



14th Transgenic Technology Meeting, TT2017

Work to be Done vs. Animal Welfare

Boris Jerchow, PhD

MY EXPERIENCE

Basic

I just want to work, but
rules and paperwork
won't let me!

ector



SAFETY ASSESSMENTS

INTERNAL R

REGUL

SAFETY

OCCUPATION

GENETIC

SAFETY

ANIMAL PROTOCOLS

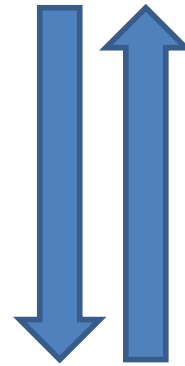
HYGIENE MANAGEMENT

GUIDE"

ANIMAL WELFARE REGULATIONS = BURDEN?

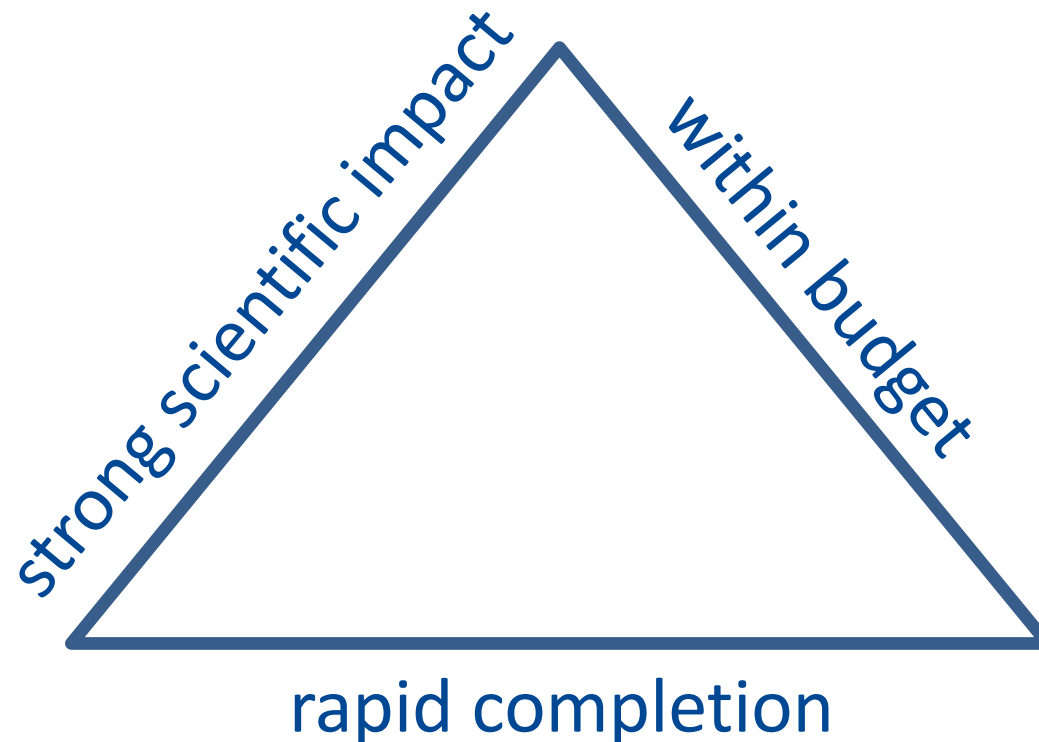


Better Animal Welfare



Better Science

WHAT MAKES A GOOD EXPERIMENT?



the project management triangle, the triple constraint, or the iron triangle;
competing constraints: resources (cost), scope (quality), and schedule (time).

WHAT MAKES GOOD ANIMAL WELFARE?

