International Journal of Surgery 72 (2019) 9–13

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

The current state of animal models in research: A review

N. Bryce Robinson, Katherine Krieger, Faiza M. Khan, William Huffman, Michelle Chang, Ajita Naik, Ruan Yongle, Irbaz Hameed, Karl Krieger, Leonard N. Girardi, Mario Gaudino*

Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY, 10065, USA

ARTICLE INFO

Keywords:
Animal model
Review
Three Rs
Sham surgery
Surgical training
Simulation

ABSTRACT

Animal models have provided invaluable information in the pursuit of medical knowledge and alleviation of human suffering. The foundations of our basic understanding of disease pathophysiology and human anatomy can largely be attributed to preclinical investigations using various animal models. Recently, however, the scientific community, citing concerns about animal welfare as well as the validity and applicability of outcomes, has called the use of animals in research into question. In this review, we seek to summarize the current state of the use of animal models in research.

1. Introduction

The use of animal models in the study of human anatomy and physiology dates back to the 6th century BCE, and their use in the pursuit of medical knowledge and research has continued for millennia [1]. Animals have provided significant contributions to modern medical understanding and advancement. Animals were used in the development of novel surgical techniques such as the tracheostomy, initially performed by Ibn Zuhr on goats in the 12th century, and laparoscopy, which originated from Georg Kellings work using dogs in the 1900s [2,3]. In the 1940s Vivien Thomas and Alfred Blalock developed a dog model which mimicked tetralogy of Fallot (TOF), allowing for the development of surgical techniques to repair TOF, the treatment of choice to this day [4].

Animal experiments have also contributed significantly to the development of vaccines, antibiotics, and our fundamental understanding of human disease processes. Albert Sabin used monkeys in the 1930s to develop the polio vaccine [5]. Insulin was discovered in the 1920s using canines, and the foundation of diabetes research relied on genetically modified mouse and rat models [6]. A majority of antibiotics are tested on animals prior to use in humans [7,8]. Indeed, animal research has made a number of significant contributions to human healthcare, and have provided invaluable data to alleviate human suffering.

Today, approximately 20 million animal subjects are used in biomedical research, dominated by mouse and rat models [9]. Historically, however, the translation of animal models to human subjects has been highly unpredictable. More recently, the use of animals in research has been called into question by the scientific community due to concerns about their clinical validity and application, as well as ethical concerns. In this review, we summarize the current state of animals in research, highlighting three areas of concern including study design and data analysis, the inherent heterogeneity of animal and human subjects, and translation of preclinical animal trials to human clinical trials. We then seek to offer future alternatives and direction regarding the use of animal subjects in research.

1.1. Study design and data interpretation

The gold standard of clinical research is the randomized controlled trial involving prospective data collection with both random allocation into intervention groups, as well as blinding of study investigators when appropriate [10]. Much of the data that has come from trials utilizing animal models to date, however, has been criticized for its inconsistency, lack of randomization and blinding, and inadequate or absent use of formal statistical analysis. A summary of 6 systematic reviews of animal experiments published in 2004 by Pound et al. identified a number of methodological problems including poor experimental design, inadequate power, and a lack of established statistical analysis. Additionally, most of the animal trials were run concurrent with or following human trials, thereby calling into question the utility of much of the published results [11].

Methodological problems with animal studies highlighted by Pound et al. include [11].

- Disparate animal species and strains, with a variety of metabolic pathways and drug metabolites, leading to variation in efficacy and

* Corresponding author. Department of Cardiothoracic Surgery, Weill Cornell Medicine 525 E 68th St, New York, NY, 10065, USA.
E-mail address: mfg9004@med.cornell.edu (M. Gaudino).

https://doi.org/10.1016/j.ijsu.2019.10.015
Received 19 August 2019; Received in revised form 8 October 2019; Accepted 10 October 2019
Available online 15 October 2019

toxicity.
- Different models for inducing illness or injury with varying similarity to the human condition.
- Variations in drug dosing schedules and regimen that are of uncertain relevance to the human condition.
- Variability in the way animals are selected for study methods of randomization, choice of comparison therapy (none, placebo, vehicle), and reporting of loss to follow up.
- Small experimental groups with inadequate power, simplistic statistical analysis that does not account for potential confounding, and failure to follow intention to treat principles.
- Nuances in laboratory technique that may influence results may be neither recognized nor reported—eg methods for blinding investigators.
- Selection of a variety of outcome measures, which may be disease surrogates or precursors and which are of uncertain relevance to the human clinical condition.
- Length of follow up before determination of disease outcome varies and may not correspond to disease latency in humans.

