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EDITORIAL

Transparency in Research involving Animals: The Basel Declaration and new principles for reporting research in BJP manuscripts

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This article discusses the background to the need for change in the reporting of experiments involving animals, including a report of a consensus meeting organised by the Basel Declaration Society and Understanding Animal Research UK that sought to Internationalise guidelines for reporting experiments involving animals. A commentary on the evolution of BJP's attempts to implement the ARRIVE guidelines and details of our new guidance for authors is published separately (McGrath, 2014).
This is one of a series of editorials discussing updates to the BJP Instructions to Authors

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Moving towards More Transparency in Research using Animals

Transparency has become a major issue in biomedical research employing animals. There is an increasing demand, by some sectors of our society, for scientists not only to provide accessible information to the public about their breakthroughs but also to provide more details about how they address animal welfare issues and on their efforts to limit animal studies to the minimum number necessary. In addition, there is a call for scientists to provide access to the results of animal studies that did not yield 'interesting' results or failed to confirm a hypothesis, i.e. so-called negative results. This is important so as to reduce the risk of unnecessary duplication by others aiming to test the same idea. However, many scientists, either in groups or as individuals, are still reluctant to openly discuss their work using animals, due to the possible threats that extremists may put upon them or their families. Making all research accessible on an equal footing of openness should reduce this pressure.

We have recently seen initiatives such as the UK Concordat on Openness on Animal Research. By July 2014, 80 organisations involved with life science in the UK signed a Concordat on Openness on Animal Research (Understanding Animal Research, 2014). By this they signed up to a series of commitments on how they would be more open about the ways in which animals are used in scientific, medical and veterinary research in the UK.

There are other ongoing attempts by agencies or groups to provide guidelines for the publication of research involving animals that give a framework for transparent reporting (Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) (Kilkenny *et al.*, 2010), Gold Standard Publication Checklist (GSPC) (Hooijmans *et al.*, 2011), International Council for Laboratory Animal Science (ICLAS) (ICLAS, 2012), Institute for Laboratory Animal Research (ILAR: http://dels.nas.edu/Report/Guidance-Description-Animal/13241?bname=ilar) (ILAR, 2011). This is in line with contemporary attitudes about providing more transparency in scientific reporting in general NISO/NFAIS (2013) National Information Standards Organization (NISO) (2013); U.S.

National Institutes of Health (NIH: http://www.nih.gov/about/reporting-preclinical-research.htm) (Nature, 2013). In this environment, it is timely for researchers to take the initiative and engage actively in this debate.

Position of the British Journal of Pharmacology

Like the journal's owners, the British Pharmacological Society (BPS), the editors of BJP endorse the principles of the UK Concordat on Openness on Animal Research and have, since their inception, accepted the principles of the ARRIVE Guidelines initiated by the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) (Kilkenny *et al.*, 2010; NC3Rs, 2015), the UK government funded organisation set up to promote the principles of the 3Rs. Indeed we co-published these guidelines along with several other journals (Kilkenny *et al.*, 2010) and published an editorial reinforcing those issues that we saw as most important for our discipline (McGrath *et al.*, 2010). We continue to argue that research involving animals is essential for the development of new drug targets and hence new drugs (McGrath, McLachlan & Curtis, 2014).

However, we are an international journal and a relatively small proportion of our articles come from work in laboratories in the UK (about 11%). Thus, we operate in an international context and must work around problems associated with very diverse national ethical frameworks and guidelines. In general we publish reports only of work that is consistent with UK law, but this can be challenging for those authors whose countries do not have a well-developed legal and ethical review framework. Even in those countries that do have one, this may diverge only in small ways from the UK guidelines, so they may feel patronised by a UK-centred approach. The Basel Declaration provides an opportunity for all countries to sign up to a universal protocol and allow rationalisation to one set of principles.

BJP is responding to this environment by changing its requirements for publishing research employing animals and here reports the recent promotion in the UK of the Basel Declaration. Like the Helsinki Declaration, which forever altered the ethical landscape of human clinical research, the aim of the Basel Declaration is to bring the community of basic scientists together and extend the implementation of ethical principles whenever animals are being used (such as the 3Rs, (Reduction, Refinement and Replacement of animal use in research, *see below*) and to call for more trust, transparency and communication on the sensitive topic of the use of animals in research. The Basel Declaration Society (BDS: http://www.basel-declaration.org), founded on October 5th. 2011, strives to promote the Basel Declaration (Basel Declaration Society, 2011).