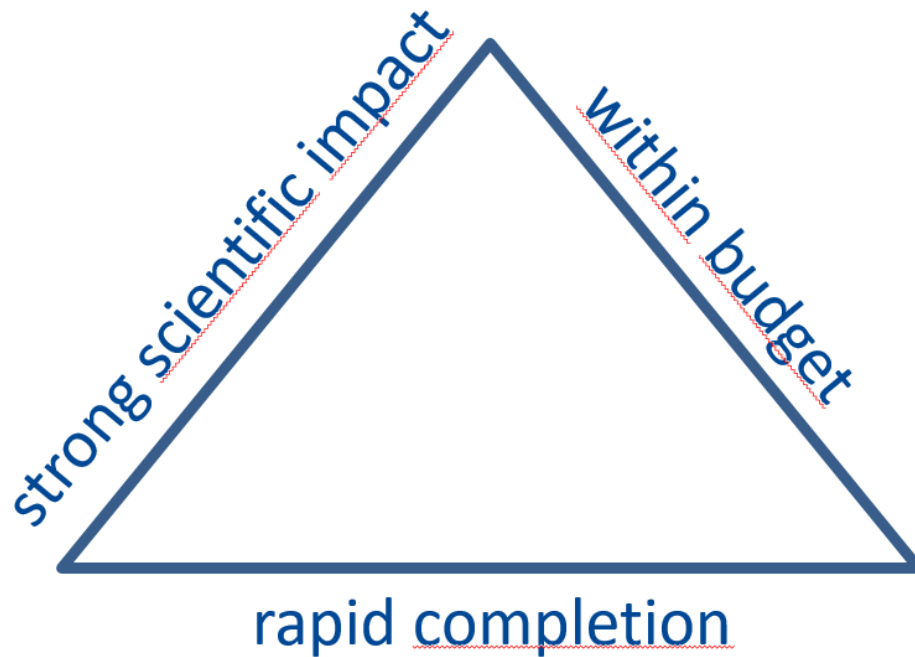
Ethically sound = morally acceptable

humane

„The Principles of Humane Experimental Technique“
William M.S. Russell and Rex L. Burch (1959)

3Rs + Reproducibility

HOW DO THEY GO TOGETHER?

