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Does Animal Research Benefit Humans? The Need for Evidence

SAFER MEDICINES TRUST

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Overview

A. Introduction—how to answer this question

B. Quality of animal studies (internal validity)

C. Reporting of animal studies

D. Quality of animal studies (external validity)

E. Translation of animal studies

F. Implications

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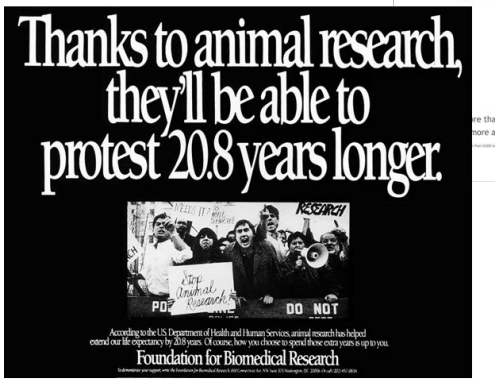
How Can We Answer This Question?

How Can We Answer This Question?

"Sacred cow"—an idea, custom or institution held to be above criticism

Photo retrieved February 3, 2020, from https://enchantingnagchampa.tumblr.com/post/69992888735

Examples



Images retrieved February 2, 2020, from Foundation for Biomedical Research. (n.d.). http://resource.nlm.nih.gov/101438472; PR Newswire. (2011). https://www.prnewswire.com/news-releases/new-billboards-ask-the-public-to-decide-who-they-would-rather-see-live-a-rat-or-a-little-girl-119271574.html; Foundation for Biomedical Research. (n.d.). https://fbresearch.org/mice-911-poster/; Understanding Animal Research. (2011, September). http://www.understandinganimalresearch.org.uk/media-library/download/document/animal-research-has-benefits-for-us-all-and-animals-too.pdf

Anecdotal Evidence

- The need for animal research is “self-evident” (Page, 2003)
- “Animal experimentation is a valuable research method which has proved itself over time.” House of Lords Report of Select Committee on Animals in Scientific Procedures, 2002
- “Virtually every medical achievement of the last century has depended directly or indirectly on research with animals.” Statement of the Royal Society's Position on the Use of Animals in Research, 2002 (This statement was endorsed by US Public Health Service, UK Dept of Health and over 500 academics who signed a public petition supporting the statement in 2005)

Sources: Page, K. (2003). Cambridge primate research centre comes under scrutiny. *The Lancet Neurology, 2*(3), 136. https://doi.org/10.1016/s1474-4422(03)00335-1; House of Lords. (2002). Chapter 4. The efficacy of animal experiments. In *Select Committee on Animals in Scientific Procedures*. Retrieved February 2, 2020, from https://publications.parliament.uk/pa/ld200102/ldselect/ldanimal/150/15007.htm; Royal Society. (2002). Statement of the Royal Society’s position on the use of animals in research. London: Royal Society.

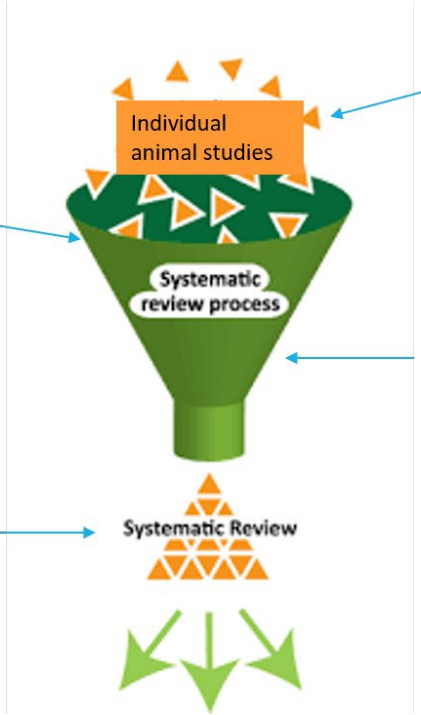
Evidence Hierarchy

Hierarchy developed and refined over many years by Centre for Evidence-Based Medicine at the University of Oxford

Systematic Reviews

Identify all relevant published and unpublished evidence in field of interest (strict inclusion/ exclusion criteria)

