University of Zurich[UZH]

Institute for Biomedical Ethics and History of Medicine

Challenges in Project Evaluation in Animal Research

The Concepts of Necessity, Suitability and Proportionality

Matthias Eggel

Animal Research requires Authorization

DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 September 2010

on the protection of animals used for scientific purposes

(Text with EEA relevance)

Authorization according to EU Directive 2010/63

Sentient animals have a moral status. Harming such a creature has to be justified.

⇒ **genuine conflict between the legally protected interests of animals not to suffer and specific legal interests of society.**

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To receive authorization you have to demonstrate (among other requirements) that the planned experiment (and the use of animals) is

a) **Necessary** (i.e. pain, harm and suffering reduced to the minimum (3R)

b) **Suitable** (i.e. scientific quality of experiment)

c) **Proportional/appropriate** (i.e. harm and suffering is outweighed by expected benefits)

Step 1: Necessity

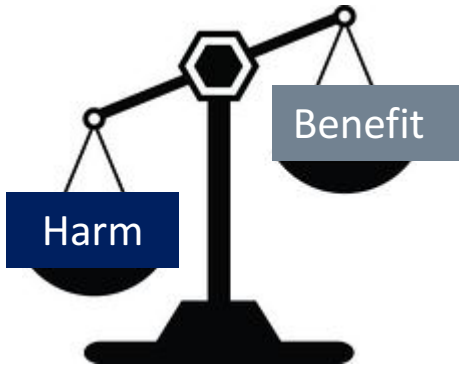
Compliance with the 3Rs (Art. 38 EU Directive)

- Replacement (no non-animal alternatives available)
- Reduction (adequate number of animals)
- Refinement (minimal harm)

Moral obligation to minimise animal suffering

„Ethical“ Limitations of the 3Rs principle:

- 3R **crucial** component for the evaluation of the harm side and **effective** in **avoiding unnecessary** animal **suffering**
- 3R and “**animal welfare**” is only a necessary but not a sufficient condition for ethically justifiable research“



Step 2: Suitability (or scientific quality)

The project ist justified from a scientific or educational point of view (Art. 38 EU Directive.

The Suitability depends on

- **Reproducibility** and **Generalizability** (iV, cV, eV))
- Criteria of **good scientific practice**, e.g. Randomization, blinding, sample size calculation, statistical analysis, etc.

Moral obligation to adhere to good scientific practice and high scientific standards

Swiss academies of the arts and sciences. Weighing of interests for proposed anmal experiments, 2017

Do we need an equivalent to the 3Rs on the benefit side in project evaluation?

Analysis of animal research applications in Switzerland:

Important information is missing on Good Scientific practice, e.g. measures against "bias", randomization, blinding, sample size calculation etc.

Evaluation of scientific rigor?

META-RESEARCH ARTICLE

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

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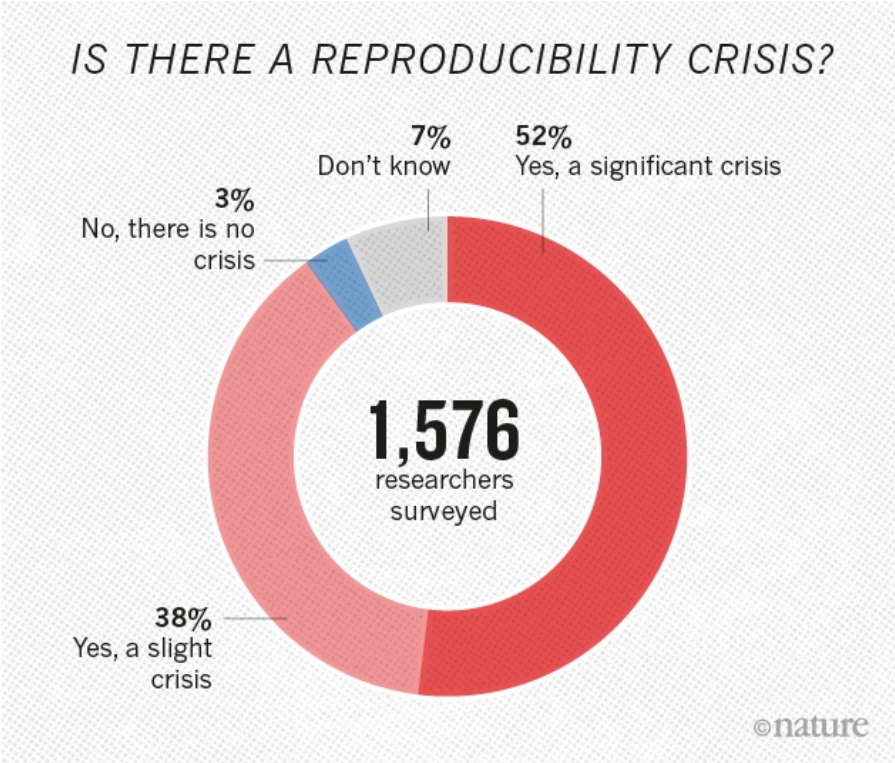


Are scientific standards sufficiently high?