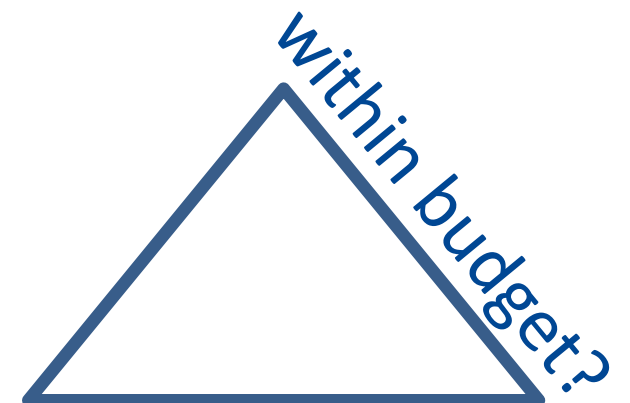


3Rs+R

Let's go through all 4Rs

REPLACEMENT

- Animal studies are expensive

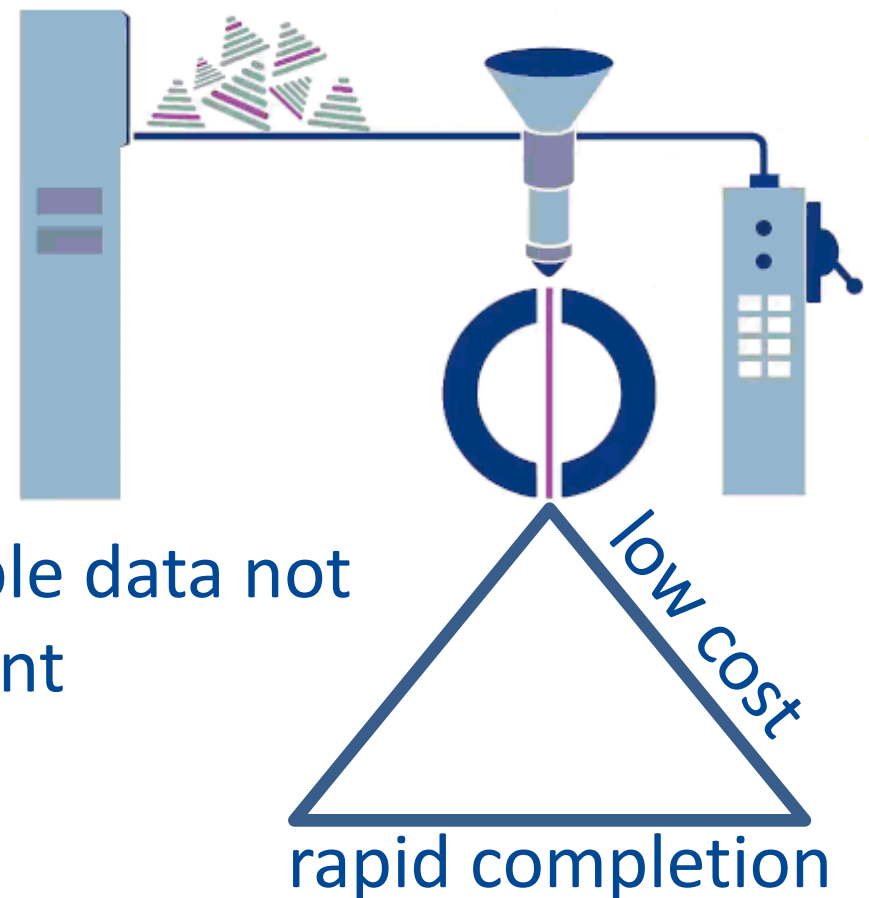


REPLACEMENT

- Literature searches mostly fall short of their potential scope

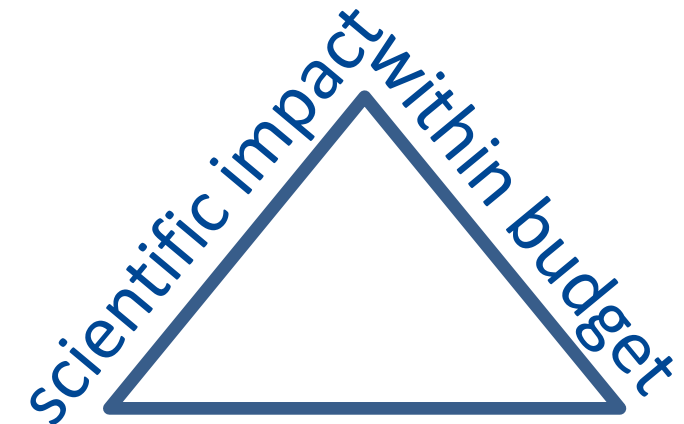
- not systematic
- not inclusive
- not exhaustive

- Risk: studies redone, available data not sufficiently taken into account

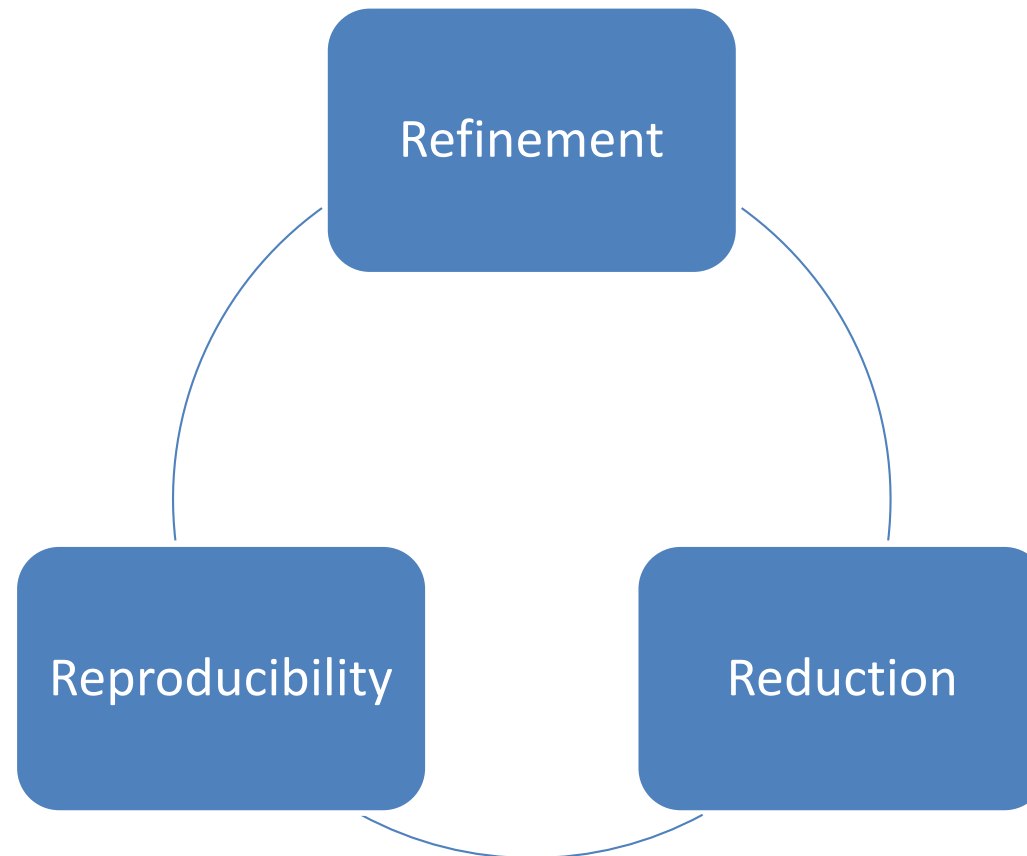


„REPLACEMENT“

- Replace the model system
 - in utero electroporation
 - transient transfection
 - different animal model