Investigators have also been criticized for lack of a clear rationale and objectives. A 2009 survey of over 250 papers published between January 1999 and March 2005 in which animal subjects were used observed that less than 60% reported a clear study hypothesis, a minimum of three animal characteristics (i.e. sex, strain, weight, age), and number of animals used. Furthermore, only 12% of studies utilized randomization of study subjects to experimental groups, and of the studies that did employ randomization, 14% also used blinding [12].

A unique challenge in the design of surgical trials is the control arm. In medical drug trials, for example, the placebo group is administered an inert pill which resembles the study medication with little to no harm posed to the patient. In surgical trials, however, the utilization of sham procedures – where a surgical procedure is performed in absence of the therapeutic intervention – in the control group exposes the subject to considerable risk without benefit. In human research, this has been justified, as the “placebo effect” associated with sham surgical procedures has been reported to help patients feel subjective symptomatic relief. In animal studies, however, this placebo effect is not pertinent. Rather, animal subjects are routinely exposed to potentially harmful and painful procedures, with no benefit [13].

Pain is another significant issue, specifically in trials where animals are undergoing invasive procedures. In research involving animal subjects, especially surgical trials, the choice of anesthetic and analgesic agents is of paramount importance to manage intervention related pain without affecting the measured outcomes [14]. The Animal Welfare Act, passed in the United States in 1970, stipulates that all experiments using animals provide adequate veterinary care, including the appropriate use of anesthetic, analgesic or tranquilizing drugs [15]. Currently, legislative bodies across the US, Europe, and Asia allow for pain to be left untreated in animal subjects as long as sufficient justification is provided [16]. Between 2002 and 2009, for example, 7–9% of animal studies tracked by the USDA utilized an animal model in which procedural analgesia was deliberately withheld because it would affect the outcome being measured [17]. Similarly, in a review of papers published across the European Union between 1986 and 2006, it was found that just 4% of papers using mouse models and 27% of papers using non-human primate models reported use of analgesics, or a justification for withholding pain control. As the design of surgical trials involving animals moves forward, special concern must be paid to this important topic, and alternatives pursued when possible [18].

1.2. The three Rs

In response to the concerns involving trial design, analysis, and reporting, several groups have set out to standardize the collection of data in animal research, and have encouraged further investigation through systematic review and meta-analysis. This was done in part to compensate for the lack of power and randomization in most published studies, and also as an attempt to limit the number of additional studies.

In 1959, Russel and Burch introduced the Three R's of animal research: Replacement, Reduction, and Refinement [19]. These three principles were designed to serve as a foundation for the development of future alternatives to the use of animals in research [20]. It was not until the 1980s, however, that legislative bodies across Europe and the United states began to develop committees and laws to govern the use of animals in research, many of which are largely based upon the three Rs.

In 2010, the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs), an independent organization based out of the United Kingdom, published the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines, a 20 item checklist describing the minimum information all scientific publications using animal models should report when publishing their findings. These guidelines were designed with the goal of both improving the information published from studies using animals, while also reducing the number of unnecessary publications [21]. As a supplement to this, Hooijams et al. proposed a gold standard of research and care involving animals in an effort to improve study outcomes and facilitate clinical translation by emphasizing the tenets of the three R's [22].

More recently, systematic reviews and meta-analyses of widely published animal research have become more common with the assistance and training of groups such as Collaborative Approach to Meta-Analysis and Review of Animal Data in Experimental Studies (CAMARADES) and Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE). These reviews have provided more insight into the shortcomings of existing animal studies, and offered several points of improvement including greater collaboration between preclinical and clinical investigators, more widespread utilization of randomization and blinding, and formal statistical analysis and reporting [23]. Despite this, there remain large amounts of discrepancies within published animal studies, perhaps due in part to the heterogeneity of both animal models, and the human conditions they are attempting to replicate.

1.3. Heterogeneity

Another issue that confronts researchers who use animal models is the wide genetic heterogeneity of both the test subject, and the disease processes and medications being tested. There are a number of examples in the literature.