So far the Declaration has been accepted in many European countries and we hope that, with appropriate promotion, it will become accepted by the rest of the world, providing a universal set of principles and guidelines. We note a set of International principles by the International Council for Laboratory Animal Science (ICLAS) (ICLAS, 2012), being set up concurrently along virtually identical lines, and we hope that these moves may become coordinated rather than competing.

The Basel Declaration

In 2010, a group of academic researchers representing various research fields that depend on research involving animals gathered in Basel (Switzerland) with the aim of developing a pro-active rather than a reactive approach. They argued that open communication is key to the public perception of the important role of animal experimentation in medical progress and also to counter threats by extremists. The desire to make the scientists' voices heard resulted in adoption of the Basel Declaration as a call for more trust, transparency and open communication on animal research. Since then, the Basel Declaration has been signed by several thousand scientists and endorsed by prominent research institutions and organisations all over the world. Specifically, the BPS has decided to join this growing movement and has endorsed the Basel Declaration. This contributes to the Basel Declaration Society (BDS)'s efforts to rally scientists around the globe. By signing the Basel Declaration, scientists commit publicly to the 3Rs and to respect the highest ethical and animal welfare standards in carrying out research using animals.

Additional major goals of the BDS are the improvement of training and education and the support of scientists engaged in public debates. A recent example is a case in Italy, where research using animals is under attack. With support from scientists in over 50 countries, the BDS is the first global grass-roots society that aims for a major impact on improving public understanding of animal experimentation by encouraging scientists to be proactive in establishing an ongoing and open dialogue with the rest of society

Report on the London Meeting of Basel Declaration Society

As part of its efforts to network with national organisations, the BDS teamed up with Understanding Animal Research UK to organise a conference in London entitled: 'Transparency in Animal Research: Implementing Openness in Publication and Communication' (Royal College of General Practitioners on July 1–2, 2013) (Basel Declaration Society, 2013a), which attracted participants from all over Europe and the USA. This conference was unique in bringing scientists together with a variety of representatives from animal welfare organisations and other interest groups (some advocating the 3Rs, others animal-free research), scientific journals, science communication groups and organisations, granting agencies, international science organisations and societies, national and European Union regulatory bodies and the pharmaceutical industry. The presence of all these stakeholders made for excellent plenaries and workshop discussions and resulted in four position papers (Basel Declaration Society, 2013b and attached as Supporting Information Appendix S1 to this article) that provide robust, consensual guidance for several of the most pressing issues in animal research, namely:

- Improving publication standards for research involving animals
- Open access to maximize the value of animal research
- Implementing the 3R Principles in Daily Research Practice – the Next Steps
- Use of Higher Mammals in Research

This editorial provides links to these position papers and reproduces them in an attached file <file> in order to ensure future availability.

1. Improving publication standards for research involving animals

Most relevant to this editorial is the adoption of a Basel Declaration Society position paper on 'Improving the publication standards of research involving animals' (Basel Declaration Society, 2013c and see Supporting Information Appendix S1). Briefly, previous systematic analysis has provided evidence that publications of some animal studies have significant deficits in study design, execution and/or statistical analysis. (This is borne out by BJP's own experience of submitted manuscripts, which are frequently rejected for these reasons. However, we must admit that some have slipped through our review process and have been published). Recently, several guidelines (ARRIVE, Gold Standard Publication Checklist (GSPC), (ICLAS), Institute for Laboratory Animal Research (ILAR)) have been produced that have tried to provide guidance on these issues, but no single one has yet been endorsed by the majority of journals. Participants representing the four above institutions attended the Basel Declaration Society conference and a position paper proposing a unifying strategy was adopted. The most important recommendation was that the different stakeholders team up with scientists and journal editors to develop and implement one set of universal rules that govern publication of animal research.

In addition to setting new standards for details to be included in publications, scientists, reviewers and editors must be asked to assess critically issues specific to animal studies as part of the regular review process. A major need identified by scientists and editors is for publishers to provide more space in manuscripts to allow authors to describe the study design, methods and analysis in sufficient detail. In addition, authors should include a description of their animal welfare and 3R efforts and an assessment of any potential suffering, i.e. items that should normally be covered by the deliberations of an Ethical Review Committee. Another major issue is the need to publish so-called negative results, i.e. studies that yield inconclusive results or none at all. The position paper recommends that authors briefly describe such results in the published text, and/or make all primary data, including 'negative results', available in 'Open Access' format as supplementary data (see also position paper 2. below; and in supporting document).

