Brun Ulfhake
Professor of Anatomy, Department of Neuroscience,
Karolinska Institutet

Member of Stockholms regional ethics review board, 1989-2012
Member of the Central ethic review board of Sweden, 2013-

Early ages:

Prior to 1989 we had institutional non compelling ethics reviews.
Unclear situation when it came to responsibilities and to decide if animal protection law was violated.

Ethics review of project licenses for animal testing in Sweden 1989-2017

With the Animal protection law of 1988 a national system of ethics review in the national judiciary and ethic project licenses were introduced

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FORSKA UTAN DJURFÖRSÖK

DJURRÄTTSALLIANSEN

Djurens Rätt.

Parliament decides on new laws

Government proposes new laws and issues the Ordinance of the law

Jordbruks verket

The National competent authority (Board of Agriculture) is authorised by government to issue detailed provisions about the law.

Sveriges Domstolar

The judiciary apply law, ordinance and provisions.

Länsstyrels Stockholm

The City council board is the national inspection authority

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The Swedish legislation was modified in 2012 to incorporate the European frame work: EU directive 2010/63/EU

COUNCIL OF
THE EUROPEAN UNION

Brussels, 26 March 2012

16009/11

Interinstitutional File:
2008/0211 (COD)

JUR 530
AGRILEG 120
VETER 43
ENV 814
RECH 342
CODEC 1803

LEGISLATIVE ACTS AND OTHER INSTRUMENTS: CORRIGENDUM/RECTIFICATIF

Subject: 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

(OJ L 276, 20.10.2010, p. 33)

LANGUAGES concerned: **BG, ES, FR, IT, PT, FI, SV**

PROCEDURE APPLICABLE according to the Council Statement of 1975.
(The procedures are explained in Council document 5980/07 JUR 49, available in the official languages, together with a translation of the structure of this cover page)

— Procedure 2(c) (obvious errors in a number of language versions)

TIME LIMIT for the agreement of the Presidency and of the European Parliament (in case of ordinary legislative procedure): 15 days

Any observations regarding this corrigendum should be notified to the Presidency:

Mr. Peter W. Linde and Mr. Mads Nabe-Nielsen:

e-mail: peteli@um.dk

madnab@um.dk

16009/11

EN

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

The Swedish legislation was modified in 2012 to incorporate the European frame work:
EU directive 2010/63/EU

Incorporating the EU 2010/63/EU: Art 38-41:

- Approved licenses were to be valid through 5 years (prior max was 3 y).
- 3R was incorporated in the Swedish legislation 2005 but further emphasised after 2012.
- Withdrawal of a project license.
- Retrospective assessment
- A public summary of project

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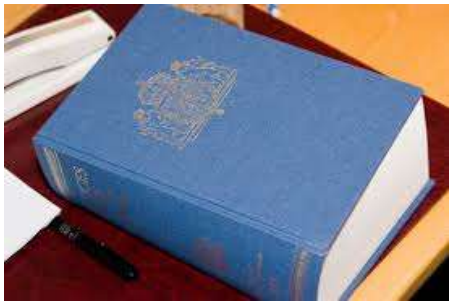


The use of laboratory animals is tightly regulated by law, ordinance and provisions

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Jordbruks verket

Statens jordbruksverks författningssamling

ISSN 1102-0970

Jordbruks verket

Statens jordbruksverks föreskrifter och allmänna råd om försöksdjur;

SJVFS 2012:26
Saknr L 150

beslutade den 21 november 2012.

Statens jordbruksverk föreskriver[1], med stöd av 26, 32, 40-40 a, 41, 41 b-41 c, 47, 50-52, 54 a-55, 57 b och 75 §§ djurskyddsförordningen (1988:539), följande. Dessutom beslutar Jordbruksverket om följande allmänna råd.

LIST OF GOVERNING LAWS, REGULATIONS, AND POLICIES

EU Directives and Conventions

2010/63/EU. COUNCIL DIRECTIVE of 22 September 2010 on the protection of animals used for scientific purposes. Implemented the 1 st of January 2013
http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF

European Treaty Series (from 2003 Council of Europe Treaty Series" (CETS)
ETS 123
The European Convention for the protection of vertebrate animals used for experimental and other scientific purposes
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31986L0609:en:HTML

ETS 170
Protocol of Amendment to the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes.
http://conventions.coe.int/Treaty/en/Treaties/html/170.htm

Swedish Laws and Regulations on animal experimentation

The Animal Welfare Act (L 1 Djurskyddslagen SFS 1988:534)
http://www.riksdagen.se/sv/Dokument-Lagar/Lagar/Svenskforfattningssamling/Djurskyddslag-1988534_sfs-1988-534/

The Animal Welfare Ordinance (L 2 Djurskyddsförordningen SFS 1988:539)
http://www.riksdagen.se/sv/Dokument-Lagar/Lagar/Svenskforfattningssamling/Djurskyddsforordning-1988539_sfs-1988-539/

The Swedish Board of Agriculture's Regulations and General Advice of Laboratory Animals (L150 Statens jordbruksverks föreskrifter och allmänna råd om försöksdjur SJVFS 2017)
http://www.jordbruksverket.se/download/18.3c1967aa13afeea1eb880002406/1370040518470/2012-026.pdf

Swedish Board of Agriculture's regulations and general advice regarding the transport of living animals (L 5 Statens jordbruksverks och allmänna råd om transport av levande djur SJVFS 2010:2 (SJVFS 2010:84) .

Swedish Board of Agriculture's regulations for operational procedurers on or injections into animals (L 41 Statens jordbruksverks föreskrifter om operativa ingrepp på eller injektioner till djur SJVFS 2009:85)
http://www.jordbruksverket.se/download/18.53b6e8e714255ed1fcc4fd4/1385713728106/2013-041.pdf

Swedish Board of Agriculture's Regulations on Public Animal Welfare Control (L 44 Statens jordbruksverks föreskrifter om offentlig djurskyddskontroll SJVFS 2008:67)
http://www.jordbruksverket.se/download/18.2caaa5d2139711ae12f80001088/1370040514362/2008_67.pdf

The Ethics review board system in Sweden (1989-2012)

Six regional ethics boards

3 lay members
3 representatives for animal protection/right organisations

3 representatives of the researchers
3 representatives for staff carrying for lab animals