THE OTHER R'S



GO HAND IN HAND

REPRODUCIBILITY

Not a classic „R“

- if animal experiments are not appropriately designed, conducted, and analyzed, the results produced are unlikely to be reliable and the animals have in effect been wasted

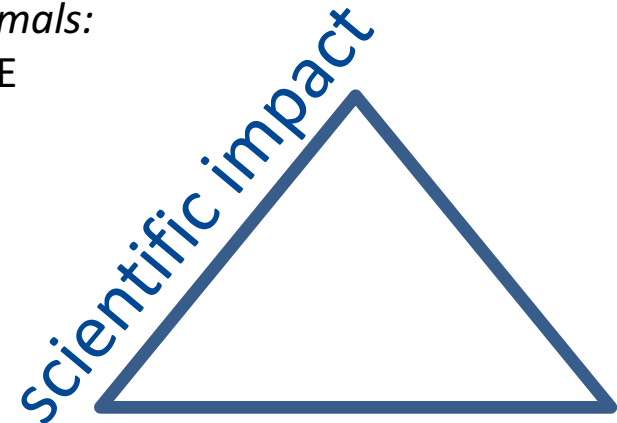
(de Vries RB, Wever KE, Avey MT, Stephens ML, Sena ES, Leenaars M. The usefulness of systematic reviews of animal experiments for the design of preclinical and clinical studies. ILAR J. 2014;55(3):427-37.)

- PREPARE guidelines

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence, norecopa.no/PREPARE

- ARRIVE guidelines

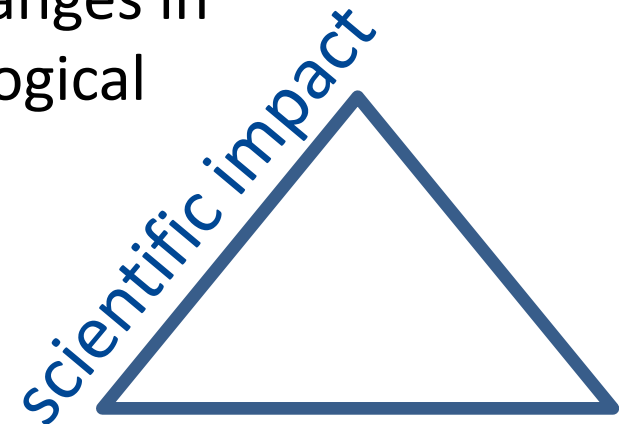
Animal Research: Reporting of In Vivo Experiments
nc3rs.org.uk/arrive-guidelines



REPRODUCIBILITY

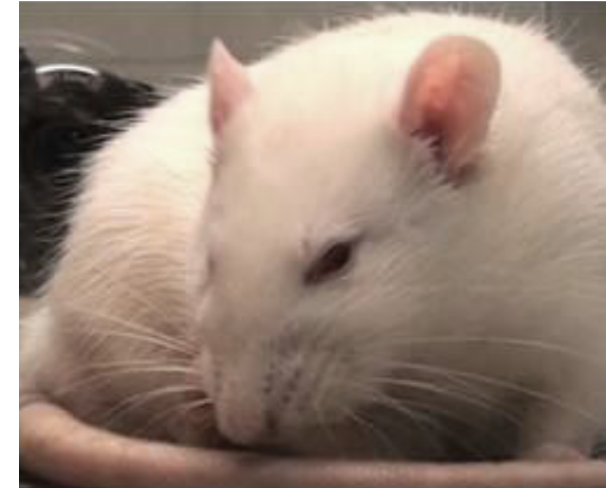
- **Confounding factors**
 - stress, anxiety
 - acute and chronic stress can lead to changes in behavior and in physiology
 - behavioral changes can include changes in food consumption and physical activity
 - physiological changes can include changes in sympathetic activation and immunological function
 - chronic stress not readily detectable

