Reviewer’s report

Title: Refining animal models in fracture research: seeking consensus for changing the agenda in optimising both animal welfare and scientific validity for appropriate biomedical use

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Reviewer: P.René van Weeren

Reviewer’s report:

General

This paper is the document that resulted as a consensus after a meeting of researchers from various disciplines, which focused at the use of animal models in fracture research. At the end of this meeting a number of recommendations, proposals for standardisation and other guidelines were adopted, which are listed in the summary of the paper and in the conclusions. The authors call it a “position paper”, indicating that with this paper they want to take a certain, defined stance with respect to a variety of items related to the topic. They have the clear ambition not only to contribute to the public debate on the item, but also to have a leading and trend-setting role in this discussion, given their recommendation that the standards proposed in this paper be used by funding bodies as an evaluation criterion for the decision on future project proposals.

This paper reflects a laudable initiative, i.e. the attempt to improve the biomedical research undertaken in the area of fracture healing by improving the character and the use of animal models in this area. There are two main reasons to do this. First is an animal welfare reason: a better and more discriminate use of animal models will reduce unnecessary suffering of experimental animals. The second reason is improving the quality of the research itself: by better standardisation and a more careful execution of experiments using animal models, the outcome of research will be more reliable. Both reasons are more than valid and, although some of the recommendations can be argued, the intent of the paper cannot but be praised.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

There are a few major comments to be made with respect to this paper, which for the most part are more of an editorial character than referring to technical matters.

First, the status of the paper is somewhat unclear. A “position paper” suggests an opinion, put forward for open debate. Style and content of the present paper give the impression, however, that the paper seeks to set standards without giving much room for opposing views and continuing debate.

Second, for a paper of this type other criteria apply than for a standard scientific paper. In fact, a paper like this should, with respect to its technical qualities as a paper, be compared to an opinion paper in Times Magazine or Newsweek, i.e. it should be of a good journalistic quality. Unfortunately, it is clear that professional journalistic input has failed, and some critical remarks with respect to the readability have to be made:

· First of all, the paper is excessively long. Although it is understood that length is not a limiting factor in e-publishing, it certainly is with respect to readability and the willingness of people to read an article.
· There is a remarkable variability of level of abstractness between and even within the different sections and paragraphs. To give an example: The reader is encouraged to think with the authors about the applicability of the “August Krogh Principle” for this type of research, but is also informed that slings for small ruminants should be checked three times a day to prevent skin sores. In many more places the paper seems to lack a balance between the philosophical and the technical approach.
· There is much repetition, sometimes more or less textual as in the case of the last part of the summary and the conclusions. See also under “specific comments”.
· It is, again from a journalistic viewpoint, not a good thing to have such a large text without a single picture. It might be argued that in scientific publications figures should only be used when strictly needed and not as mere illustrations. That is fine, but in that case please apply the same rigid rule to the text.

A not-so-much journalistic but more scientific remark is that some statements are made without proper
backing by facts or references. That is hardly avoidable in a paper that is basically an opinion paper, but care should be taken. For instance the statement on the apparent lack of compassion from medical doctors for their research animals (on p. 26) is rather bold and can easily be taken as an offence.

The list of recommendations at the end of the paper is useful, although here too some effort towards shortening the statements and making them more-to-the-point would be a good investment. Some of them are really stating the obvious, for example generating evidence-based data is the goal of any scientific study and not solely a hallmark of a “justified animal study”. Bad science is never justified, regardless of whether animals are involved or not.

It is recommended that the study be substantially shortened and thoroughly rewritten with help of a professional science journalist, or somebody with equivalent skills. Further, the ambition of the study should be clearly defined (“setting the guidelines” or “starting up the discussion”), the study may then be a very useful contribution to the enhancement of the effectiveness of animal models in fracture repair and the reduction of unnecessary suffering of experimental animals, hence promoting animal welfare.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Summary
The summary is concise, but is not a real summary as it is merely the combination of a part of the introduction and (almost textually) the list of recommendations from the conclusions. It is understood that a paper like this cannot be summarised in a short abstract, but now it feels as a duplication within a paper that is already much too long.

Introduction
The introduction sets the stage well, is concise and well-written.

Minor remark:
P6, last line of citation: Superscript “61” unclear.