2. Open Access to primary data

Open access to primary data was the main focus of a second workshop. The resulting second position paper (http://www.basel-declaration.org/basel-declaration/open-access-to-maximize-the-value-of-animal-research/) (Basel Declaration Society, 2013d and see Supporting Information Appendix S1). Urges journals to deposit all primary data online in curated open access databases and also to provide Open Access space to deposit so called 'negative' results. In addition, funding agencies are asked to insist that all results are made available either by publication or deposition in open access databases. This seems likely to be the most effective way to achieve this end, with funding agencies and journals working together, i.e. the funding agencies mandate the recipients of their funding, first to publish primary data and secondly to do so in 'Open Access' resources, which someone needs to develop and to which the journals need to provide links. Resources and Open Access databases are already in place for several vertebrate model systems. Resources and repositories such as INFRAFRONTIER/EMMA (2015) (www.infrafrontier.eu) or KOMP (2015) (https://www.komp.org) for mice, the Zebrafish International Resource Center, ZIRC (2015) (http://zebrafish.org), the Rat Genome Database (http://rgd.mcw.edu) (Shimoyama *et al.*, 2015) and FlyBase (2014) (http://flybase.org) have established successful models for sharing animal models, protocols and genetic information, as well as a wealth of cross-referenced data. Ideally, these existing resources and repositories should be adapted for general use and a common entry portal to all resources and new repositories should be established to allow for straightforward keyword-based searches. The creation of the necessary infrastructure is certainly not trivial and will require additional financial resources, but in the long run study design in research involving animals would be improved and unnecessary duplication avoided. While this approach is feasible for the public sector, the extent to which this could be used by industry needs to be determined, in particular taking commercial interests into account.

3. Implementation of the 3Rs (Replacement, Refinement and Reduction of animal use in research)

The conference developed a series of Next Steps in disseminating best practice worldwide, summarised in the third position paper (Basel Declaration Society, 2013e and see Supporting Information Appendix S1), including the need to further improve education and promotion of the 3Rs at an early stage in scientists' careers, embedding the principles in the culture of research organisations and professional bodies as well as better informing the public. It was pointed out that funding dedicated to achieving the 3Rs is insufficient in most countries, e.g. specific research funding streams are needed to support the development and validation of non-animal alternative methods. Promotion of the 3Rs by those who accept them in those countries yet to accept them, is considered essential.

4. Higher Mammals

As the public has a high level of concern for the use of mammals, it is of particular importance that the researchers

using them communicate their studies transparently, to help clarify any misunderstandings and prejudices. Indeed, it has been the experience that scientists who get help from communication specialists to discuss their research with the general public are faced with fewer threats.

Public concern for the use of animals in research is often focussed on particular mammals including domesticated species (such as pigs, cats and dogs) and non-human primates. This is the case despite them representing only a small fraction of research animals used (e.g. in Europe ~0.4%). However, the vast majority of participants supported the notion that 'higher' mammals remain essential models for both basic and translational research. Higher mammals are used when rodent and rabbit models have been shown not to be appropriate for physiological or behavioural reasons, or for studies of evolutionary questions.

In particular, it is preferable that pre-clinical trials be conducted in several species before trialling new treatments in humans. Examples were convincingly illustrated by several of the presentations during the two-day conference, which showed that many species from the most primitive to the most evolved had distinctive parts to play in the discovery of knowledge. The corresponding position paper emphasizes that the use of higher mammals must be carefully justified and that their highly evolved nervous systems demand special care and attention to animal welfare. This is summarised in the fourth position paper, 'Use of Higher Mammals in Research' (Basel Declaration Society, 2013f and see Supporting Information Appendix S1).

Conference outcomes overall

As well as allowing scientists to engage with the different stakeholders and critics of animal research, the London Conference produced important results and guidelines as summarized above. These corroborate the notion that transparency and open dialogue increase understanding of both the needs of scientists and the concerns of critics in a mutually beneficial way. Therefore, the Basel Declaration and its Society will continue to spearhead openness and dialogue between the various stakeholders and national organisations at a global level. This should result in better research involving animals. The well-being of living creatures entrusted to us is essential for studies to advance knowledge and enable medical progress for both humans and animals.