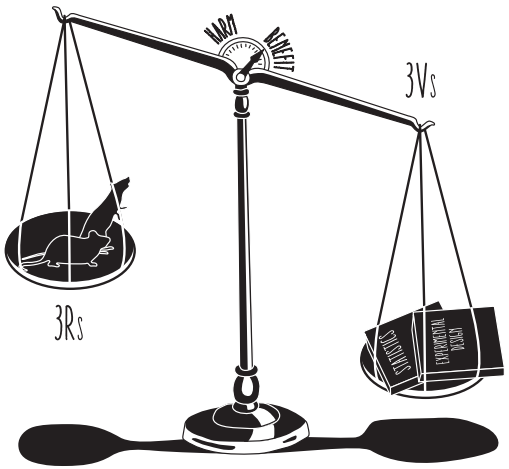
If not, should this not be spotted at the level of project evaluation?

Could Project Evaluation increase scientific quality?

Analogously to the 3Rs, the 3Vs could be implemented into project evaluation:

- Internal validity (iV)
- Construct validity (cV)
- External validity (eV)

DFG, Swiss Federal Food Safety and Veterinary Office



Hanno Würbel, 2017

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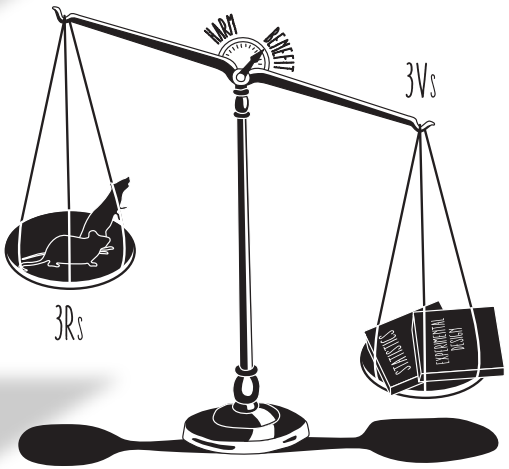
Similar concepts:

- Arrive: Animal Research: Reporting of In Vivo Experiments
- Prepare: Planning Research and Experimental Procedures on Animals: Recommendations for Excellence
- 6R by Strech/Dirnagl (Robustness, Reporting, Registration)



Hanno Würbel, 2017

Step 3: Proportionality

The evaluation of the ethical permissibility in the form of a Harm-Benefit-Analysis (HBA)

Requirements:

„Necessity“ and „Suitability“ have been evaluated (Instrumental Essentiality)

Rationale:

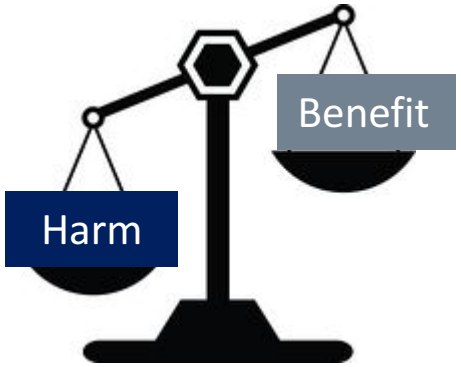
- A „Necessary“ and „suitable“ project may still be disproportional
- Evaluation of „goal-related essentiality“ represents a „Paradigm Shift“

Moral obligation that benefits outweigh harm

The Concept of Proportionality

Article 38 (2) d Directive 2010/63/EU: Project Evaluation

[…] a **harm-benefit analysis** of the project, to assess whether the **harm** to the animals in terms of suffering, pain and distress is **justified** by the **expected outcome taking into account ethical considerations**, and may ultimately **benefit human beings, animals or the environment**;



Weighing of harms and benefits (by taking ethical considerations into account)

What is the Role of Ethics in project evaluation?

The "ethical" foundation of EU Directive and the rationale of the HBA are based on:

- **=> Utilitarian Philosophy**
  - Weighing of different legally protected interests is allowed
  - Whether an action is morally correct depends on the consequences of an action
  - The action that produces the greatest benefit to the greatest number of individuals is to be preferred

Whatever "Ethics" means in this context, it has to comply with the applicable law

Hierarchy of benefits?

- Ethical evaluation reduced to evaluation of different kinds of “benefits” within a utilitarian and pathocentric framework and weighing them against harm?
- Most publications on the HBA prioritize **societal benefit** (e.g. new drugs, treatments, technologies) over **epistemic benefit** (i.e. Knowledge)

Who will benefit? When will benefit be realized? How will humans, animals and the environment benefit? Likelihood of generating societal benefit?