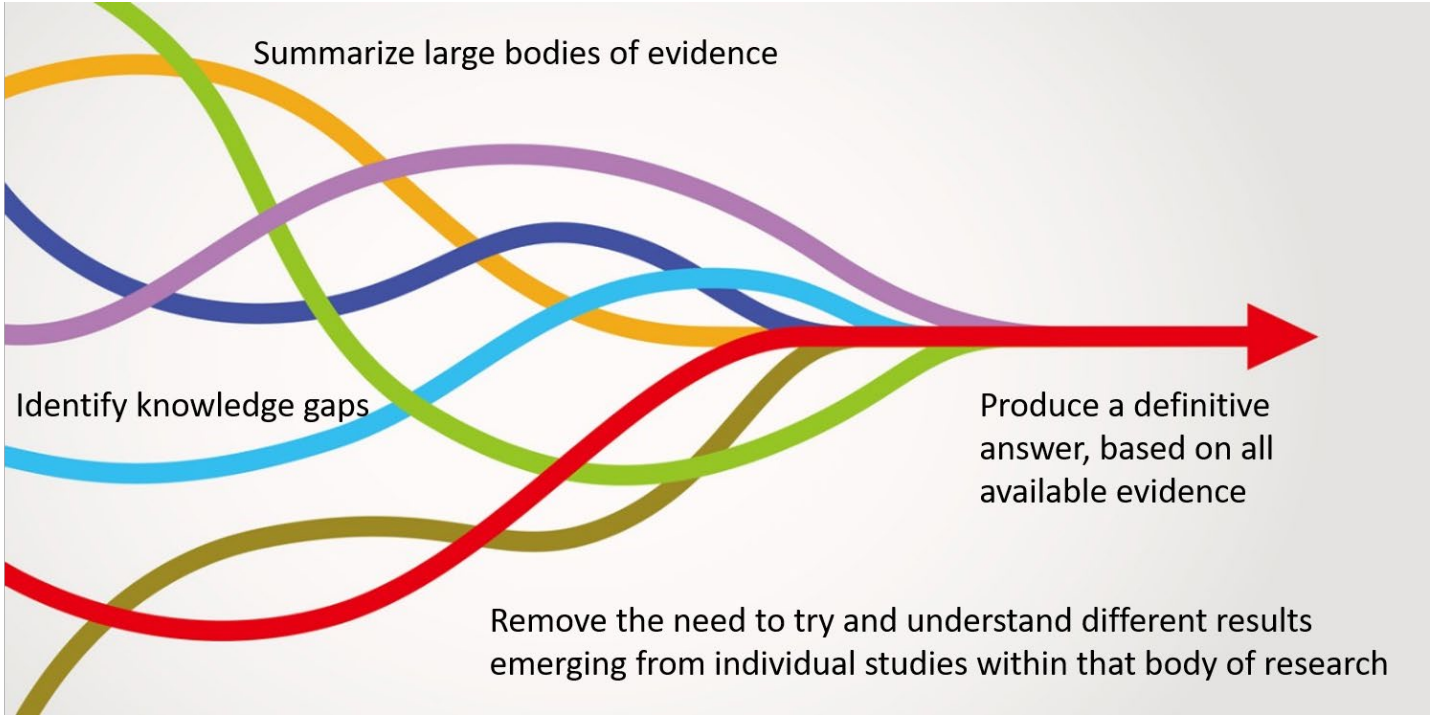
Assess quality of each individual study



Synthesise findings from individual studies (may include statistical techniques)

Interpret the findings, present an impartial summary with due consideration of any flaws in the evidence

What Can Systematic Reviews Do?



Sandercock and Roberts, *The Lancet*, 2002

responses towards a type I cytokine profile. *J Hepatol* 1999; **30:** 376–82.
14 Soriano V, Garcia-Samaniego J, Bravo R, et al. Interferon alfa for the treatment of chronic hepatitis C in patients with HIV. *Clin Infect Dis* 1996; **23:** 585–91.
15 Pesce A, Taillan B, Rosenthal E. et al. Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet* 1993; **341:** 1597.
16 Sulkowski MS, Moore RD, Mehta SAH, et al. Hepatitis C and progresion of HIV disease. *JAMA* 2002; **288:** 199–206.
17 Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection. *Lancet* 2000; **356:** 1800–05.

Systematic reviews of animal experiments

The axiom "before testing a new treatment in man, test it first in animals if possible" has been part of drug development for the past 50 years or so. Testing in animal models is believed to increase the chances of identifying drugs that are sufficiently promising to justify the effort and expense of further clinical development. However, a recent study of the process of testing a potential treatment for acute stroke suggests that the relation between animal experiments and clinical trials is not so straightforward.

I Horn and colleagues did two systematic reviews of the cost savings to the pharmaceutical companies concerned could also have been substantial.

A second important observation from the systematic review of animal experiments by Horn and colleagues[3] was that the methodological quality of the included animal studies was poor. It seems natural to insist that animal research should be subject to the same rigorous scientific methods used in clinical trials in human beings, yet such a point is sometimes viewed as controversial.[5] Methodological issues that have been found to be important in clinical trials, such as allocation concealment and blinding of outcome assessment,[5] were neglected in many of the animal experiments identified by Horn and colleagues. Systematic reviews of clinical trials were instrumental in helping methodologists to identify the determinants of bias in individual trials and to assess the impact of publication bias and other selection biases when making inferences on the totality of available evidence. Similarly, systematic reviews of the animal data have the potential to provide important insights into the determinants of bias in animal experiments.

Even a high-quality systematic review of high-quality animal experiments will only inform the conduct of human clinical trials if the results from animal experiments can be generalised to human beings. Again, research syntheses can help. Systematic reviews of animal experiments might include a range of different animal

Source: Sandercock, P., & Roberts, I. (2002). Systematic reviews of animal experiments. *The Lancet, 360*(9333), 586. https://doi.org/10.1016/s0140-6736(02)09812-4

Pound, et al., 2004

Where is the evidence that animal research benefits humans?

Pandora Pound, Shah Ebrahim, Peter Sandercock, Michael B Bracken, Ian Roberts on behalf of the Reviewing Animal Trials Systematically (RATS) Group

Much animal research into potential treatments for humans is wasted because it is poorly conducted and not evaluated through systematic reviews

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Peter Sandercock *professor*

continued over

BMJ 2004;328:514–7

Clinicians and the public often consider it axiomatic that animal research has contributed to the treatment of human disease, yet little evidence is available to support this view. Few methods exist for evaluating the clinical relevance or importance of basic animal research, and so its clinical (as distinct from scientific) contribution remains uncertain.[1] Anecdotal evidence or unsupported claims are often used as justification—for example, statements that the need for animal research is "self evident"[2] or that "Animal experimentation is a valuable research method which has proved itself over time."[3] Such statements are an inadequate form of evidence for such a controversial area of research. We argue that systematic reviews of existing and future research are needed.

Assessing animal research

Despite the lack of systematic evidence for its effectiveness, basic animal research in the United Kingdom receives much more funding than clinical research.[1 4 5] Given this, and because the public accepts animal research only on the assumption that it benefits humans,[6] the clinical relevance of animal experiments needs urgent clarification.

Several methods are available to evaluate animal research. These include historical analysis,[7] critiques of animal models,[8] investigations into the development of treatments,[5] surveys of clinicians' views,[9] and citation analyses.[10] However, perhaps the best way of producing evidence about the value of animal research is to conduct systematic reviews of animal studies and, where possible, compare the results of these with the results of the corresponding clinical trials. So what do studies that have done this show?

P+ *Details of the search strategy and references w1-w18 are on bmj.com*

Source: Pound, P., et al. (2004). Where is the evidence that animal research benefits humans? *BMJ, 328*(7438), 514–517. https://doi.org/10.1136/bmj.328.7438.514

Daily Telegraph 27/2

Experiments on animals should end, say doctors

By Roger Highfield
Science Editor

DOCTORS are calling for a moratorium on animal experiments until their contribution to health is properly evaluated.

Prof Ian Roberts, of the London School of Hygiene and Tropical Medicine, and other members of the "Reviewing Animal Trials Systematically Group" say there is "little evidence" that the research has contributed to treating human disease, adding that justification rests on "anecdotal evidence or unsupported claims".

Their call for the moratorium in today's *British Medical Journal* is rejected by the Royal Society, which says in a report that virtually every medical treatment developed in the past century rests in some way on vivisection.

It also comes as Lord Sainsbury, the science minister, is due to announce plans for a "virtual" national centre, consisting of a network of researchers, for The Three Rs – refinement, reduction and replacement of animal testing.