In a systematic review comparing the treatment effects in six separate animal experiments with human clinical trials, concordance between human clinical trial and animal study outcomes was highly variable, with some studies publishing similar outcomes, and others demonstrating the opposite effect. For example, Tirilazad, a drug investigated for its role in acute ischemic stroke, improved the neurologic outcomes and reduced overall infarct size in 18 separate animal studies. In humans, however, Tirilazad was associated with an increased risk of death and dependency. Conversely, the use of tissue plasminogen activator in acute ischemic stroke has shown a reduction in overall stroke infarct size and improved neurocognitive testing in both animal studies and subsequent human trials [24]. This difference in treatment effect can be explained, in part, by the genetic differences between animal models and humans, and their reaction to intervention.

A possible contributing factor to this heterogeneity could be because the selection of animal models for experiments is not always evidence-based. Several considerations must be taken, including cost, housing, feeding, veterinary support, and a particular group's familiarity with a model. Because of this, the animal model chosen for a study may not be suited for the clinical question under investigation [25]. As a result of this heterogeneity, the results of animal studies do not always carry over when trialed in human subjects.

1.4. Translation to human clinical research

The ultimate goal of animal research is for the information obtained from trials to benefit human clinical research. Typically, before human clinical trials are initiated, animal models are tested to investigate the safety and efficacy of new devices, procedures, and drugs. The data gathered from these preclinical trials is one of the most often cited reasons for the use of animal models in research, with authors typically pointing to the alleviation of unnecessary human suffering. Over the past decade, however, it has become increasingly clear that conclusions drawn from animal studies cannot be simply transferred to human studies.

Several recently published large meta-analyses and systematic reviews have highlighted the poor translation of the data and knowledge obtained from animal trials to subsequent human trials. Some have criticized study design and data interpretation. Improvements in the internal validity of published studies, however, have not led to an increase in the translation of animal research into human clinical research, likely reflective of the inherent differences between humans and the animal species being tested [26].

One review of over 60 highly cited animal studies in top journals between 1980 and 2000 found that only about a third translated to human randomized trials [27]. For example, there have been over 100 vaccines against HIV-like viruses developed which have demonstrated efficacy in animal models, however none, to date, have worked in humans [28–30]. In cancer research, the average rate of successful translation of animal research to human clinical trials is about 8% [31].

A 2001 systematic review of fluid resuscitation in animal models found that the degree of statistical heterogeneity, low power, and missing data calls into question study conclusions and reliability. This was due in large part to the trials being underpowered. In fact, none of the more than 40 trials included in the review would have been large enough to reliably detect a 10% absolute difference between the intervention (in this case, hemorrhage) and control groups [32].

One notable exception to this trend is transplantation research, which has largely benefitted from the use of animal models in preclinical research. In the 1960s, a group at Harvard showed the utility of anti-metabolite medications on renal allograft survival in canines, ushering in the modern era of surgical organ transplantation for end-stage disease [33]. Animal models have proven particularly useful in organ transplantation, providing a model where organs can be exposed to the complexity of the in-vivo immunologic and physiologic environment. Today, mouse and porcine models have largely replaced the earlier canine models, and continue to contribute to the advancement of organ transplantation in humans.

Since the introduction of solid-organ transplantation, however, a severe shortage of available donor organs has developed as the demand for organ transplantation across areas such as Europe grows by as much as 15% each year [34]. In an effort to increase the availability of organs, recent research has looked into using animal organs for humans, or xenotransplantation. Currently, there are a number of barriers to effective xenotransplantation, including immunologic, physiologic, and ethical concerns, not to mention the expense associated with such research [35]. Xenotransplantation, however, remains an important field of research for increasing the available organ pool.

When examining the literature as a whole, however, it is clear that animal models continue to divert scarce research funding, provide limited advancement in clinical studies, and are heavily biased without proper analysis and reporting [36]. In the United Kingdom (UK), while the overall number of animals used in research decreased by 7% from 2017 to 2018, the number of dogs and non-human primates (NHP) actually increased by 22% and 17%, respectively. It remains encouraging, however, that the total number of canines and NHP utilized per year has decreased by almost 25% between 2008 and 2018 (Table 1) [37]. Similar trends can be seen in the United States (Table 2).