Refinement

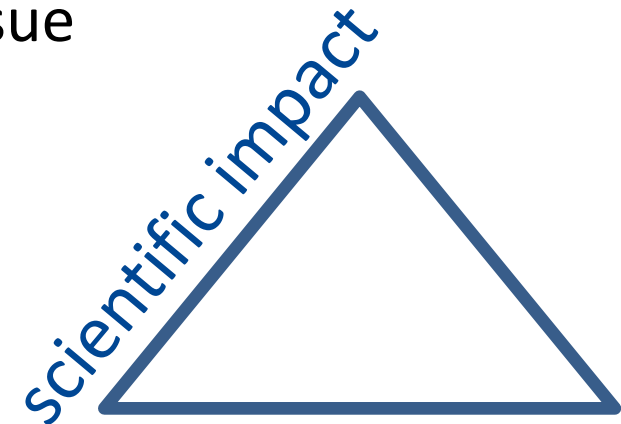


REPRODUCIBILITY

- Confounding factors
 - pain, distress
 - induce acute and chronic stress
 - pain management with side effects, reproducible, controllable
 - multimodal regimen
 - “we have always done it this way” issue

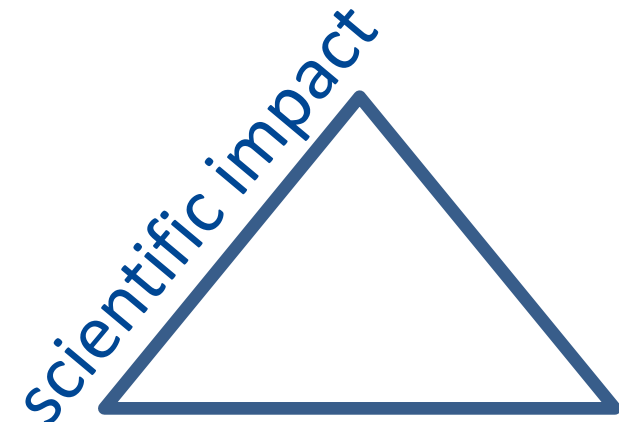
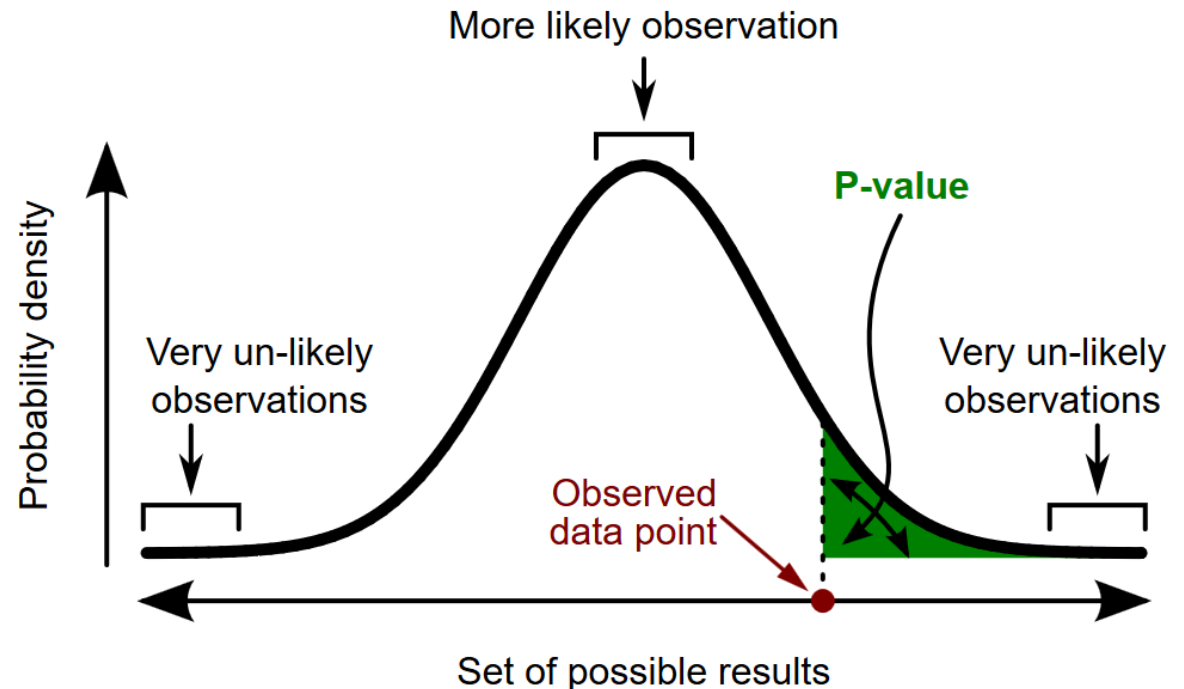