Prof Roberts said yesterday that research on animals had not seen the same revolution as in human clinical trials, where analyses are carried out on the totality of studies.

"You want a good overview of what all experiments show," he said. "When there have been systematic reviews of animal experiments, a lot have been very poorly designed, very small and contribute next to nothing.

"Whatever your views on vivisection, you should be against research that does not contribute any knowledge."

The doctors want a programme of research to review existing animal data, to find out if the animal research can be applied to humans, hoping to end the long debate between pro and antivivisectionists about their value in improving human health.

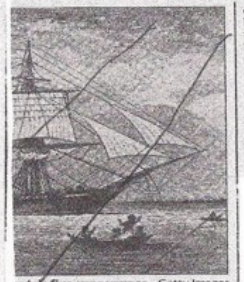
"Ideally, new animal studies should not be conducted until the best use has been made of existing animal studies and until their validity and generalisability to clinical medicine has been assessed," said Prof Roberts.

"We are only asking that the same standards as are applied in human research are applied to animal research. We would not tolerate haphazard potentially biased reviews of human research. So why should we tolerate this for animal research?"

The report was attacked by the Coalition for Medical Progress, an umbrella group of university scientists, research charities, patient groups, pharmaceutical companies and biotech firms to explain the need for animal research in biomedical studies.

Philip Connolly, the coalition director, said: "This paper misleads in implying there is little evidence to support research using animals."

He cited the Royal Society report that "quotes polio, kidney dialysis, stomach ulcers and cystic fibrosis as just four areas where the advances are clear. The evidence is in our hospital wards, clinics and homes with the effective medicines we take."



win's five-year voyage Getty Images

of animal research in the biotechnology industry agree that better use could be made of animal studies. Lord Sainsbury, UK science minister, is expected shortly to announce a national centre to develop alternatives to animal testing.

Society for Accountability of Animal Studies in Biomedical Research: www.s-a-b-r-e.org

writes in the British Medical Journal.

The call coincides with the publication by the Royal Society, Britain's national academy of science, of a guide backing animal research. "People have benefited immensely from scientific research involving animals, with virtually every medical achievement in the past century reliant on the use of animals in some way," it says.

But the Rats researchers, from various UK and US universities, say animal studies could make a much more valuable contribution if they were better designed and reviewed systematically in the way that clinical trials are. They identified six existing reviews of animal experiments in various fields including stroke, wound healing and heart disease. All highlighted serious deficiencies in methodology, the scientists say.

"We are only asking that the same standards as are applied in human research are applied to animal research," says Ian Roberts, professor at the London School of Hygiene and Tropical Medicine, one of the authors of Rats report. "We would not tolerate haphazard potentially biased reviews of human research so why should we tolerate this for animal research?"

Privately, some defenders

Guardian Science 27/2

Animal tests 'poorly conducted'

Much animal research is wasted because it is poorly conducted and not properly evaluated, doctors argue in today's British Medical Journal.

Trials for a drug to combat strokes and laser therapy to heal wounds were conducted with animal experiments while other research on humans went ahead despite evidence of harm in animal studies, they say.

"This suggests that the animal data were irrelevant, calling into question why the studies were done in the first place," they write.

The researchers, members of a group called Rats, Reviewing Animal Trials Systematically, call for systematic checks on all animal data to establish how far such information can be applied to humans.

Ian Roberts, one of authors, says: "We are only asking that the same standards as are applied in human research are applied to animal research." *James Meikle*

guardian.co.uk/animalrights

The Times 27/2

Tests 'no benefit'

Animal experiments are often poorly designed and contribute less than they might to the development of new medicines, according to a team writing in *British Medical Journal*. Several cases are reported in which human clinical trials have gone ahead even after animal experiments have shown no benefit.

Evaluation of animal studies is urged

A group of medical scientists today calls for "urgent rigorous evaluation" of the contribution of animal studies to clinical medicine. Much animal research is wasted because it is poorly conducted and not thoroughly evaluated, the Reviewing Animal Trials Systematically (Rats) group

Financial Times 27/2

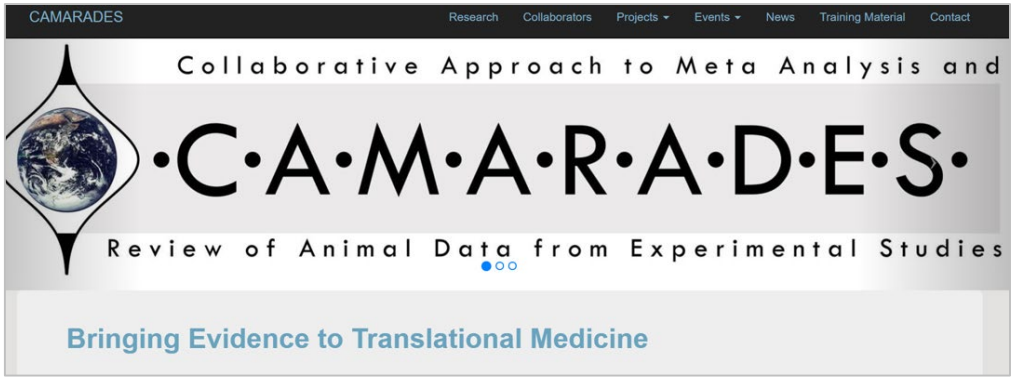
Sources: Highfield, R. (2004). *Experiments on animals should end, say doctors*. Daily Telegraph.; The Times. (2004). *Tests 'no benefit'*.; Financial Times. (2004). *Evaluation of animal studies is urged*.; Guardian. (2004). *Animal tests 'poorly conducted'.*

BMJ, The Times

- **Letters to BMJ**
  - The paper by Pound, et al. “should never have been published in a peer-reviewed journal.”
  - Publishing this paper by Pound, et al. was “spectacularly ill judged. It is not only scientifically invalid but it exhibits many of the failures of reason, endemic in the anti-vivisection literature that undermine the case against animal research.”

- **The Times**
  - “The article in the British Medical Journal, by a group of anti-vivisectionists led by Pandora Pound of Bristol University…” – Mark Henderson (Head of Communications at the Wellcome Trust and former science editor of the Times)

CAMARADES



- Camarades received the first Medical Research Council (MRC) funding to conduct systematic reviews of animal studies (2004)
- Now conduct numerous systematic reviews, develop SR methodology and provide training in SRs
- 11 global participating centers

Source: CAMARADES. (n.d.) Retrieved from http://www.dcn.ed.ac.uk/camarades/

SYRCLE

- Conduct SRs of animal studies
- Provide training and education in SRs
- Provide support and coaching in SRs
- Provide tools and guidelines for conducting SRs

Source: SYRCLE. (n.d.). Retrieved from https://www.syrcle.network/

What Have SRs of Animal Studies Found So Far?