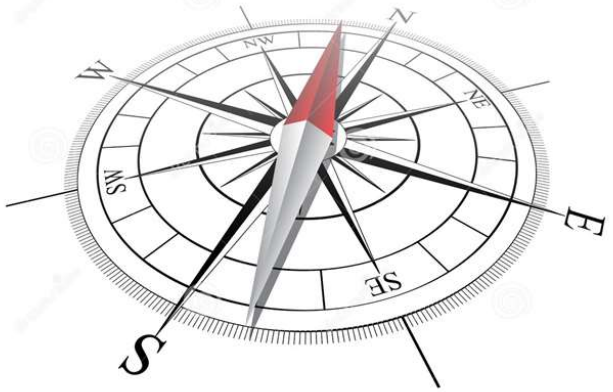
The Chair is a judge from the judiciary

Ethics

High quality animal testing
- an issue with several stake holders

The usefulness of research:
reproducibility crises

Law makers, regulations and supervision



The public standing and how this changes over time

3R
Replace, Refine and Reduce

A resource book for lay members of ethical review and similar bodies worldwide.

by

Maggy Jennings and Jane A. Smith

The lay member's role

Lay involvement in ethical review bodies (ERBs) overseeing laboratory animal use is common practice in a number of countries around the world, and in some cases is a regulatory requirement. This chapter explores the valuable contributions that lay members can make and discusses some practical matters associated with the role.

Defining a 'lay member'

Lay participants in ERBs come from a variety of backgrounds and fields of work. Examples include academics from the arts or social sciences, managers in areas unrelated to animal use, lawyers, ethicists, administrative staff, librarians, safety officers, and people from the local community, clergy or public services.

Some countries require that certain types of lay participant are represented in their ERBs and examples are listed below. These definitions make clear that lay members should have no vested interest in the matters under review, and may also be independent of the institution where the research is conducted; but beyond this, opinions differ on exactly who counts as 'lay'. However, rather than placing too much emphasis on the definition of 'lay member', it is more important to focus on the *roles* that lay members can play and the benefits that these bring.

Examples of 'required' lay participants

N.B. these are minimum requirements, and other kinds of lay people may also be involved.

Australia: "*a person who is both independent of the institution and who has never been involved in the use of animals in scientific or teaching activities, either in their employment or beyond undergraduate education*" (Australian Government National Health and Medical Research Council 2013).

Canada: "*an institutional member whose normal activities, past or present, do not depend on or involve animal use for research, teaching or testing*" and "*person(s) representing community interests and concerns who have not been involved in animal use for research, teaching or testing*" (Canadian Council on Animal Care 2006).

New Zealand: a person who "*should bring the perspective of a member of the public*", who is *"not employed by, or associated with*" the organisation concerned, "*nor associated with the scientific community or an animal welfare agency*" (New Zealand Ministry of Agriculture and Forestry 2000).

UK: "....*actively seek a wider membership taking into account the views of people who do not have responsibilities under [UK law on laboratory animal use] as well as one or more persons who are independent of the establishment*" (Home Office 2014).

USA (PHS Policy): a "*member whose primary concerns are in a non-scientific area (for example ethicist, lawyer or clergy)*" and "*at least one public member to represent the general community interests in proper care and use of animals*", who "*should not be a laboratory animal user*" and a *"member not affiliated in any way with the institution*" (National Research Council 2011).

The Ethics review board system in Sweden (1989-2012)

Regional ethics review boards
rule by majority decisions

- Approved
- Approved with conditions
- Rejected

The applicant could/can appeal to:
1989-2012 higher administrative court
(~1 year; no expertise; 1-2 cases approved).
2013- The Central Ethics Board

The central ethics review board in Sweden (2013-)

1 lay members
1 representative for animal protection/right

3 senior representatives for research

The Chair is a senior judge from the judiciary

The applicant and the responsibilities at the establishment

Swedish national law

Responsibilities for the care and use of lab. animals at the establishment:

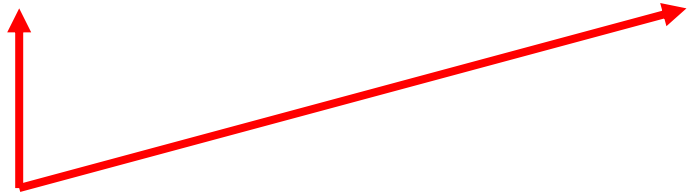
Ethic license applicant
(function B).

The ethic license holder

is responsible for animals in experiment under an Ethics approved project license. Must have the approval of the site license holder to apply for ethics review.

The site-license holder

Responsible for all the operational aspects of establishment incl. supervision of animals in experimental projects.



The national inspection authority is the City Council Board

Missions of the Ethics review board

To provide exemptions from the Animal welfare act

Inflicting any harm on animals without a valid ethics approved project license is violating the law and will go to prosecution with a maximal penalty of 2 years in prison.

To follow the guide lines of the ethic review process for reassurance that alternative methods are not available, to minimize number of animals and to minimize harm to the animals as well as environmental impact.

To withdraw licenses approved in cases where it is an appropriate action.

Missions of the Ethics review board

Handling of cases (laid down in >30 paragraphs of the regulations!)

§ 5 A Regional Ethical Committee shall make a decision in the case at the latest 40 work days after a complete and correct application has been received by the committee.

--

§ 7 A Regional Ethical Committee shall check that the application for ethical approval includes the requested information and that there is a relevant operating license.

If the application is incomplete or incorrect, the committee shall as soon as possible communicate to the applicant that there is a need for supplementary information. At the same time, the committee shall communicate if this means that the decision will be made at a later time.

§ 8 A Regional Ethical Committee shall check that the popular science summaries, submitted by the applicant according to Ch. 2,. § 16, contains the requested information and, if needed, request supplementary information from the applicant.

The Committee shall supplement the popular science summaries with

1. the severity classification as established by the Committee,
2. any additions or amendments that have been decided, as well as
3. any decision on retrospective assessment, including which parts and from what aspect.

Second paragraph 2 only applies if amendments entail that the popular science summaries would become inaccurate.

CH. 6. EDUCATION AND COMPETENCE

…there is no specification!!

In the EWG framework document:

Person(s) carrying out project evaluation in Article 38

Those involved in project evaluation should have access to training in the process, in particular on how the objectives of the project, the application of the Three Rs and the assessment of severity classification should be evaluated, and on how the harm-benefit analysis (HBA) should be undertaken

…..