1.5. Future direction

The use of animals in research will, for the foreseeable future, be necessary to help drive scientific discovery in a variety of medical fields. The ethics of this is an ongoing narrative. In a review of recently published studies using animals, Ferdowsian et al. found a lack of ethical justification for the deliberate harm inflicted on study subjects in several federally approved trials, with questionable benefits and outcomes. In some of the studies, animals were exposed to painful conditions without any report of measures taken to minimize an individual subjects suffering [38–41]. Across the world, governmental bodies and institutional review boards have developed legislation and ethical approval processes to limit current animal-based research studies to those where all alternatives are fully considered and animal suffering is minimized [42]. While it is outside the scope of this review to fully delve into the complexity of the sociopolitical discussion involving animals in research, it is an important consideration when discussing this topic. For a more detailed review please see the American Medical Association position paper on the use of animals in research. [8].

As the use of animals in research moves forward, it is important to bring a commitment to the “three R's of animal research” (reduce, refine, replace) to the forefront [43]. This dictum highlights the need to reduce, refine, and ultimately replace the use of animal subjects in research. It is paramount that animals not be subjected to research unnecessarily, and that the data obtained from trials not be wasted or misrepresented. The number of animals used should be minimized in all cases, and alternatives used when available. In fact, some countries, such as the Netherlands, are already laying the foundations to phase out the use of animals in the testing of medications and chemicals [44,45]. In an effort to reduce the number of additional studies, the US Department of Agriculture provides an online search tool which enables investigators to query a set of databases in the search for prior literature on a given topic [46].

One such alternative in the medical education arena, where an estimated 60,000 animals are used annually, is simulation [9]. A paradigm shift has occurred over the past decade, away from the see one-do one-teach one model and the use of animals, towards simulation, especially in surgical education. In fact, the Accreditation Council for Graduate Medical Education (ACGME) requires a simulation and skills laboratory in all surgical training programs across the US [47]. The use of virtual reality (VR) in laparoscopic skills training has already been validated and widely accepted [48–50]. This technology has the potential to dramatically reduce the number of animals used in the academic teaching setting, while simultaneously reducing the long cost in high fidelity models.

The contribution animal's models have had to human research is undeniable. Many modern advancements simply would not have been made possible without a high fidelity, highly reproducible model, with the added benefit of preventing potential human harm. A deeper look at the current landscape, however, raises questions. With the introduction of alternative such as simulation, we must reexamine the use of sentient animals in human research, with an eye towards reduction, refinement, and, ultimately, replacement.

Ethical approval

Ethical approval was not required.

Sources of funding

There were no sources of funding for this research project.

Author contribution

All authors listed have made contributions to the review. NBR and

Table 1
Number of Animal Procedures in Great Britain in 2018. Data obtained from Understanding Animal Research. http://www.understandinganimalresearch.org.uk/news/communications-media/animal-research-numbers-in-2018/, 2018 (Accessed October 08, 2019).

Species	Experimental Procedures	Creation & Breeding of GA animals not used in experimental procedures	Total Procedures (2018)	Percent of total Animals used	Percent change from 2017
Mice	1,078,738	1,489,459	2,568,197	72.96%	−7.67%
Fish	297,811	216,529	514,340	14.61%	+0.05%
Rats	170,665	7239	177,904	5.05%	−26.35%
Birds	146,860	1187	148,047	4.21%	+12.15%
Other mammals	82,754	427	83,181	2.36%	−10.51%
Reptiles	104	0	104	0.003%	+13.04%
Amphibians	6827	3046	9873	0.28%	+4.69%
Primates	3207	0	3207	0.09%	+8.34%
Cats	159	0	159	0.005%	−19.70%
Dogs	4481	0	4481	0.13%	+16.48%
Horses	10,424	0	10,424	0.30%	−1.66%
Total	1,802,030	1,717,887	3,519,917	100%	−7.11%

Table 2
USDA annual reporting of animal usage by fiscal year 2008–2017. https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/SA_Obtain_Research_Facility_Annual_Report, 2019 (accessed October 08, 2019).

Species	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
All other covered species	118,468	145,378	303,107	156,047	166,976	137,363	171,375	130,066	161,497	109,599
Cats	20,305	20,160	21,578	21,712	22,531	24,221	21,083	19,932	18,898	18,146
Dogs	70,305	67,337	64,930	64,805	64,247	67,772	59,358	61,101	60,979	64,707
Guinea Pigs	227,629	203,098	213,029	211,791	204,211	190,881	169,528	172,864	183,237	191,766
Hamsters	153,607	150,051	145,895	145,595	137,314	136,850	121,930	98,420	102,633	98,576
Nonhuman primates	71,256	70,444	71,317	68,922	64,525	64,107	57,735	61,950	71,188	75,825
Other farm animals	30,371	29,620	38,008	37,679	36,547	33,058	27,393	27,786	20,597	22,643
Pigs	58,763	57,966	53,260	59,224	56,477	55,729	45,392	46,477	50,226	51,020
Rabbits	234,808	222,167	210,172	197,425	186,766	169,645	150,344	138,348	193,391	145,841
Sheep	14,286	13,551	13,271	13,225	13,263	11,535	10,315	10,678	12,196	14,045
TOTAL	**999,798**	**979,772**	**1,134,693**[a]	**976,425**	**952,855**	**891,161**	**834,453**	**767,622**	**820,812**	**792,168**