- Provide evidence on:
  - How well animal studies are conducted (quality)
  - How animal studies are reported
- And can throw light on:
  - Translation from animals to humans

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Quality of Animal Studies

Quality of Animal Studies Overview

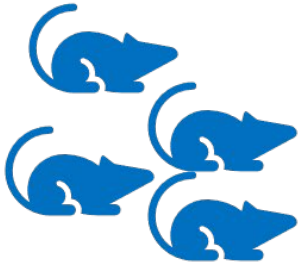
- **Validity**—important concept in context of research quality, indicates how sound research design and findings are
- **Internal validity**—quality of the study itself, i.e., conducted according to agreed scientific standards, well designed, low risk of bias, etc.
- **External validity**—ability of the findings to be extrapolated (generalized) to other research settings, populations, species

Internal Validity

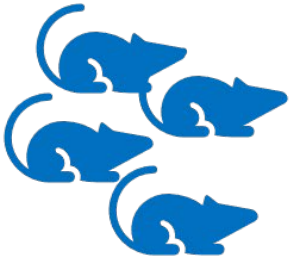
- Minimize bias
- Sample size calculation
- Control for confounding factors

Reducing the Risk of Bias

Treatment group



Control group



Failure to Reduce Risk of Bias

Systematic reviews (SRs) have found that few animal studies take steps to minimize bias:

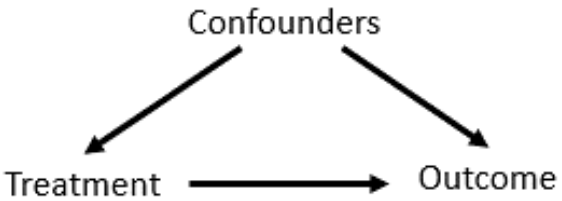
- Only between 29% (Hirst, et al., 2014) and 37% (Henderson, et al., 2015) of animal studies allocated animals to treatment or control groups in a **random** fashion
- Few reported **adequate allocation concealment**: 0% (Henderson, et al., 2015); 12% (Perel, et al. 2007); 15% (Hirst, et al., 2014)
- Few reported **masked outcome assessment**: 21% (Perel, et al 2007); 29.5% (Macleod, et al. 2015); 35% (Hirst, et al., 2014);
  - Essential to take steps to minimize bias, otherwise findings untrustworthy—studies that do not take steps to minimize bias are more likely to report positive outcomes than studies that do—i.e., more likely to suggest that animal research is beneficial

Sample Size Calculations

- The size of a study—i.e., how many animals are in the study—is important
  - Must state sample size calculation in advance, otherwise possible to keep adding animals until desired result is obtained
  - Macleod, et al. (2015): 0.7% of animal studies reported a sample size calculation
  - Furthermore, without power calculations to determine sample size the study risks being underpowered
  - Underpowered studies cannot give reliable results

Image: Clipart Library. (n.d.) Retrieved February 17, 2020, from http://clipart-library.com/clipart/67164.htm

Confounding Variables



- Animal strain, source, sex, age, weight, pathogen status
- Animal diet, bedding, housing, water delivery, lighting, noise, vibration, temperature, humidity
- Sex of the researcher handling animals
- Dose administration
- Pain and drugs that manage pain
- Stress and suffering

Studies that do not control for confounding variables are more likely to report positive outcomes than studies that do (Scott, et al. 2008)

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Reporting of Animal Studies

Reporting of Animal Studies—1

- Research methods should be reported fully to show exactly how research conducted
- Basic information, e.g., number of animals used in experiments, is often very poorly reported (Pound and Nicol, 2018)
- Loss of animals from a study through death or exclusion often poorly reported (Holman, et al. 2016)—as a result, treatment effect sizes are likely to be overestimated

Reporting of Animal Studies—2

- Research methods should be reported fully to show exactly how research conducted
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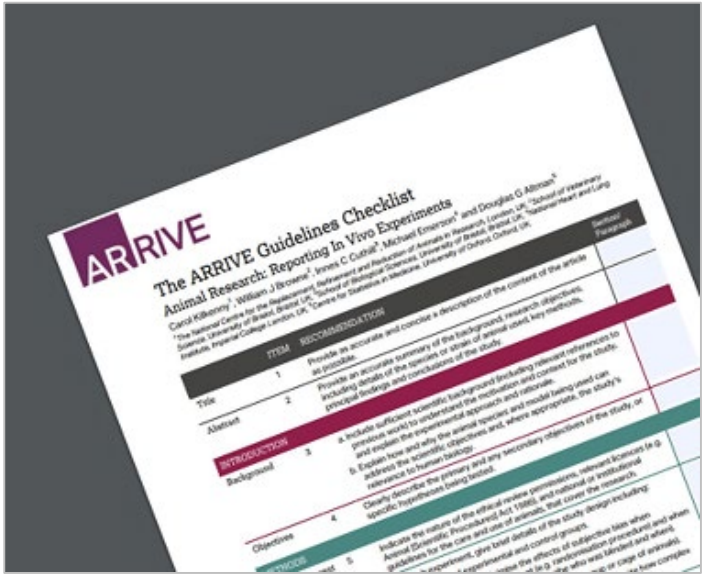


Source: Kilkenny, C., Browne, W., Cuthill, I. C., Emerson, M., & Altman, D. G. (2010). Animal research: Reporting in vivo experiments: The ARRIVE guidelines. *British Journal of Pharmacology, 160*(7), 1577–1579. https://doi.org/10.1111/j.1476-5381.2010.00872.x

Selective Analysis and Outcome Reporting Bias

- Among many analyses performed only those with the “best” results are presented for publication
- Ultimately this leads to a body of evidence with an inflated proportion of published studies with statistically significant results (Tslidis, et al., 2013)

Image retrieved February 17, 2020, from https://phychologyproject.weebly.com/objective-4.html

If It Seems Too Good to Be True, It Probably Is

- A statistical technique can evaluate whether the number of published animal studies with positive findings is too large to be true
- Tsilidis, et al. (2013) assessed 4,445 animal studies for 160 potential treatments of neurological disorders
- Found that 1,719 of them had a positive result, whereas only 919 would be expected to have such a result
- Suggests strong biases in study design or reporting, *resulting in spurious claims of effectiveness*