It is important that those carrying out the PE have a good understanding of the expected harms to the animals and the proposed benefits of the research, as the harm-benefit assessment is a central element of the authorisation process…

Initial training:

Module 1 – "National legislation";

Modules 2 and 9 - "Ethics, animal welfare and the Three Rs" (levels 1 and 2);

Module 25 - "Project Evaluators"

National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes

A working document on the development of a common education and training framework to fulfil the requirements under the Directive

- Replacing consensus document II of 23-24 January 2013 -

Missions of the Ethics review board

Prior supportive utilities (1989-2004/6):

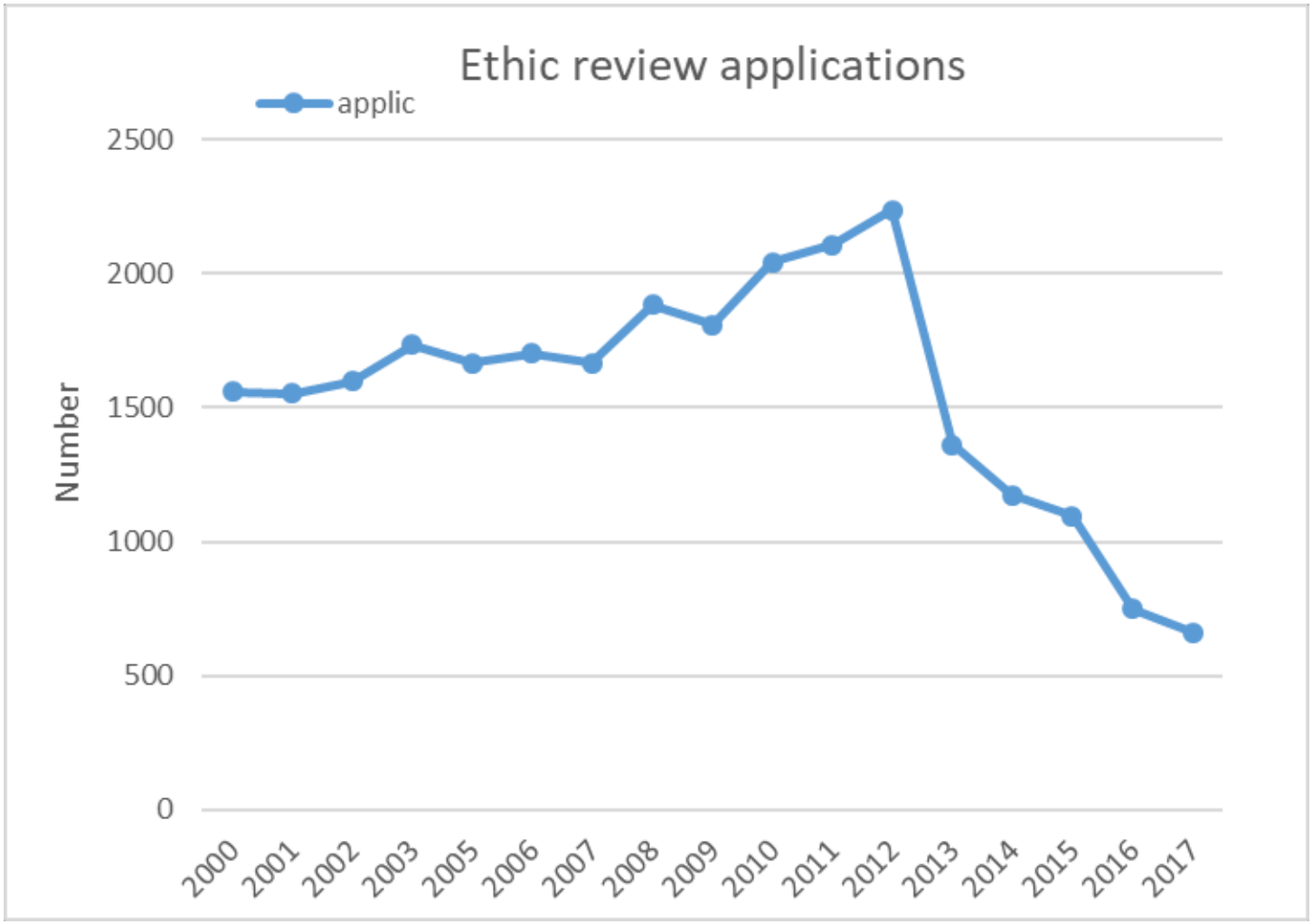
- Central ethic review committee (CFN)
- Science expert panel
- A publication series of general advises on certain research fields

2006-

These services were closed 2004 and replaced with the advice to the ethics boards to seek advice by themselves. No funding was offered towards these needs!

