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EDITORIAL

BJP is changing its requirements for scientific papers to increase transparency

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BJP is changing its procedures for the submission of articles so that authors can optimize transparency and experimental design. This relates to current moves to strengthen the robustness of the basic research that underpins drug discovery and therapeutics. To this end we are publishing new Instructions to Authors (ITA). Some are already in place and take immediate effect while others will be introduced over the next few months. Emphasis is placed on gathering essential information that authors often forget to include; this will also facilitate peer-review by hard-pressed reviewers. We have been in discussion with the Editors of other Pharmacology journals and plan that similar changes will be taking place across the sector. This will ensure that the various generic guidelines are more clearly specified for pharmacology.

The major changes will be supported by three editorials:

1. In order to link published work to the growing network of databases we are introducing hyperlinks to drug targets and key drugs in the authoritative Guide to PHARMACOLOGY database of the International Union of Basic and Clinical Pharmacology, which is now produced with the support of BPS. This is then further linked to other biological and chemical databases, placing the work first in a pharmacological then in a broader scientific context. (McGrath *et al.*, 2015a).
2. We have assessed the implementation of the 2010 ARRIVE guidelines for reporting experiments involving animals and respond by significantly strengthening our requirements, especially relating to disclosure of information, rather than urging compliance with respect to every conceivable issue (McGrath & Lilley, 2015). As an international journal we believe that this must be done on a worldwide basis, taking account of differing practices but adhering to one ethical standard (McGrath *et al.*, 2015b).
3. Inadequacy of experimental design and statistical validity of analysis of drug-related research that underpins the discovery of new medicines has attracted recent criticism. We will publish new guidance for reporting statistical analysis and experimental design (Curtis *et al.*, 2015).

LINKED EDITORIALS
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General background

With this article we kick off a series of editorials that are interrelated. They discuss how we are responding to the current 'Transparency Agenda' as set out in the recent UK Concordat on Openness on Animal Research (Understanding Animal Research, 2014), the Research Councils UK guidance to grant applicants (http://www.rcuk.ac.uk/media/announcements/150415/: Research Councils UK, 2015), the USA NIH Guidelines on reporting preclinical research (US National Institutes of Health, 2014a), the ARRIVE Guidelines (Kilkenny *et al.*, 2010) initiated by the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs), the UK government funded organisation set up to promote the principles of the 3Rs (NC3Rs, 2015), and the Basel Declaration, an international consensus calling

for more trust, transparency and open communication on animal research (Basel Declaration Society, 2011 and see McGrath *et al.*, 2015b).

We will be making changes to the instructions to authors that tidy up and rationalize the old instructions, as is inevitable from time to time, and, as a general principle, require authors to state their practices rather than tick boxes that are seen only by the reviewers, making the reporting of research more transparent and consistent.

This is our contribution to the current consensus that is endorsed by many other leading journals (US National Institutes of Health, 2014b), but specified for our field of Pharmacology. As the recent consensus document initiated by NIH said, 'The hope is that that these guidelines will not be viewed as onerous, but as part of the quality control that justifies the public trust in science' (McNutt, 2014; Nature Editorial, 2014).

Scientific journals must continuously evolve to provide the highest standards of reporting in a changing world. BJP is about to change a number of requirements for papers submitted for publication to reflect current developments in electronic publication and the requirement for clarity and transparency. This editorial introduces this and will be followed by a series of articles providing more detail on specific aspects.

Scientific Journals are the place where scientists communicate their work to anyone who is interested in knowing what has been discovered. The readers are most often other scientists who want to then add more knowledge to this store and along the way the knowledge can help produce new inventions. This is the rubric of pre-clinical medical research. The knowledge is mostly biological and the inventions are new forms of treatment for human ailments. Devising new medicines is of enormous social and economic importance so it is important that we do our best to ensure confidence in the disclosures (published papers).