Defining “a justified” animal study
This section uses 2½ pages to make clear why animal models are so terribly inadequate, and ½ page to state that criteria for the use of these models in musculoskeletal research should be reconsidered. One of the conclusions is that good research should be hypothesis-driven. That is true, but not restricted to the use of animal models. It is understood that this section takes a stance against the indiscriminate use of animal models, which is o.k., but it is a bit over the top.

A comment should be made on the large citation (p7, bottom) about the use of animal models with reference to the internet site “http:/www.mrmcmmed.org”, which appears to be a site maintained by the “Medical Research Modernization Committee”, an organisation of researchers who attribute part of the lack of progress in medical research to the use of inappropriate models. That is fine and they may certainly be right, but what is the authority of this group? They are now being cited in the paper as if their view is the eternal truth, set in stone, which thus has to be taken for granted. There seems to be no independent, critical, scientific attitude from the authors of the paper in this case.

Minor remark:
P7, heading “a justified” ..(closing parentheses).

Anesthesia and pain management
This is an important section, as this item is directly related to animal welfare. However, acknowledging the importance of the item, it suffers from the same flaws that characterise the other parts of the paper: it is long, sometimes repeats itself, and is of a very varying level of abstractness. Another comment is that pain management is one aspect of animal welfare, but certainly not the only one. Deprivation of normal behaviour is another aspect, which may even have more impact than a certain pain level and which is hardly discussed (probably because of the lack of behaviourists in the panel). This is one of the reasons why the paper in its entirety gives a somewhat unbalanced impression.

Considerations for establishing standards in surgical, biological and mechanical aspects of in vivo models for research in mechano-regulation of bone repair
There was clearly much expertise on this item in the panel. The section goes relatively far in-depth. The information is interesting and to-the-point, but at times the text gives the impression of having been written for a textbook, rather than for a position paper. Less detail would do. Further, there is some duplication with
other sections from the paper, e.g.:
· P17, line 9 from bottom: the three R’s are explained (and were already at the start of the anaesthesia-section).
· P19, last paragraph: in part repetition of limiting factors of animal models as listed in the introduction.

Minor remarks:
P15, line 10 from bottom: remove double dot after “bone”.
P21, line 5: …of critically sized..

Fracture model standardization
The call for standardised models is understandable and most probably justifiable. An essential question that is not answered in this section is how standardised models can account for the extremely varied and complex situations encountered in (human) real life situations (the dissimilarity of those complex situations with the animal models being one of the major points of critique of those models, as extensively and rightfully pointed out in the introduction)?

The somewhat challenging statement on the compassion of human surgeons for their research animals (P26, 2nd paragraph) has been mentioned earlier.

Minor remark:
P10, line 10 from bottom: ..as fracture healing…

Model standardisation
This section is largely a repetition of what has been said earlier.

Minor remark:
P26, line 7 from bottom: ..number of animals used,…

Post-operative management and evaluations
This section is relatively detailed and sometimes stating the obvious (“applying GLP guidelines is useful…”). There is, again, some imbalance. We are taught to trim the claws of sheep (which is good practice indeed, but not less true for other species such as goats or horses), but nothing is said about for example specific post-operative nutritional requirements, parasite control, ventilation requirements, etc., etc. I do not think these details to be necessary for this paper, but why not remain on the same level throughout the paper?

The internet site mentioned here gives the Swiss guidelines for housing of experimental animals. Those can without any doubt serve as an example, but they are referred here as having global authority.

Minor remarks:
P28, line 3: Phrase does not sound well, probably:…drugs, as well as with the wound healing…
P29, line 8: Where does superscript “c” refer to here?

Ethical aspects
Whereas the entire paper is very (too) extensive in many parts, the contribution from the ethical side is disappointing. This section does not contain a single reference, and is very superficial. The ethical aspect of animal experimentation is of growing importance and paramount in ensuring acceptance of these experiments by the general public. There is in the present paper a very large discrepancy, both in quantitative and in qualitative terms, between the technical sections and this section.

Need for international harmonization
There is no doubt that international harmonisation is needed and that setting a step towards this harmonisation is one of the main purposes of this paper. However, this section focuses very much on EU policy, whereas the use of animal models for fracture research is being practised on a somewhat wider scale.

Conclusions
This section is largely a repetition of the summary, see earlier comment.

Minor comment:
P33, line 5 from bottom: “..surgeon with an advanced..

References
Minor comment:
P38, number 37: ..der Knochen. (Change „k“ to „h“).

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.