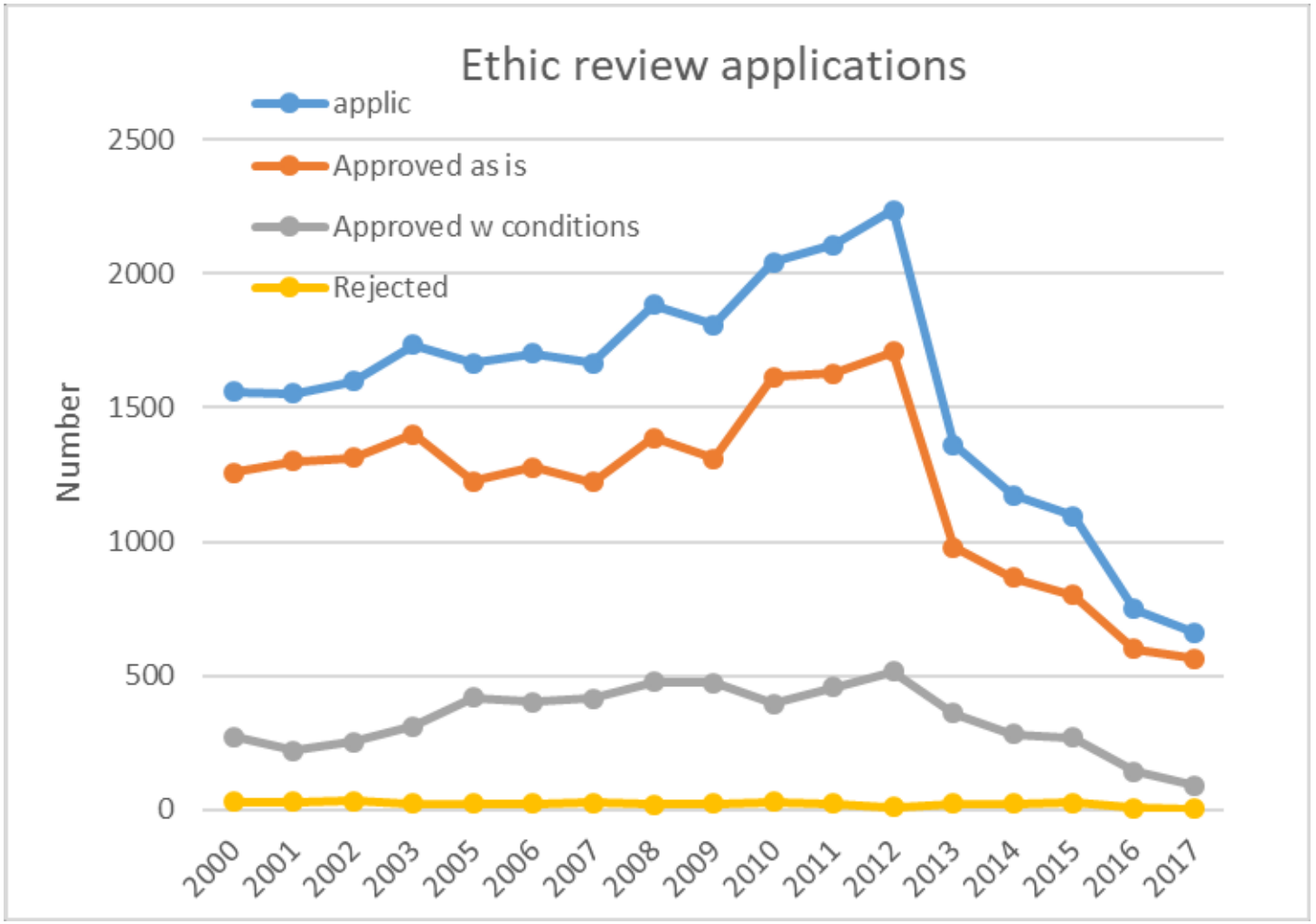
Missions of the Ethics review board

Some performance metrics:



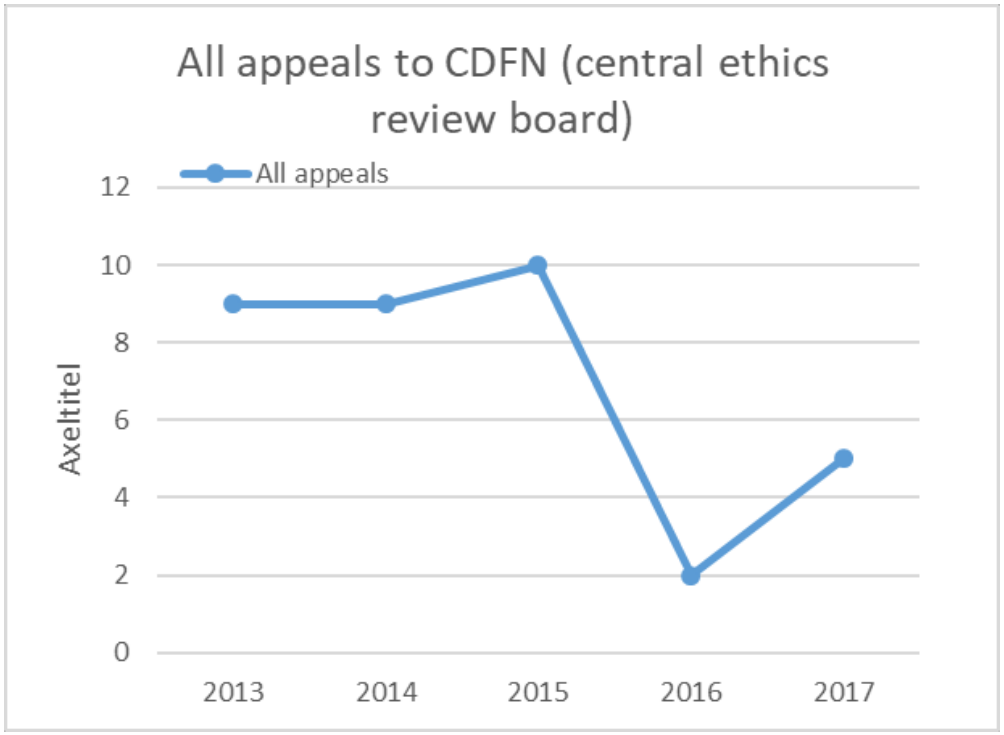
Missions of the Ethics review board

Some performance metrics:



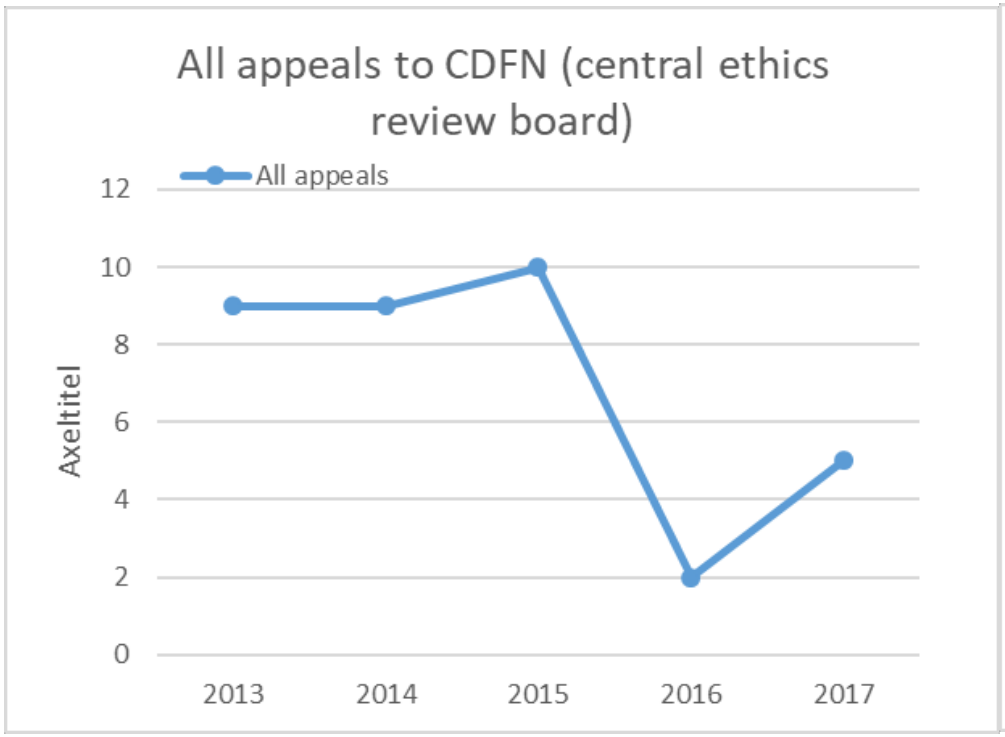
Missions of the Central ethics review board