[a] Includes 126 Marine Mammals.

MG designed the study. NBR, KK, FK, WH, MC, AN, IH, RY, KK, LNG, and MG participated in collecting the data, analysing the data, drafting the manuscript, revising the manuscript. All authors read the final manuscript and approved it.

Trial registry number

1. Name of the registry: Not applicable.
2. Unique Identifying number or registration ID: Not applicable.
3. Hyperlink to the registration (must be publicly accessible): Not applicable.

Guarantor

Mario Gaudino MD, corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

Not applicable. The study is a review article.

CRediT authorship contribution statement

N. Bryce Robinson: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Katherine Krieger:** Data curation, Resources, Writing - original draft, Writing - review & editing. **Faiza M. Khan:** Conceptualization, Data curation, Investigation, Writing - original draft. **William Huffman:** Data curation, Resources, Writing - original draft. **Michelle Chang:** Data curation, Resources, Writing - original draft. **Ajita Naik:** Validation, Resources, Writing - review & editing. **Ruan Yongle:** Validation, Resources, Writing - review & editing. **Irbaz Hameed:** Data curation, Formal analysis, Validation, Writing - review & editing. **Karl Krieger:** Supervision, Validation, Writing - original draft. **Leonard N. Girardi:** Supervision, Validation, Conceptualization, Writing - original draft, Writing - review & editing. **Mario Gaudino:** Supervision, Validation, Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors have no conflicts of interest.

References

[1] A.C. Ericsson, M.J. Crim, C.L. Franklin, A brief history of animal modeling, Mo. Med. 110 (3) (2013 Jun) 201–205.
[2] F.S. Haddad, Ibn Zuhr and experimental tracheostomy and tracheotomy, J. Am. Coll. Surg. 199 (4) (2004 Oct) 665.
[3] G.S. Litynski, Laparoscopy–the early attempts: spotlighting Georg Kelling and Hans Christian Jacobaeus, J. Soc. Laparoendosc. Surg. 1 (1) (1997 Mar) 83–85.
[4] S. Timmermans, A black technician and blue babies, Soc. Stud. Sci. 33 (2) (2003 Apr) 197–229.
[5] A.B. Sabin, Oral poliovirus vaccine. History of its development and prospects for eradication of poliomyelitis, J. Am. Med. Assoc. 194 (8) (1965 Nov 22) 872–876.
[6] A.J. King, The use of animal models in diabetes research, Br. J. Pharmacol. 166 (3) (2012 Jun) 877–894.
[7] O. Zak, T. O'Reilly, Animal models in the evaluation of antimicrobial agents, Antimicrob. Agents Chemother. 35 (8) (1991 Aug) 1527–1531.
[8] J.M. Loeb, W.R. Hendee, S.J. Smith, M.R. Schwartz, Human vs animal rights. In defense of animal research, J. Am. Med. Assoc. 262 (19) (1989 Nov 17) 2716–2720.
[9] Research NRC (US) and I of M (US) C on the U of LA in B and B. Executive Summary