It is obvious that results must be credible, which means that experimental design and statistical analysis, the basis upon which most authors derive and declare an effect, must be carried out properly. It therefore becomes crucial that experiments are optimally designed, and the assumptions upon which statistical tests are based, are adhered to. Indeed, rather than concocting inappropriate statistics to claim an effect of marginal biological importance, some studies would do better to show the data (Drummond & Vowler, 2011; Motulsky, 2015).

As Editors, we are frequently astonished by the absence of necessary information from submitted manuscripts. The authors almost always provide the information when asked and have often provided it in written form when they applied for their funding. However, they have not seen fit to include it in the publication of their work by which they will be judged in perpetuity.

Furthermore, when scientists are under pressure to 'publish or perish' their desperation to find something 'significant' may push them to 'make fools of themselves' (Colquhoun, 2014) by devising statistical tests to show a 'difference' between rather similar sets of data, when it might be more circumspect to consider whether this 'difference' is of any biological importance. So, reducing the possibilities for spurious use of statistics should reduce the likelihood of authors deluding themselves as well as wasting other people's time.

Achieving this is, of course, dependent on the education and training of scientists and on how they organise to do their work, and can be influenced by the organisations that fund them. However, journals are the visible face of science and can be the scapegoats when science itself comes under fire. If the science that they publish is somehow substandard is that the fault of the journals? It is not generally the case that journals underwrite or endorse the conclusions of the work they publish. However they have an inherent responsibility to assure the quality of their published content through the process of pre-publication peer review.

What can journals do to guarantee standards? Most importantly the values of reported numerical data and their interpretation should be correct and fair. This is impossible to police with 100% effectiveness, but transparency of reporting is the minimum necessary requirement to allow an interrogation. In principle the editors should also ensure that an article reports what was done well enough for someone else to repeat it. Finally, the work should be well enough designed that it can answer the questions that it sets.

That doesn't sound much but if what was done is not reported fully and transparently then the knowledge obtained cannot be properly peer reviewed and any resultant publication cannot form a sound platform for others.

This underlies recent criticism of basic medical research. Some analysts have suggested that a high proportion of new drugs effective in preclinical studies fail to translate into treatments (Scott *et al.*, 2008) and that key experimental findings cannot be repeated (Mullard, 2011). There are of course many possible reasons for this other than bad experimental design or improper statistics, e.g. on-target adverse effects and off-target toxicity. However, others have then made a false corollary suggesting that experimental work, particularly work involving animals, is wasteful (Pound & Bracken, 2014) and this is propagated in the literature as if it were a general truism (Godlee, 2014). This is despite the obvious fact that all new drug targets that ***do*** result in a new therapy have come through this route regardless of the attrition rate (McGrath *et al.*, 2015c).

The most important message is that we need to strive to improve standards. Everyone needs to play their part in optimising standards, including Universities training the scientists, institutes employing them and government, industrial and philanthropic bodies funding them. An accreditation system for laboratories and scientists might help. However, journals can have an influence by setting standards for work that they publish and the rapid development of electronic media places more tools at their disposal. For example BJP regularly publishes guidance on best practice in statistics for pharmacology (British Journal of Pharmacology, 2015a) and Animal Models in Pharmacology Research (British Journal of Pharmacology, 2015b).

Is there a problem?

1. Linkage to and among databases

Scientific papers are still largely presented as if they were printed on paper. Now that most publications operate

completely electronically there is an opportunity to enrich content with electronic links to databases. Placing new work in the context of what is already known is normally left to the judgment of the authors, moderated by peer review. However with the availability of powerful databases, each piece of work can be linked to the state of the art. A major feature of current biological science is the creation and curation of databases documenting drug targets in terms of the genome, proteins and phenotypes and their interlinkage. Pharmacology increasingly uses molecules and techniques that rely on these databases but has not been effective, particular in publications, in linking in the pharmacological 'data' especially functional information on drug targets and the drugs (ligands) that act upon them. There is also a perceived need for nomenclature standards, without which linkages between databases become impossible.