Refinement



REPRODUCIBILITY

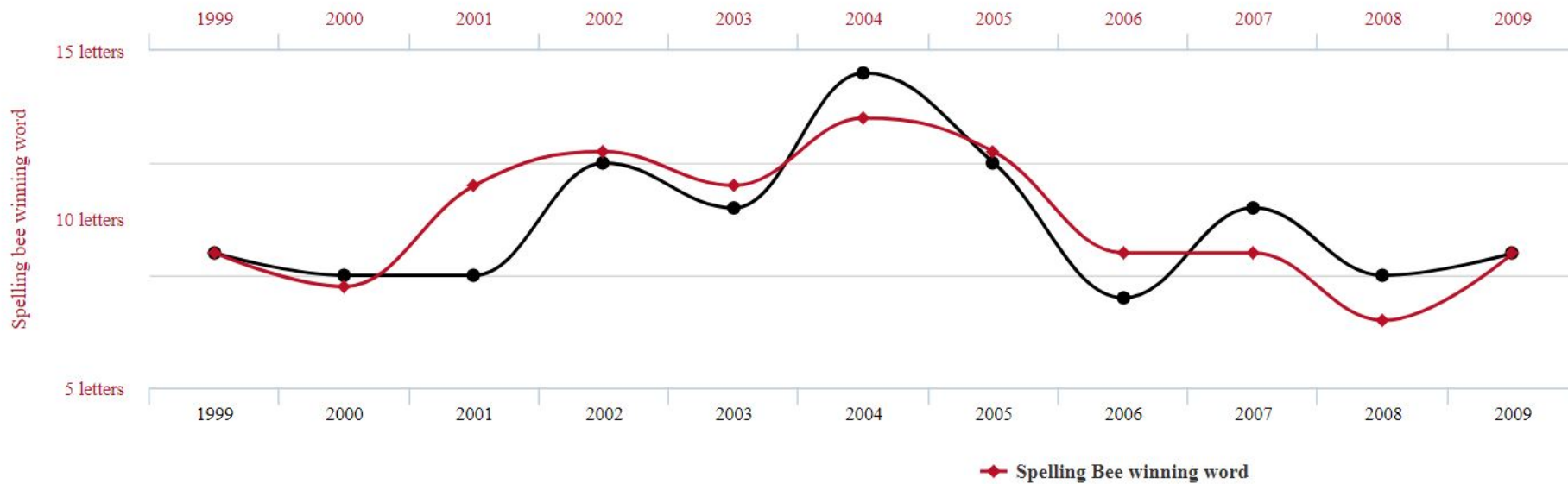
- Statistical planning
 - Data available for relevant difference, standard deviation, ...
 - Pilot study
- Avoid bias
 - Randomization
 - Blinding
 - Share raw data
 - Publish negative results



(Reduction)

