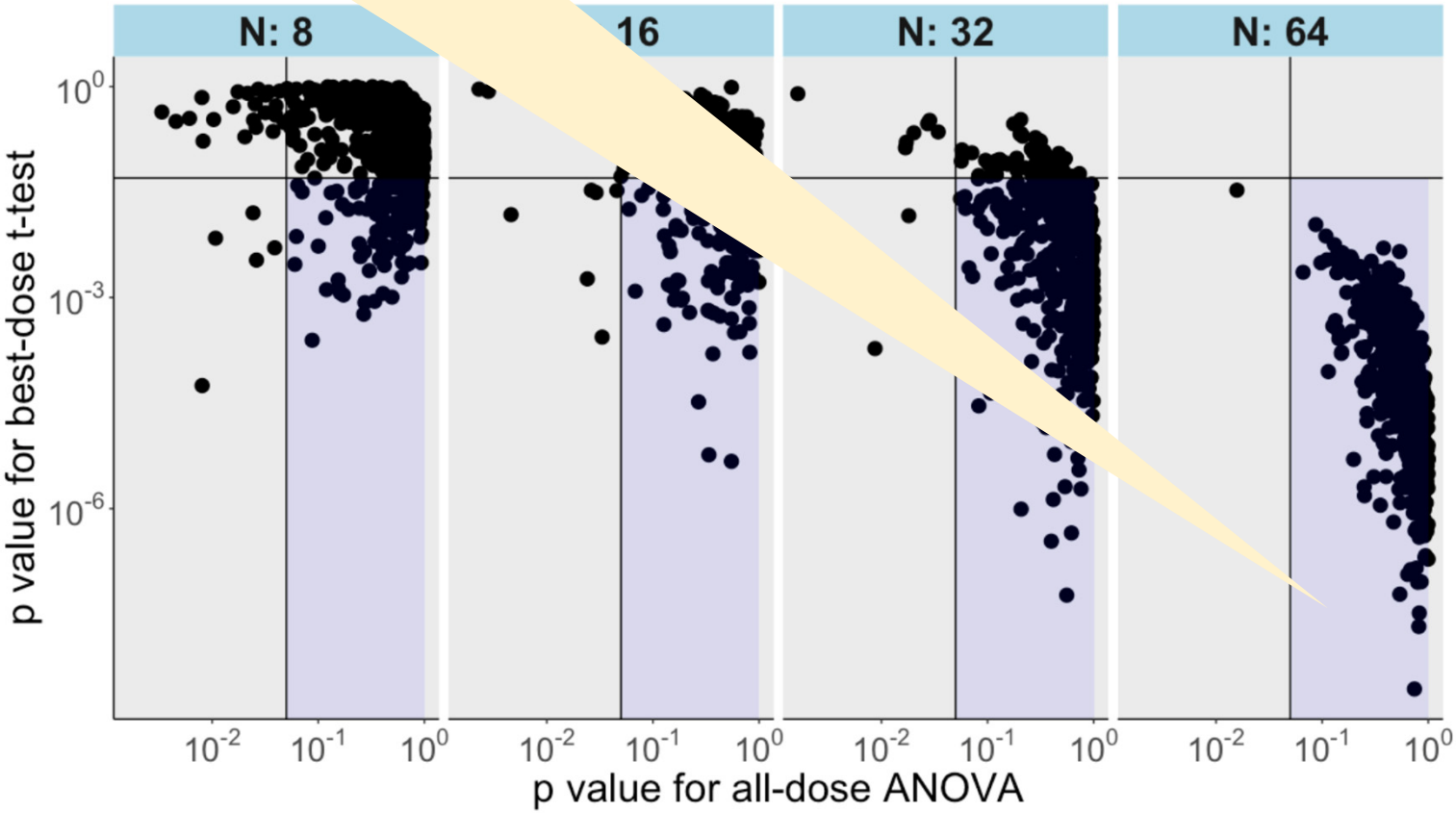
If the use of study outcomes for decision-making is not pre-specified, studies can be designed to bias the interpretation in a favored direction