Herwig Grimm, Ethics within legal limits, 2013

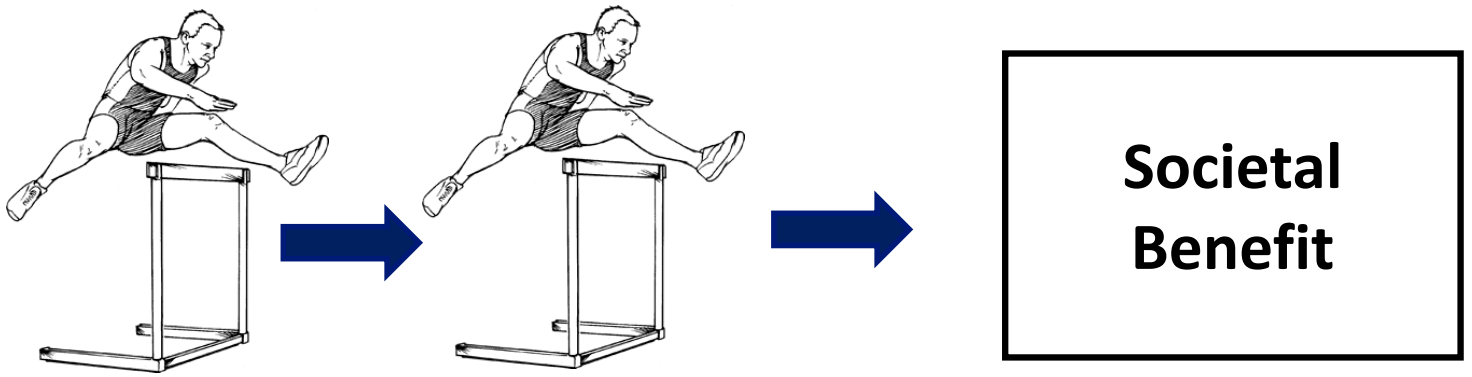
Is it possible to evaluate societal benefits in prospective project evaluation?

Uncertainty regarding outcome

- Assumption of positive outcome
- However, you never **know beforehand the *outcome* of a project**
- Only **if I knew the *outcome* beforehand** (e.g. the hypothesis being verified and not falsified) a **prospective *benefit* assessment becomes plausible and the Experiment illegal**
- **Inherent uncertainty** in (hypothesis-driven) research

Uncertainty regarding translatability

- **Translatability** is a **precondition** for the generation of societal ***benefit***
- A good model provides relevant data for the target species
- Ideally the model is almost identical to the target species
- However, there will **always** be **differences** and thus there will **always** be **uncertainty** regarding translatability



Societal Benefit as direct consequence of a research project?

Project Idea -> Experiments -> **Knowledge Gain ->** clinical Trials-> Patient-> increase in patient health (= societal **benefit)**

- Development of the anti-cancer drug **Ipilimumab** was based on **433 publications** over **46 years**
- Development of the cystic fibrosis drug **Ivacaftor** was based on **355** publications over **47 years**
- Only counting the most influential contributions while omitting smaller contributions

Williams, S.R.; Lotia, S.; Holloway, A.K.; Pico, A.R. From scientific discovery to cures: Bright stars within a galaxy. *Cell* **2015**, *163*, 21–23.

What can we reasonably expect from research (at the level of project evaluation)?

- Good science produces **valid data** (knowledge), not societal benefit
- **Lack of direct societal benefit does not** indicate bad science

- Practical (maybe also legal and ethical) reasons against hierarchy of benefits (at the level of project evaluation)

What can we reasonably expect from research (at the level of project evaluation)?

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Focus on criteria that have proven useful in the scientific peer-review process (e.g. SNF, DFG)

– expected gain of knowledge;
– scientific importance of the project for research field(s);
– Originality
– Scientific Quality, etc.

Necessity, Suitability and Proportionality

The three pillars of “ethically justified“ animal research

Scientific quality

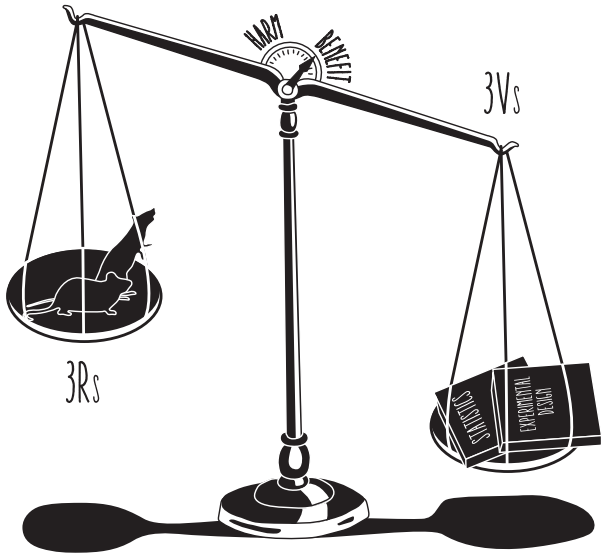
Suitability (3V)

Necessity (3R)

Proportionality (HBA)

Animal Welfare

„Ethical Value“ of expected knowledge gain



Würbel, 2017

Kim Caesar/Springer Nature

Summary:

- An assessment of suitability is a necessary precondition for maximizing epistemic benefit
- 3Rs and the minimization of suffering are necessary preconditions for ethical animal research
- The 3R and 3V are necessary but not sufficient preconditions for ethically permissible animal research and a meaningful HBA

- A hierarchy between different benefits (at the level of project evaluation) can be challenged from a scientific, practical, legal and ethical point of view

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Thank you very much for your attention

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