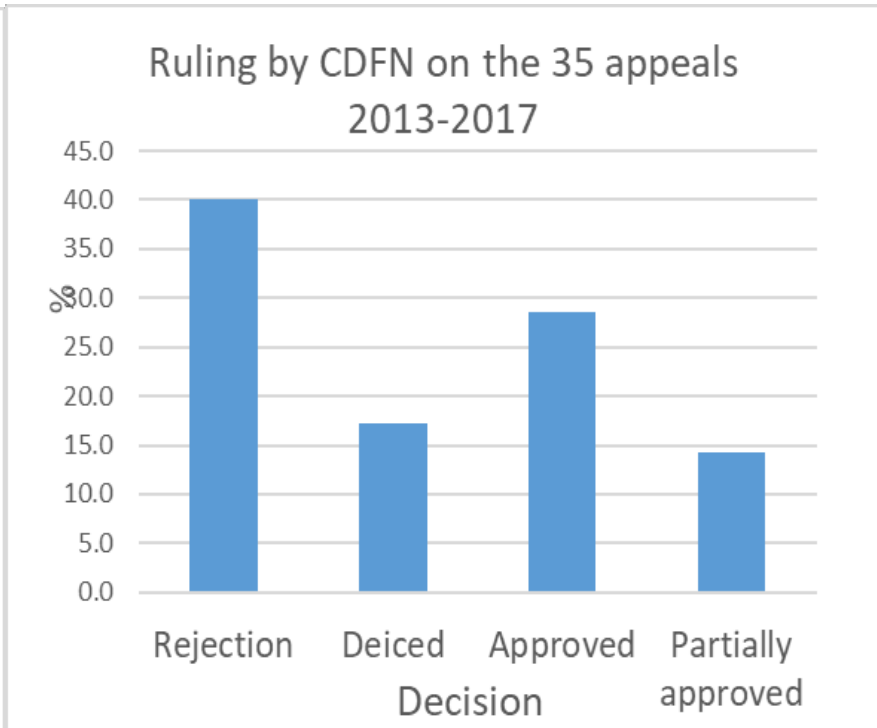
Some performance metrics:



Missions of the Central ethics review board

Some performance metrics:





Missions of the Central ethics review board

Some performance metrics:

Restrospective assessment:		
	2018	60
	2019	130
	2020	175
	2021	111

Have we been successful??

There is room for improvements of the ethics review process

Brussels, 8.11.2017
SWD(2017) 353 final

COMMISSION STAFF WORKING DOCUMENT
Accompanying the document

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

In accordance with Article 58 of Directive 2010/63/EU on the protection of animals used for scientific purposes

{COM(2017) 631 final}

The Principles of Humane Experimental Technique (1959): The 3 R's

Russell and Burch

Reduction

Minimize the number of animals used

Refinement

Techniques to reduce pain and distress

Replacement

Substitute animal with non-animal methods

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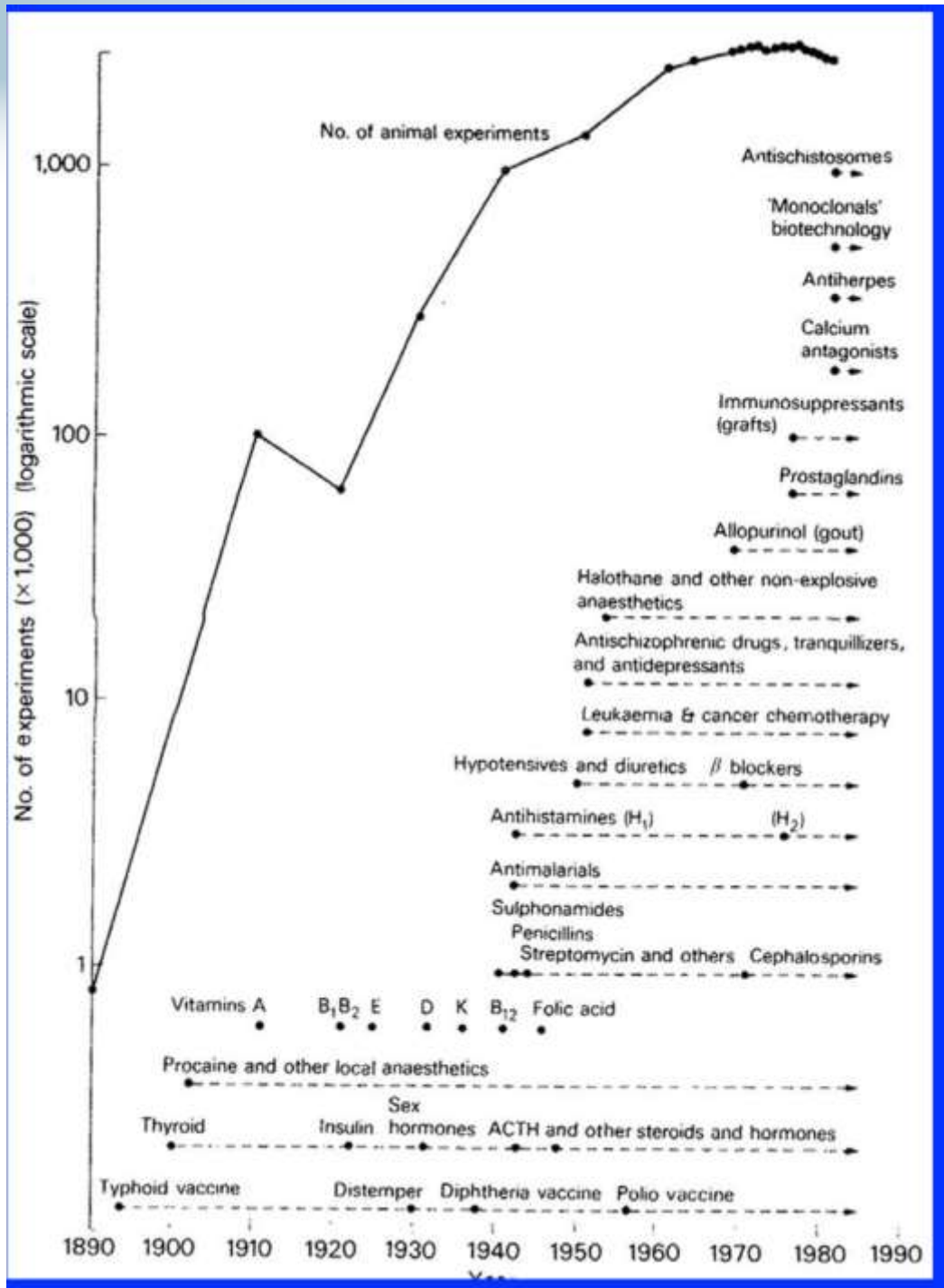
Are we using fewer laboratory animals today?