Heads I win, tails you lose



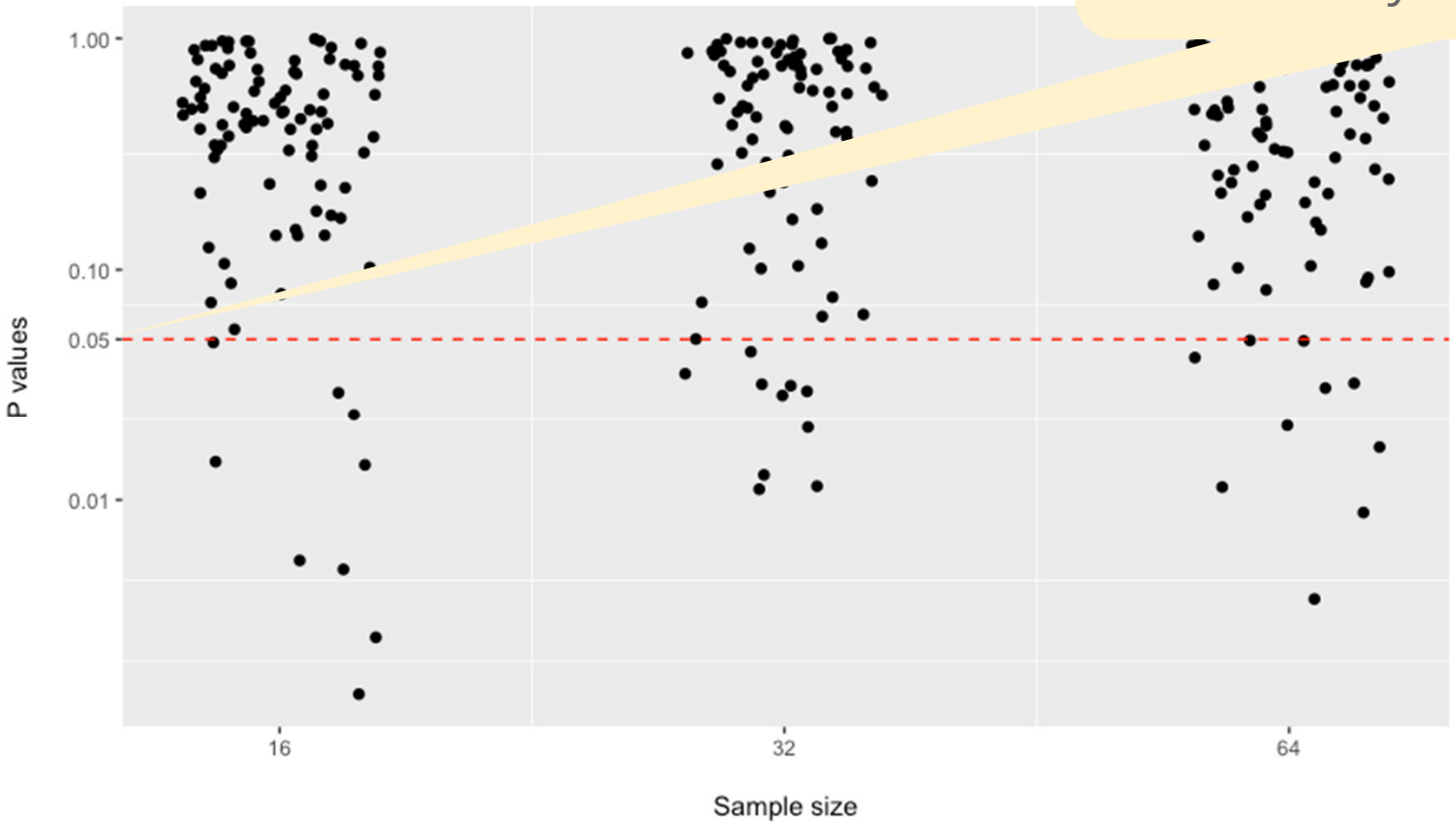
With the sample size large enough, best-dose analysis can turn almost any negative study into positive

you lose



Heads I win, tails you lo

Adding a non-prespecified analysis of sex factor can turn a negative study into „positive“



Two samples drawn from the same normally distributed population and compared by t-test (100 iterations)

Be alerted to false discovery rate!

- Effect size tends to be over-estimated in:
  - under-powered studies
  - studies with low internal validity (i.e. studies with uncontrolled bias)
  - studies reporting „unexpected“ results

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Pre-specification …

… does not change the data

… builds confidence in data, improves validity

Types of Research Bias:

1. Selection Bias
2. Measurement Bias
3. Recall Bias
4. Publication Bias
5. Confirmation Bias
6. Reporting Bias
7. Experimenter Bias
8. Sampling Bias
9. Analysis Selection Bias
10. Procedural Bias