[Internet], National Academies Press (US), 1988 [cited 2019 Jul 11]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK218267/.
[10] B. Sibbald, M. Roland, Understanding controlled trials. Why are randomised controlled trials important? BMJ 316 (7126) (1998 Jan 17) 201.
[11] P. Pound, S. Ebrahim, P. Sandercock, M.B. Bracken, I. Roberts, Where is the evidence that animal research benefits humans? BMJ 328 (7438) (2004 Feb 28) 514–517.
[12] C. Kilkenny, N. Parsons, E. Kadyszewski, M.F.W. Festing, I.C. Cuthill, D. Fry, et al., Survey of the quality of experimental design, statistical analysis and reporting of research using animals, PLoS One 4 (11) (2009 Nov 30) e7824.
[13] A. Louw, I. Diener, C. Fernández-de-Las-Peñas, E.J. Puentedura, Sham surgery in orthopedics: a systematic review of the literature, Pain Med. 18 (4) (2017 01) 736–750 Malden Mass.
[14] L. Carbone, J. Austin, Pain and laboratory animals: publication practices for better data reproducibility and better animal welfare, PLoS One 11 (5) (2016) e0155001.
[15] Public law 91-579 animal welfare Act amendments of 1970, Animal Welfare Information Center| NAL | USDA [Internet]. [cited 2019 Sep 30]. Available from: https://www.nal.usda.gov/awic/public-law-91-579-animal-welfare-act-amendments-1970.
[16] National Research Council (US), Committee for the Update of the Guide for the Care and Use of Laboratory Animals. Guide for the Care and Use of Laboratory Animals [Internet], eighth ed., National Academies Press (US), Washington (DC), 2011 [cited 2019 Sep 30]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK54050/.
[17] L. Carbone, Pain in laboratory animals: the ethical and regulatory imperatives, PLoS One 6 (9) (2011) e21578.
[18] K. Taylor, Reporting the implementation of the Three Rs in European primate and mouse research papers: are we making progress? Altern. Lab. Anim. 38 (6) (2010 Dec) 495–517.
[19] Hughes M, Health JBS of P. The principles of humane experimental technique [internet]. Johns Hopkins Bloomberg Sch. Public Health. [cited 2019 Aug 8]. Available from: http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc.
[20] N. Burden, K. Chapman, F. Sewell, V. Robinson, Pioneering better science through the 3Rs: an introduction to the national centre for the replacement, refinement, and reduction of animals in research (NC3Rs), J. Am. Assoc. Lab. Anim. Sci. 54 (2) (2015 Mar) 198–208.
[21] C. Kilkenny, W. Browne, I.C. Cuthill, M. Emerson, D.G. Altman, NC3Rs Reporting Guidelines Working Group. Animal research: reporting in vivo experiments: the ARRIVE guidelines, Br. J. Pharmacol. 160 (7) (2010 Aug) 1577–1579.
[22] C.R. Hooijmans, M. Leenaars, M. Ritskes-Hoitinga, A gold standard publication checklist to improve the quality of animal studies, to fully integrate the Three Rs, and to make systematic reviews more feasible, Altern. Lab. Anim. 38 (2) (2010 May) 167–182.
[23] C.R. Hooijmans, M.M. Rovers, R.B.M. de Vries, M. Leenaars, M. Ritskes-Hoitinga, M.W. Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med. Res. Methodol. 14 (2014 Mar 26) 43.
[24] P. Perel, I. Roberts, E. Sena, P. Wheble, C. Briscoe, P. Sandercock, et al., Comparison of treatment effects between animal experiments and clinical trials: systematic review, BMJ 334 (7586) (2007 Jan 27) 197.
[25] R.B.M. de Vries, P. Buma, M. Leenaars, M. Ritskes-Hoitinga, B. Gordijn, Reducing the number of laboratory animals used in tissue engineering research by restricting the variety of animal models. Articular cartilage tissue engineering as a case study, Tissue Eng. B Rev. 18 (6) (2012 Dec) 427–435.
[26] P. Pound, M. Ritskes-Hoitinga, Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail, J. Transl. Med. 16 (1) (2018 07) 304.
[27] D.G. Hackam, D.A. Redelmeier, Translation of research evidence from animals to humans, J. Am. Med. Assoc. 296 (14) (2006 Oct 11) 1731–1732.
[28] L.J. Gamble, Q.L. Matthews, Current progress in the development of a prophylactic vaccine for HIV-1, Drug Des. Dev. Ther. 5 (2010 Dec 22) 9–26.