CORRELATION OF DATA

Letters in winning word of Scripps National Spelling Bee correlates with

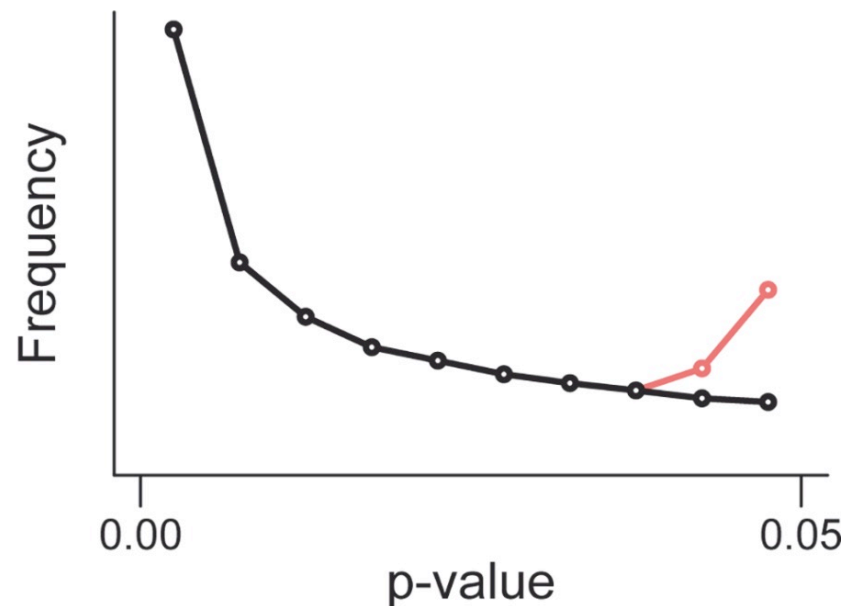


CORRELATION OF DATA

- Looking for patterns in data is legitimate.
- Applying a statistical test of significance, or hypothesis test, to the same data that a pattern emerges from is wrong.
- When enough hypotheses are tested, it is virtually certain that some will be statistically significant but misleading
- 5% of randomly chosen hypotheses turn out to be significant at the 5% level by chance alone

P-HACKING

- Meta analyses show significantly increased proportion of studies with p-values just below 5%



Head ML, Holman L, Lanfear R, Kahn AT, Jennions MD (2015) The Extent and Consequences of P-Hacking in Science. PLoS Biol 13(3): e1002106.doi:10.1371/journal.pbio.1002106

- Studies that yield significant results are more readily accepted by journals: p-hacking incentivized.

META-RESEARCH ARTICLE

Authorization of Animal Experiments Is Based on Confidence Rather than Evidence of Scientific Rigor

2016

Lucile Voet¹ Thomas S. Reichlin¹ Christina Nathues² Hanno Würbel^{1*}

1 ... may compromise scientific validity and induce unnecessary harm to animals caused by inconclusive research.

University of Bern, Liebefeld, Switzerland

m,

Why animal research needs to improve

RESEARCH ARTICLE

2011

Many of the studies that use animals are flawed and too prone to bias to be trusted.

p -Curve and p -Hacking in Observational Research

2016

Stephan B. Bruns¹, John P. A. Ioannidis^{2*}

1 Meta-Research in Economics Group, University of Kassel, Kassel, Germany, 2 Departments of Medicine, Health Research and Policy, and Statistics, and Meta-Research Innovation Center at Stanford, Stanford University, Stanford, United States of America



IS THERE A REPRODUCIBILITY CRISIS?



Nature, 25 May 2016

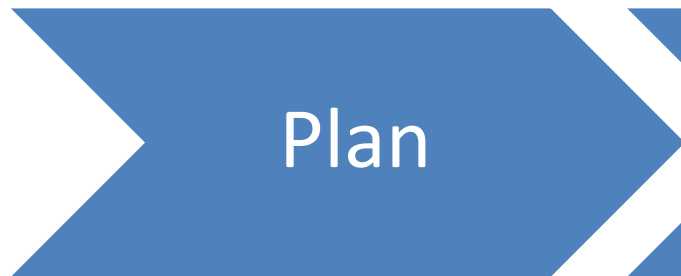
LACK OF SCIENTIFIC VALIDITY INDUCES UNNECESSARY HARM IN ANIMALS

- Generation of new hypotheses
- Development of new research directions
- policy made based on the results

A CULTURE OF CARE

3Rs

PREPARE guidelines



norecopa.no/PREPARE

Do &
Document

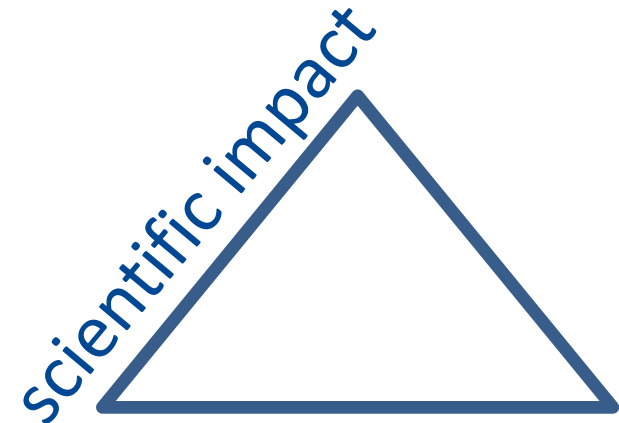
Reproducibility

ARRIVE guidelines



NC3Rs.org.uk/arrive-guidelines

- Replace
- Refine
- Reduce





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