Example of Poor Reporting—1

thebmj

BMJ 2018;360:j5845 doi: 10.1136/bmj.j5845 (Published 10 January 2018)

FEATURE

Check for updates

INVESTIGATION

Oxford TB vaccine study calls into question selective use of animal data

Researchers were disappointed when a clinical trial of a new tuberculosis vaccine failed to show benefit, but should it have gone ahead when animal studies had already raised doubts and what does it mean for future research? **Deborah Cohen** investigates

Deborah Cohen *associate editor, The BMJ*

In July 2009, researchers began a clinical trial in infants in South

People who have spoken to *The BMJ* about this saga consider

Source: Cohen, D. (2018). Oxford TB vaccine study calls into question selective use of animal data. *BMJ*, *360*(j5845). https://doi.org/10.1136/bmj.j5845

Example of Poor Reporting—2

- BMJ claimed Oxford University researchers were **selective in reporting** their animal study results
- They claimed that researchers presented results that suggested a vaccine worked in animals, to gain funding for human trials of the vaccine
- The group gained funding for the human trials, which ultimately failed
- Independent systematic review concluded that insufficient evidence had existed to support claims about the efficacy of the vaccine and that these claims had been overstated

Publication Bias

- Phenomenon whereby studies more likely to be published if they present “positive” findings, i.e., findings that a treatment has been effective
- In field of stroke, as a result of negative studies not being published, estimated that benefits of animal studies overstated by a third (Sena, et al., 2010)
- In field of cancer, estimated that publication bias could account for a 45% overestimation of effect size of cancer drug Sunitinib (Henderson, et al., 2015)

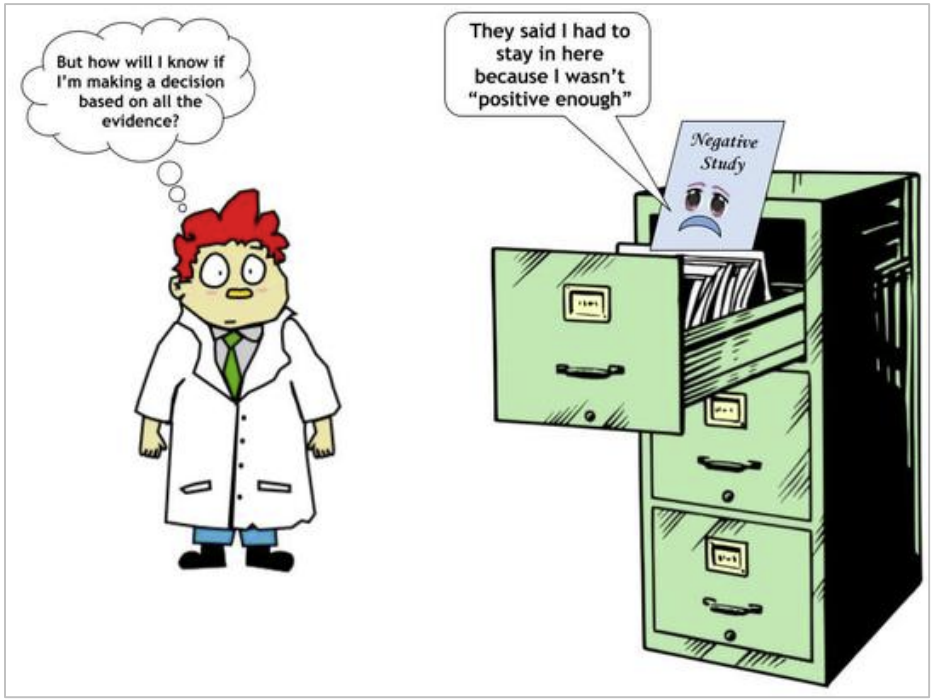


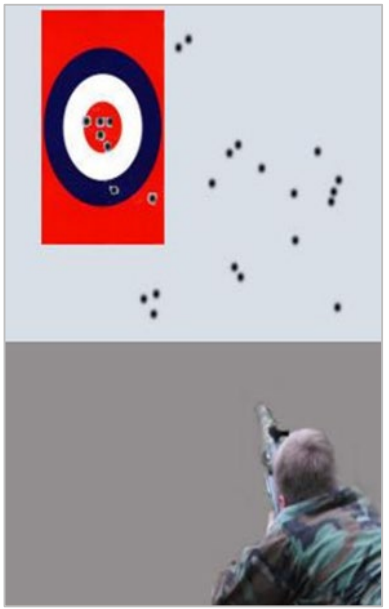
Image retrieved February 17, 2020, from https://junkscience.com/2018/03/publication-bias-and-the-canonization-of-false-facts/

Biased Reporting (Publication Bias)

7 studies reported

26 studies performed

The true picture



Why it is important to look at all the studies

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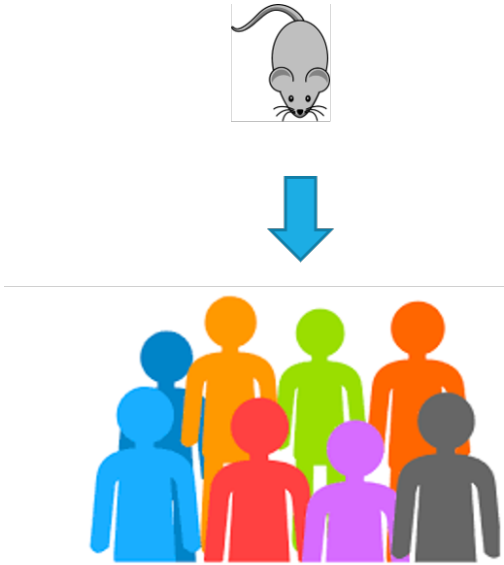
Quality of Animal Studies (External Validity)

External validity: the extent to which research findings from one study can be applied to other settings, populations, species

External Validity

Several factors important to external validity in context of animal research:

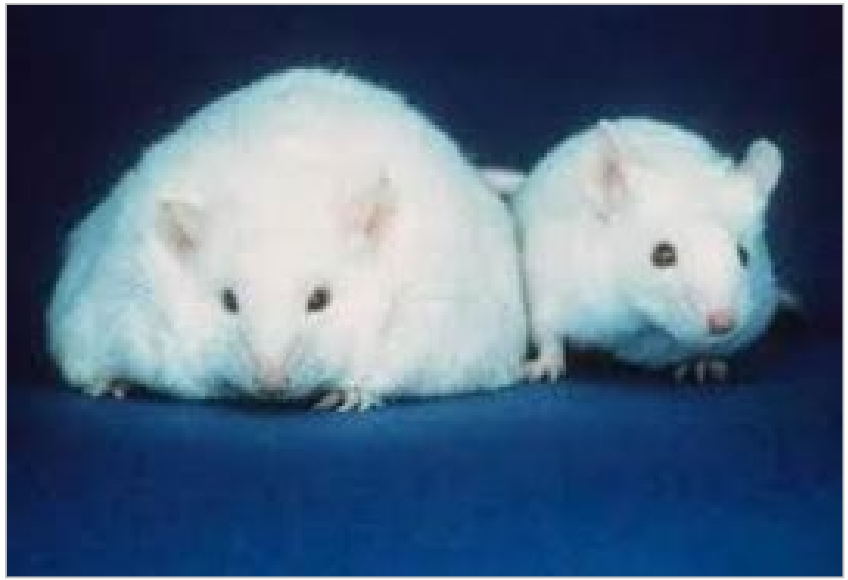
- **Disease "modeling":** animals have to "model" (mimic) the relevant human disease accurately, so that the results are relevant to humans
- **Context**: the context in which a drug is given to animals will be similar to the context in which humans are given the drug
- **Representativeness**: the sample of animals will reflect as closely as possible the human population that suffers from that disease



Disease Modeling—1

- Animals are used to “model” or mimic the relevant human disease
  - E.g., stroke will be artificially induced in an animal, the animal will be given an experimental drug, and, if successful, the drug will be given to humans with stroke in clinical trials
- Humans get stroke because of risk factors that accumulate over a lifetime
  - E.g., drinking, smoking, high blood pressure—animal models of stroke typically involve surgery to block the middle cerebral artery
- Most human diseases evolve over time as part of human life course
  - E.g., it may be possible to grow breast tumors on mice, but this does not represent the human experience—most human breast cancer occurs post-menopause

Disease Modeling—2

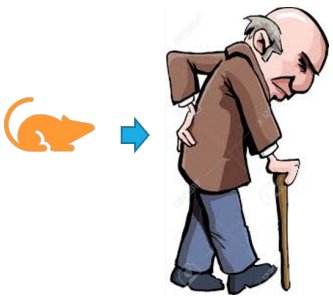


Context

The context in which a drug is given to animals should be similar to the context in which it is given to humans

- Drugs for multiple sclerosis (MS) administered to animals before neurological impairment induced—BUT as these drugs work by blocking the induction of the disease, they are not relevant to humans; human patients cannot be identified prior to onset of MS
- The drug Tirilazad successfully treated animals with experimental stroke if given within 10 minutes of stroke—BUT impossible for humans to access acute stroke expertise and have drug administered within 10 minutes
  - In clinical trials, humans were given Tirilazad within more realistic 5 hours—trials unsuccessful (Howells and Macleod, 2013)

Representativeness of Animal Samples



- The characteristics of animals should reflect as closely as possible the human population that suffers from the disease in question
- Animals used in research tend to be young whereas many human diseases manifest in older age
- Animals used in research tend to be healthy, but many human diseases have associated conditions, e.g., humans with stroke may have atherosclerosis, diabetes, chronic hypertension
  - Experimental studies of stroke that use healthy rather than comorbid animals overestimate the effects of the treatment (Crossley, et al., 2008)
- Animals used in research are only given the experimental drug, yet humans with disease are often on a range of different medications for other conditions (polypharmacy)

Species Differences

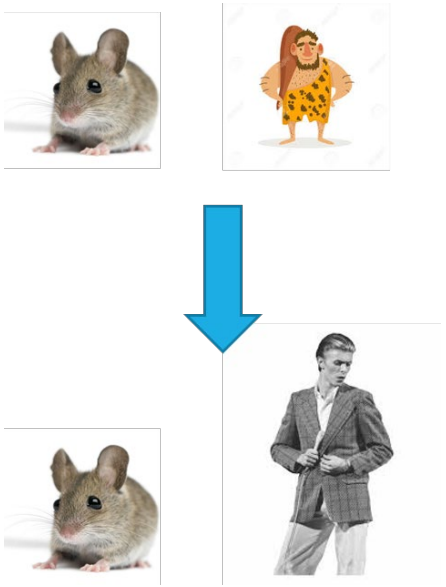
- Another factor impacts external validity in animal research—differences in the underlying biology of animals and humans
- Some aspects of external validity (disease modeling, context, representativeness of samples) can be improved to some extent
- But animal–human species differences cannot be overcome, i.e., will always impact on external validity and make findings from animal studies unreliable

Evolutionary Biology—1

- Mice and humans have genetic, biochemical, and physiological similarities—mice may help us understand processes that arose early in evolution
- **But** lineages that led to modern rodents and primates diverged around 85 million years ago
- Mice and humans now have very different life histories, diets, levels of physical activity, are exposed to different environmental toxins and pathogens, have different microbiomes and different immune systems
- Mice not useful for understanding chronic, noncommunicable diseases—causes enmeshed in our unique, evolved life histories (Perlman, 2016)

Evolutionary Biology—2

- Mice and humans have genetic, biochemical, and physiological similarities—mice may help us understand processes that arose early in evolution
- **But** lineages that led to modern rodents and primates diverged around 85 million years ago
- Mice and humans now have very different life histories, diets, levels of physical activity, are exposed to different environmental toxins and pathogens, have different microbiomes and different immune systems
- Mice not useful for understanding chronic, noncommunicable diseases—causes enmeshed in our unique, evolved life histories (Perlman, 2016)



Nonhuman Primates

- Nonhuman primates often cited as having great genetic similarity with humans
- But in complex living systems even minor differences can result in significant differences in biological processes / outcomes
- TGN1412 tested in nonhuman primates precisely because of close relation with humans

In a trial of 6 human volunteers, minutes after being infused with a dose 500 times smaller than that found safe in animal studies, all 6 humans went into multiple organ failure

'LIKE A HORROR FILM' What was the 'Elephant Man' drug testing trial, what is TGN1412 and what happened to the men involved?