Editorial Action by British Journal of Pharmacology

In the interests of transparency, BJP will adopt the consensual principles advocated by the Basel Declaration Society and the UK Concordat on Openness on Animal Research. To implement these principles, authors will be required to provide, as a condition of publication, additional information on the ethical framework, experimental design and analysis of their experiments and encouraged to place the primary data in repositories that can be accessed by other scientists.

The editorial board of BJP is, thus, changing its Instructions to Authors from mid-2015 to reflect the Basel Declaration consensus principles:

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- more robust detail on experimental design on experiments involving animals,
- justification for the choice of experimental model,
- clearer information on the legal and ethical framework and approval by Ethics Committees
- more detail on animal welfare.

Many of these issues/matters concern good experimental design and appropriate statistical analysis. It is a common mistake for example, to think that fewer experiments necessarily produce better science. One of the most common errors that we find in review is that too *few* experiments lead to under-powered studies that do not lead to sound conclusions and so would require more experiments in the long run to clarify false leads. This is discussed in more detail in a separate editorial (Curtis *et al.*, 2015).

Open Access to Primary Data

We will present the opportunity for authors to provide, in supplementary files, the primary 'raw data' that underlies the summary data normally provided and which provides other researchers with the opportunity to interrogate their data in different ways. For this, complete details of experimental protocols and practices must be clearly described. Authors will also be encouraged to deposit data in external repositories if these are appropriate and useful places to put them.

We will also request authors to place, in a supplementary file, information on "negative data", i.e. experiments that did not provide evidence that added to their arguments; we are sceptical about how much this opportunity will be taken up in a regular manuscript, and it would be hard for it to be mandated. There are suggestions, however, that funding bodies may insist that the results of all experiments be published, so that it may become mandatory. It is important that what might appear to be 'failures', that account for some of the animals used in a study, may result because the protocols proved impossible to implement, the animals became unhealthy, etc. rather than yielding datasets which 'failed' to support or reject an hypothesis in some way. While transparency in this respect may seem distracting to the scientist, being clear and open about all aspects of their work will further remove the misconception of secrecy. Thus accounting for animal numbers should be included in the animal welfare section of all publications.

This end might also be achieved by a separate publication showing that a hypothesis is incorrect. Thus, in a parallel move, our sister journal, Pharmacology Research & Perspectives, is pro-actively pursuing a policy of encouraging the publication of papers involving target validation – publica-

tion of negative findings including preclinical papers that show a hypothesis is incorrect or papers on drugs that have failed in early clinical development (http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2052-1707) British Journal of Pharmacology (2015a).

Since BJP is compliant with the principles of Open Access, http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1476-5381/homepage/FundedAccess.html (British Journal of Pharmacology, 2015b), these proposals also meet the criteria of the Basel Declaration's position papers, in which Open Access is advocated. We encourage other journals to follow these same principles.

Implementation of the 3Rs (Replacement, Refinement and Reduction of animal use in research)

We will require that authors provide a more structured Methods Section so that reviewers and readers can easily find the required information on research techniques, ethical requirements and experimental design without searching. These principles are not exclusive to Research involving Animals so we have divided the requirements into those required for all experimental work (Curtis *et al*., 2015) and those particular to research involving animals or animal tissue. This is described in detail in another article (McGrath & Lilley, 2015). The information required must be inserted at a specific place in the manuscript, facilitating its discovery by reviewers and readers. Every manuscript will require a section on 'Compliance with design and statistical analysis requirements', while those involving animals will, in addition, require a section on 'Compliance with ethical requirements for studies using humans or animals'. We will ask authors to state that they adhere to the guidelines of ARRIVE and the Basel Declaration but will also ask them to provide specific information that is required by this adherence.

Higher Mammals

BJP operates on the principle that animal experiments will remain essential in the foreseeable future for biomedical research. The choice of model and species must be decided by the authors and will depend upon the problem to be solved. We will, however, encourage authors to be clear about when, how and why they use animals in research and to consider carefully whether their research involving animals cannot be conducted using alternative methods.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://dx.doi.org/10.1111/bph.12956

Appendix S1 Improving the publication standards of research involving animals.