This is now all possible by employing the Guide to PHARMACOLOGY, an expert-driven guide to pharmacological targets and the substances that act on them (Alexander *et al.*, 2013; Pawson *et al.*, 2014). This takes the form of an open-access database and contains links to other relevant databases in biology and chemistry. It is run under the auspices of IUPHAR, the International Union of Basic and Clinical Pharmacology so carries official international approval. Major strengths are the classification of all human genome drug targets and nomenclature thereof and the inclusion of functional pharmacological data in which other databases are very deficient. By linking drug targets and ligands to the Guide to PHARMACOLOGY a journal can link through to the other databases and place the work in the paper firmly in the context of the greater world of current knowledge as contained in the databases. The essence of the database is permanently archived in the biennially published Concise Guide to Pharmacology (Alexander *et al.*, 2013).

2. **Transparency in Research involving animals**
Along with six other journals, BJP published the ARRIVE guidelines in 2010 (Kilkenny *et al.*, 2010) and accompanied this with a 'Pharmacology-specific' Editorial to emphasize what we thought was important (McGrath *et al.*, 2010). In the peer-review process we asked authors to comply with these guidelines.

   In 2014 we reviewed a random sample of published papers with an eye to whether we were succeeding or not.

   The bad news was that we still had deficiencies in some design and statistical analysis matters despite this being a focus of ours; this related largely to clarity of numbers of animals used, authors often glossing over group sizes that might be too small, leading to exactly the confidence issue mentioned above. So this was really part of the same issue of experimental design in general.

   In addition there were inadequacies in explaining welfare issues in some papers; no suggestion of poor welfare, just lack of detail, again leading to potential loss of confidence for those who might wish to build on the work.

   The good news was that authors referred to the ARRIVE guidelines and many made an effort to incorporate aspects that they would not previously have thought to include.

   Nevertheless we concluded that the normal peer-review process is not succeeding in 'enforcing' the guidelines enough and must be adapted.

3. **Experimental design and statistical analysis.**
The criticism levelled at pre-clinical research, that experimental design and statistical analysis could be improved, needs to be taken seriously. Our experience as editors has been that, on first submission, many manuscripts do not reach the required standard in these respects and are frequently rejected on that basis. We wondered whether quality had changed over the last few years.

   Acknowledging the irony that a full statistically valid survey was unlikely to yield incontrovertible results, due to the many changes that have taken place over time, we did a brief analysis.

   We randomly selected a recent volume (171) and 15 consecutive papers from a 20 year old month-matched volume (112) of British Journal of Pharmacology and evaluated the first 15 consecutive papers from each. In the recent volume, 11/15 disclosed in Methods the correct use of a post hoc test following analysis of variance. In the issue published 20 years ago, only 3 of 15 of papers did this. Indeed, most papers in the sample of volume 112 had no statistical analysis section in Methods. Worse, a large proportion made no mention of any use of statistical tests at all, anywhere in the paper.

   The improvement therefore is substantial and tangible. However, of the papers sampled from the recent volume (171) of British Journal of Pharmacology, only 27% report use of equal group sizes, only 13% ensured at least n = 5 independent samples were used per group throughout the study, and none reported randomization or blinded analysis, all of which should really be required.

   We deduce from this that, in the present day, the majority of papers published in British Journal of Pharmacology use the 'correct' statistical analysis, but the provenance of the numerical data can be questioned. This inevitably reduces confidence in the study and its conclusions. The problem, in short, lies in the design of the studies (or in reporting the design) more than in the analysis.

Our Response

Changes coming up in BJP

BJP is changing several aspects of what is required of potential authors, and is creating more electronic linking to databases, more transparent reporting of experiments involving animals and more robust requirements for experimental design and statistical analysis. In turn it is changing the format of its articles to reflect this and enrich content. This is all in line with the current consensus for providing more transparency

and openness in scientific reporting and is made possible by the recently-introduced online-only format of the journal.

Our Instructions to Authors have been extensively revised and we will set out the background to the new requirements in a series of short editorials over the coming months.

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