Volunteers left writhing in agony and projectile vomiting before their immune systems crashed and they suffered multiple organ failure

Source: Allen, F. (2017, February 21). *'Like a horror film' What was the 'Elephant Man' drug testing trial, what is TGN1412 and what happened to the men involved?* The Sun. Retrieved February 18, 2020, from https://www.thesun.co.uk/news/2917810/elephant-man-drug-testing-trial-tgn1412/

Genetically Modified Animals

- Genetically modified (transgenic or humanized) mouse models intended to enhance external validity of animal models but have not improved translation to humans
- Suffer from same problems as ordinary animal models—i.e., appear to mimic humans in some ways, but not in others
- Animal–human species differences cannot be overcome

Image: vabadov. (2019). Retrieved February 18, 2020, from https://www.istockphoto.com/vector/funny-mouse-dressed-up-in-human-clothes-gm1134272999-301354554

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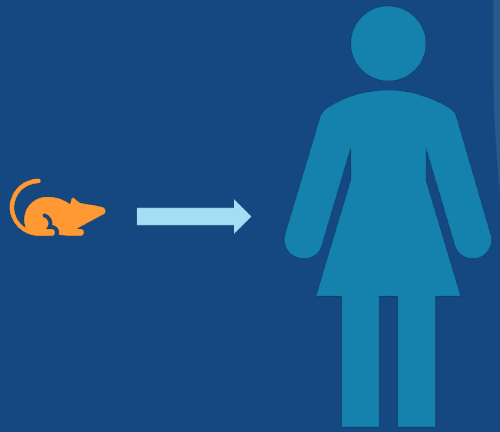
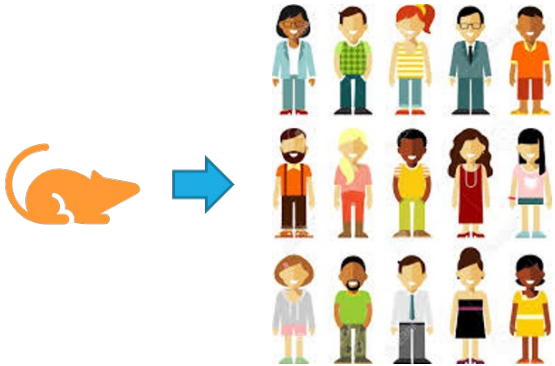


Translation to Humans

Study by Perel, et al.

Condition	Animal studies	Human studies	Concordance
Corticosteroids for head injury	Evidence of benefit	Increased mortality	Discordant
Anti-fibrinolytics in hemorrhage	Inconclusive	Reduced bleeding	Discordant
Thrombolysis in acute ischemic stroke	Evidence of benefit	Evidence of benefit (but with increased risk of hemorrhage)	Discordant
Tirilazad in acute ischemic stroke	Evidence of benefit	Increased mortality	Discordant
Antenatal corticosteroids to prevent neonatal respiratory distress syndrome	Reduced respiratory distress; effect on mortality inconclusive	Reduced respiratory distress and mortality	Partially concordant
Bisphosphonates to treat osteoporosis	Increased bone mineral density	Increased bone mineral density	Concordant

Translation Rates



- Cardiovascular: 20% success rate (Kola and Landis, 2004; Vatner, 2016)
- Crohn’s disease: 18% (Parker and Kohler, 2010)
- Cancer: 5% success rate (Kola and Landis, 2004); Hutchinson and Kirk 2011) / less than 8% (Mak, et al., 2014)
- Alzheimer's: 0.4% success rate (Cummings, et al., 2014)
- Traumatic brain injury: 0% success rate (Marshall, 2000; Xiong, et al., 2013)
- Motor neuron disease: 0% (Perrin, 2014)
- Inflammatory response: 0% (Seok, et al., 2013)

E.g., Translation in the Field of Stroke

- Decades of research using stroke animals models—success rate 0.1% (Howells, et al., 2012)
- Numerous drugs successful in animals but ineffective in humans with stroke
  - More than 1,000 potential neuroprotective drugs tested in animals—500 found to benefit animals, but not one benefits humans
- Some drugs successful in animals but increase risk of death in humans (Diaspirin, Enlimobab, Selfotel, Tirilazad)
- Only one drug available for acute stroke : Alteplase (“clot-buster”)
  - Only 10%–12% stroke patients eligible for alteplase
  - Half of these will remain dependent or die
    - Alteplase went straight to clinical trials after success with heart attack, i.e., not dependent on animal studies for its development

Can We Answer the Question: “Does Animal Research Benefit Humans?’

1. Most animal research is at present of such poor quality that no reliable conclusions may be drawn from it
2. Animal-human species differences will continue to make extrapolation from animals to humans unreliable
3. Rates of translation from animals to humans indicate that much animal research fails to benefit humans
4. There is no systematic evidence to support the assertion that animal research benefits humans

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In Europe, the regulations state that the suffering of research animals must be outweighed by the benefits of the research to humans or the environment.

In view of what we have explored so far, can animals' suffering be justified?

Implications

Harm-Benefit Assessment


PLOS ONE

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RESEARCH ARTICLE

Retrospective harm benefit analysis of pre-clinical animal research for six treatment interventions

Pandora Pound, Christine J. Nicol

Published: March 28, 2018 • https://doi.org/10.1371/journal.pone.0193758

- Harm–benefit assessment (HBA) is conducted as part of the licensing of animal studies in UK and rest of Europe
- A prospective evaluation “to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome” European Union Directive 2010/63/EU
- We conducted a retrospective study of animal research, to weigh the harms experienced by animals against the benefits of that research for humans