Are we using fewer laboratory animals today?

The number of laboratory animals used world-wide in 2008 was estimated to 115 million based on statistics from 37 countries (the Dr. Hadwen Trust for Humane Research); animals bred for research then killed as surplus, animals used for breeding purposes, and animals not yet weaned are not included in this number. Despite extensive legislative efforts to regulate the use of laboratory animals and to prevent unwarranted use (at least in developed countries) as well as the offering of an impressive range of incentives to promote replacement of laboratory animals with alternative platforms (in vitro, in silico, virtual simulation etc.) over the past 50-years, the use of laboratory animals in the sciences increase; in UK alone the use of laboratory animals has grown annually at a rate of 6% for more than a decade.

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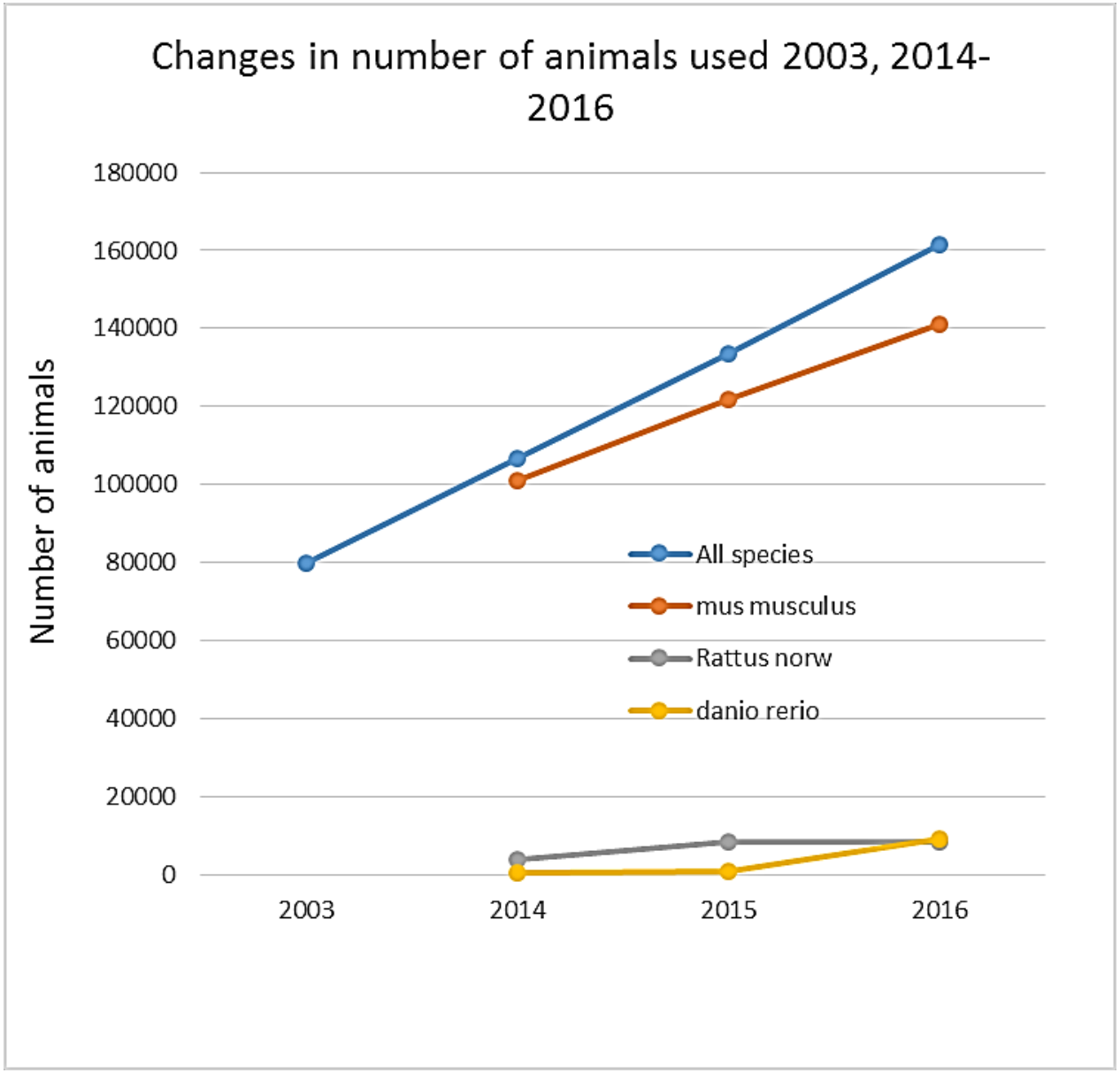
Among non-profit organizations, KI is the largest breeder and user of laboratory animals (35-50%) in Sweden. Gross revenues were >7 billion SEK (2016).

Aggregated the Comparative medicine infrastructure laboratory animal research represents an investment of ~2000 MSEK (2010-2018).

In 2018, the aggregated operation has an annual turn-around of ~240 MSEK including about 140 dedicated staff and a user community of >1000 researchers.

The size and diversity of this operation **commits KI to be in the forefront developing animal welfare, implementing the 3Rs and in the provision of LAS E&T.**

Karolinska Institutet



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WORLD VIEW *A personal take on events*

Why animal research needs to improve

Many of the studies that use animals to model human diseases are too small and too prone to bias to be trusted, says **Malcolm Macleod.**

This is the golden age of medical research. Around the world, scientists are spending more money, writing more papers and building more shiny institutes. Almost all grant applications suggest that a positive funding decision will support research that could lead to new treatments for condition X — usually a growing scourge of modern society.

Many medical discoveries have made real differences to the lives of a great number of people, but could the research be done better?

It seems self-evident that we should encourage high-quality work, but what makes for high quality is a matter of opinion, which hardens over the years into dogma on the assumption that the most established and most venerated got there for a reason, so if one wishes their good opinion then one should do as they did.