[29] Tirilazad mesylate in acute ischemic stroke: a systematic review. Tirilazad International Steering Committee, Stroke 31 (9) (2000 Sep) 2257–2265.
[30] E.D. Hall, P.A. Yonkers, J.M. McCall, J.M. Braughler, Effects of the 21-aminosteroid U74006F on experimental head injury in mice, J. Neurosurg. 68 (3) (1988 Mar) 456–461.
[31] I.W. Mak, N. Evaniew, M. Ghert, Lost in translation: animal models and clinical trials in cancer treatment, Am. J. Trans. Res. 6 (2) (2014) 114–118.
[32] I. Roberts, I. Kwan, P. Evans, S. Haig, Does animal experimentation inform human healthcare? Observations from a systematic review of international animal experiments on fluid resuscitation, BMJ 324 (7335) (2002 Feb 23) 474–476.
[33] R.Y. Calne, G.P. Alexandre, J.E. Murray, A study of the effects of drugs in prolonging survival of homologous renal transplants in dogs, Ann. N. Y. Acad. Sci. 99 (1962 Oct 24) 743–761.
[34] A. Ravelingien, F. Mortier, E. Mortier, I. Kerremans, J. Braeckman, Proceeding with clinical trials of animal to human organ transplantation: a way out of the dilemma, J. Med. Ethics 30 (1) (2004 Feb) 92–98.
[35] Z. Zhang, E. Bédard, Y. Luo, H. Wang, S. Deng, D. Kelvin, et al., Animal models in xenotransplantation, Expert Opin. Investig. Drugs 9 (9) (2000 Sep) 2051–2068.
[36] M.B. Bracken, Why animal studies are often poor predictors of human reactions to exposure, J. R. Soc. Med. 102 (3) (2009 Mar 1) 120–122.
[37] Animal research numbers in 2018 | understanding animal research [internet], Understanding Animal Research. [cited 2019 Aug 7]. Available from: http://www.understandinganimalresearch.org.uk/news/communications-media/animal-research-numbers-in-2018/.
[38] H.R. Ferdowsian, J.P. Gluck, The ethical challenges of animal research, Camb. Q. Healthc. Ethics 24 (4) (2015 Oct) 391–406.
[39] D.J. Langford, A.L. Bailey, M.L. Chanda, S.E. Clarke, T.E. Drummond, S. Echols, et al., Coding of facial expressions of pain in the laboratory mouse, Nat. Methods 7 (6) (2010 Jun) 447–449.
[40] S. Kääb, H.B. Nuss, N. Chiamvimonvat, B. O'Rourke, P.H. Pak, D.A. Kass, et al., Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure, Circ. Res. 78 (2) (1996 Feb) 262–273.
[41] G. Conti, C. Hansman, J.J. Heckman, M.F.X. Novak, A. Ruggiero, S.J. Suomi, Primate evidence on the late health effects of early-life adversity, Proc. Natl. Acad. Sci. U. S. A. 109 (23) (2012 Jun 5) 8866–8871.
[42] S. Festing, R. Wilkinson, The ethics of animal research. Talking Point on the use of animals in scientific research, EMBO Rep. 8 (6) (2007 Jun) 526–530.
[43] Reduce, refine, replace, Nat. Immunol. 11 (11) (2010 Nov) 971.
[44] M. Emerson, Refinement, reduction and replacement approaches to in vivo cardiovascular research, Br. J. Pharmacol. 161 (4) (2010 Oct) 749–754.
[45] A.M. Holmes, J.A. Rudd, F.D. Tattersall, Q. Aziz, P.L.R. Andrews, Opportunities for the replacement of animals in the study of nausea and vomiting, Br. J. Pharmacol. 157 (6) (2009 Jul) 865–880.
[46] Alternatives Literature Searching, Animal welfare information center | NAL | USDA [internet], [cited 2019 Aug 7]. Available from: https://www.nal.usda.gov/awic/alternatives-literature-searching.
[47] D. Stefanidis, N. Sevdalis, J. Paige, B. Zevin, R. Aggarwal, T. Grantcharov, et al., Simulation in surgery: what's needed next? Ann. Surg. 261 (5) (2015 May) 846–853.
[48] N.E. Seymour, A.G. Gallagher, S.A. Roman, M.K. O'Brien, V.K. Bansal, D.K. Andersen, et al., Virtual reality training improves operating room performance, Ann. Surg. 236 (4) (2002 Oct) 458–464.
[49] G. Ahlberg, L. Enochsson, A.G. Gallagher, L. Hedman, C. Hogman, D.A. McClusky, et al., Proficiency-based virtual reality training significantly reduces the error rate for residents during their first 10 laparoscopic cholecystectomies, Am. J. Surg. 193 (6) (2007 Jun) 797–804.
[50] T.P. Grantcharov, V.B. Kristiansen, J. Bendix, L. Bardram, J. Rosenberg, P. Funch-Jensen, Randomized clinical trial of virtual reality simulation for laparoscopic skills training, Br. J. Surg. 91 (2) (2004 Feb) 146–150.