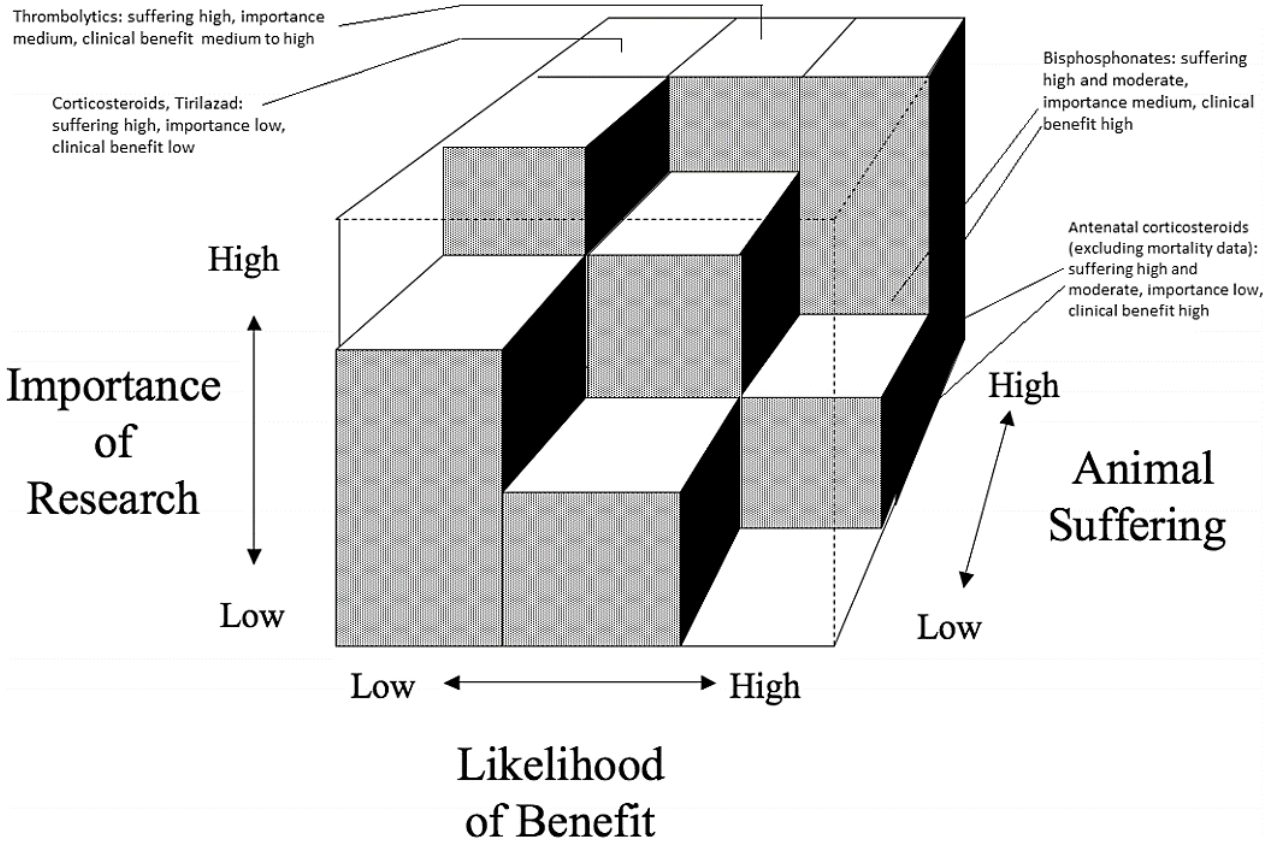
Source: Pound, P., & Nicol, C. J. (2018). Retrospective harm benefit analysis of pre-clinical animal research for six treatment interventions. *PLOS ONE, 13*(3), e0193758. https://doi.org/10.1371/journal.pone.0193758

Reanalysis of Study by Perel, et al.

	Benefits to humans?	**Harms to animals**
Antifibrinolytic drugs	Animal data inconclusive, but antifibrinolytics widely used in clinical practice	Ranged from mild to severe
Corticosteroids	No clinical benefit (in fact, increased mortality for humans	Mostly severe
Tirilazad	No clinical benefit (in fact, increased mortality for humans)	Severe
Antenatal corticosteroids	Clinical benefit—routine use in hospitals in high-income countries is recommended	Mostly moderate to severe
Thrombolytics drugs	Can be used with certain selected stroke patients, clinical benefits controversial	Mostly severe
Bisphosphonates	Clinical benefit—primary preventive treatment for postmenopausal women with osteoporosis	Mostly moderate, some severe

Bateson's Cube

212 studies; 27,149 animals



Source: Pound, P., & Nicol, C. J. (2018). Fig 2. HBA using Bateson's cube. In Retrospective harm benefit analysis of pre-clinical animal research for six treatment interventions. *PLOS ONE, 13*(3), e0193758. https://doi.org/10.1371/journal.pone.0193758.g002

Examples of Harms

- **Thrombolytic drugs for stroke**: some animals had stroke induced while conscious and restrained
- **Corticosteroids for traumatic brain injury**: Some animals had no or light anesthesia prior to restraint and infliction of traumatic brain injury, some left to die
- **Antenatal corticosteroids for respiratory distress in neonates**: newborns and fetuses not given anesthesia during experiments, some left to die, some suffered harms as a result of mistakes in procedures or experiment going wrong
- **Tirilazad for stroke**: animals underwent repeated assessments after having stroke induced, some died as a result of mistakes in procedures or experiment going wrong

Lack of Welfare

- 97% (n = 206 studies) did not report use of analgesia for animals during or after experiments
- 13% (n = 27 studies) did not report use of anesthesia during experiments
- 1% (n = 3 studies) reported postoperative care for animals

Harms and Benefits: The Views of Ethicists

- If there is certainty about the harms to animals, and doubt about its benefits, can animal research be justified?
- DeGrazia and Sebo (2015) argue that an expectation of sufficient net benefit to humans must be a condition of morally responsible animal research
- “Since the best working hypothesis is that the human benefits of animal research are either small or unclear, we are not in a position to claim justification. If the benefits are small, they cannot outweigh large harms to animals; if they are unclear, even as to probabilities, then we do not know there to be any outweighing benefit.” (Bass, 2012, pp. 94–95)

Further Ethical Issues

- Poorly conducted animal studies produce unreliable and inconclusive findings
  - Suffering endured by animals loses moral justification because animal use cannot contribute to clinical benefit
- Where negative findings from animal studies are not published the animals used cannot contribute to scientific knowledge—again, their suffering loses moral justification
  - Additional risk that the animal studies may be repeated unnecessarily because findings from original unsuccessful experiments not publicized
- Implications for humans—unmet need, adverse effects of drugs, etc.—beyond scope of lecture

Conclusions

- Review regulations that permit animals to suffer severe harms
  - Directive 2010/63/EU and current US policy allow severe unalleviated pain, suffering, or distress
- Tighten licensing and authorization process so that poor-quality studies with little hope of human benefit are not approved or funded
  - Licensing authorities and funders should adopt a precautionary approach that does not automatically assume animal research will benefit humans
- Conduct more retrospective harm-benefit analysis to explore accountability
- Fund research that is relevant to humans and that does not use animals
- Conduct research to systematically evaluate clinical relevance of animal research—still unclear

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