Take experiments that use animals to model human diseases. Empirical study of the quality of these experiments is an emerging field, but it does suggest that all is not well. The most reliable animal studies are those that: use randomization to eliminate systematic differences between treatment groups; induce the condition under investigation without knowledge of whether or not the animal will get the drug of interest; and assess the outcome in a blinded fashion. Studies that do not report these measures are much more likely to overstate the efficacy of interventions.

Unfortunately, at best one in three publications follows these basic protections against bias[1]. This suggests that authors, reviewers and editors accord them little importance.

Other basic aspects of the design of experiments in animals also receive scant attention. In the face of pressures to reduce the number of animals used, investiga-

> CHEAP, **UNDER-POWERED** STUDIES ARE MORE LIKELY TO HAVE **EXCITING** (IF FALSE) RESULTS THAN LARGE, EXPENSIVE STUDIES.

overestimation of drug efficacy by about one-third[3], increasing risk for both clinical-trial participants and the pharmaceutical industry.

Experimental approaches are not very different throughout the life sciences, so the biases are probably similar too. A scientist's environment is full of potential hazards, such as non-renewal of funding, and potential rewards — getting published and receiving grants. As long as cheap, underpowered studies are more likely to have exciting positive (if false) results than expensive, well conducted, large studies — and as long as journals don't seem to know the difference — the pressure will remain to do what everyone else does.

So we need to change the rules. If publication in high-impact journals continues to be a yardstick, then the review process must do much more to assess bias. The ARRIVE (Animal Research: Reporting *In Vivo* Experiments) guidelines[4], endorsed by, among others, Nature Publishing Group, are a good start. But, as Don Quixote observed, the proof of the pudding will be in the eating.

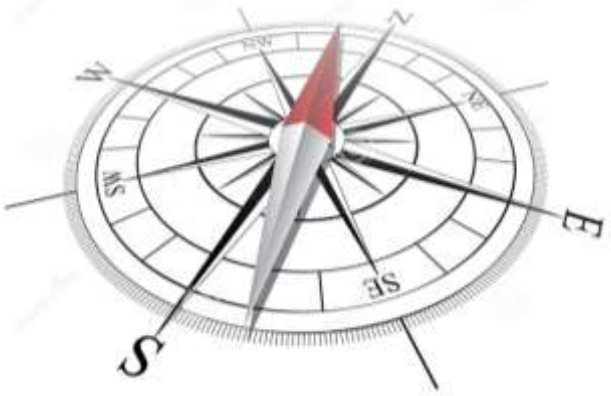
There must also be better ways to publish neutral studies. If the focal cerebral ischaemia literature reflects the life sciences generally, then 16% of studies go unpublished, and tackling publication bias would increase the number of manuscripts published every year by 160,000. At current growth rates we would expect this increase anyway over the next four years, so sorting out publication bias should be possible.

At the very least, we should look for ways to register all experiments — so that investigators can receive credit for work done and so that those seeking to summarize what is known have access to all relevant data. Such a system could be flexible, with

Ethics

High quality animal testing
- an issue with several stake holders

The usefulness of research:
reproducibility crises



Law makers, regulations and supervision

The public standing and how this changes over time

3R
Replace, Refine and Reduce

Some recognized problems:

- Often not fully understood that all the 3 R's are to be described in the project application – often only replace
- Lack of information in the applications on how the statement that "it is not possible to use other methods" was obtained
- Lack of information on refinement – only the used method is described and not which other methods could have been possible and why those were not chosen
- Lack of information/knowledge on statistics makes it difficult to judge the possibility of reduction (especially difficult with regard to breeding)

- Legal requirements of animal testing: lack of knowledge and clear information what is really required by different authorities (e.g. humane endpoints, alternatives, GLP)
- Lack of knowledge in all procedures
- Lack of knowledge on where to find information on alternatives and what alternatives can really provide
- Lack of spreading of negative results or non-working procedures
- Lack of animal welfare research

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Implementation of the 3 R's in project evaluation - the role of the competent authority (2013)

- To ensure adequate education of the persons evaluating projects (including continuous education e.g. attaining of conferences, special education days)
- To provide guidance for project evaluators (regulations and recommendations as a framework and other guidelines)
- To provide and promote discussion platforms
- To provide adequate application forms for project authorization
- To provide (impartial) expert knowledge – experts, databases, updated information on the 3 R's
- Electronic database of all project authorizations

My personal reflections:

- Members of the Ethics boards must receive appropriate education and training.
- Members of the Ethics boards must have access to expertise covering all aspects of husbandry and research on lab animals.
- Maybe a two step process would facilitate the ethic discussion:

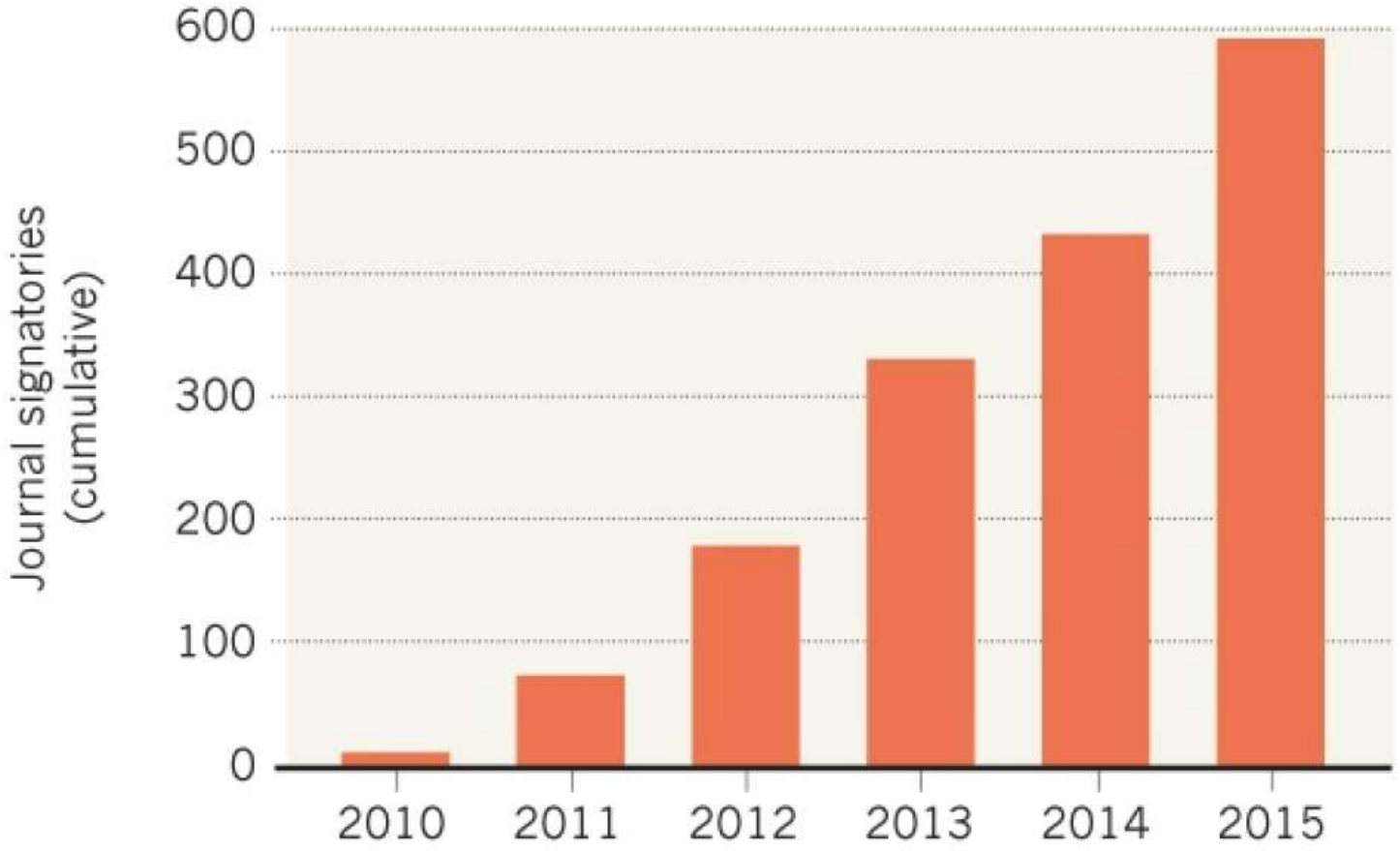
  First a technical assessment by experts

  Followed ethic discussion (HBA) and ruling on the application.
- Do not apply fees. If this must be financed there are other means to bring in the funding. Fees for the applicant will be normative on the application.

Print

SURGE IN SUPPORT FOR STUDY GUIDELINES

In 2015, more than 150 journals signed up to the ARRIVE checklist for animal studies — the highest number of signatories in a single year since it was released.



NC3Rs

Karolinska Institutet

Comments, Opinions, and Reviews

Good Laboratory Practice

Preventing Introduction of Bias at the Bench

Malcolm R. Macleod; Marc Fisher; Victoria O'Collins; Emily S. Sena; Ulrich Dirnagl; Philip M.W. Bath; Alistair Buchan; H. Bart van der Worp; Richard Traystman; Kazuo Minematsu; Geoffrey A. Donnan; David W. Howells

Background and Purpose—As a research community, we have failed to demonstrate that drugs which show substantial efficacy in animal models of cerebral ischemia can also improve outcome in human stroke.

Summary of Review—Accumulating evidence suggests this may be due, at least in part, to problems in the design, conduct and reporting of animal experiments which create a systematic bias resulting in the overstatement of neuroprotective efficacy.

Conclusions—Here, we set out a series of measures to reduce bias in the design, conduct and reporting of animal experiments modeling human stroke. (***Stroke*. 2009;40:e50-e52.**)

Key Words: animal models ■ basic science ■ drug trials ■ education ■ experimental ■ outcomes ■preventing bias ■ translational research

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Council Directive 2010/63/EU

Art.4.3: Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, **eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm** to the animals

Art.13.3: Death as an end-point of a procedure shall be avoided as far as possible and replaced by **early** and **humane end-points**.

Where death as the end-point is unavoidable, the procedure shall be designed so as to:

a) result in the death of as few animals as possible; and

b) reduce the duration an intensity of suffering to the animal to the minimum

RESEARCH ARTICLE

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

OPEN ACCESS

Citation: Pound P, Nicol CJ (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

Pandora Pound[1] *, **Christine J. Nicol**[2]

1 Population Health Sciences, University of Bristol, Canynge Hall, Bristol, United Kingdom, **2** School of Veterinary Science, University of Bristol, Langford House, Langford, United Kingdom

* pandora.pound@bristol.ac.uk

Abstract

Background

The harm benefit analysis (HBA) is the cornerstone of animal research regulation and is considered to be a key ethical safeguard for animals. The HBA involves weighing the anticipated benefits of animal research against its predicted harms to animals but there are doubts about how objective and accountable this process is.

Objectives

i. To explore the harms to animals involved in pre-clinical animal studies and to assess these against the benefits for humans accruing from these studies; ii. To test the feasibility of conducting this type of retrospective HBA.

What we need is a coherent network of expert services supporting the ethics review process and the work at the ethic review board.

This is also needed to make the retrospective assessment useful and standardized

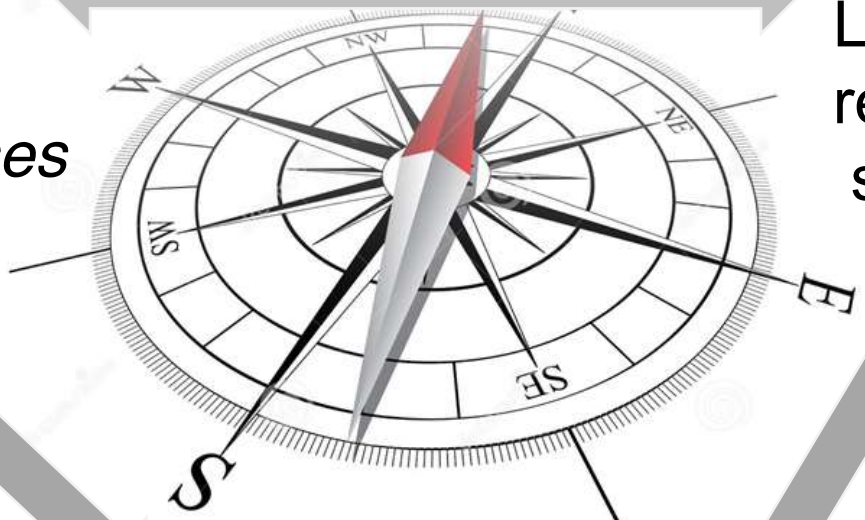
The resources exist at least in part but they are not easily accessible in everyday work-

Brun Ulfhake

Ethics

High quality animal testing
- an issue with several stake holders

The usefulness of research:
reproducibility crises



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