Author's response to reviews

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

Authors:

Jorg A Auer (jauer@vetclinics.unizh.ch)
Allen Goodship (goodship@rvc.ac.uk)
Steven Arnoczky (arnoczky@cvm.msu.edu)
Simon Pearce (simon.pearce@aofoundation.org)
Jill Price (jprice21@hotmail.co.uk)
Lutz Claes (lutz.claes@medizin.uni-ulm.de)
Brigitte von Rechenberg (bvonrechenberg@vetclinics.unizh.ch)
Margarethe Hofmann-Amtenbrinck (margarethe.hofmann@bluewin.ch)
Erich Schneider (erich.schneider@aofoundation.org)
R. Muller-Terpitz (mueller.terpitz@uni-bonn.de)
F. Thiele (felix.thiele@ea-aw.de)
Klaus-Peter Rippe (rippe@ethikdiskurs.ch)
David W. Grainger (david.grainger@utah.edu)

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Author’s response to reviews: see over
MS: 9102691161235338: Refining animal models in fracture research: seeking consensus for changing the agenda in optimising both animal welfare and scientific validity for appropriate biomedical use

Authors: Joerg A Auer, Allan Goodship, Steven Arnoczky, Simon Pearce, Lutz Claes, Brigitte von Rechenberg, Margarethe Hofmann-Amtenbrinck, Erich Schneider, R. Muller-Trepitz, Felix Thiele, Klaus Peter Rippe and David W Grainger

Response to Review:

We appreciate the reviewers’ insightful comments and careful review. Our revisions should improve the quality and content of the manuscript substantially. We respond to each below. Thank you!

Reviewer 1 comments:

1) The report is excessively long, and as such is unlikely to be read in detail by the target audience. A significant reduction in length could be achieved by avoiding repetition of key points in each of the sections. The current document contains separate sections dealing with each of the broad types of animal model (e.g., for fracture repair, implant testing, etc.). I suspect these were drafted by different individuals on the working group, who all make similar points – the need for standardised models, the need for good study design, for competency in surgery and anaesthesia, etc. These are all valid points, but do not need to be repeated, and dealt with at length in each section. Carefully selected examples to illustrate the confounding influences of these factors, for each of the groups of models mentioned, could be included in a single general section. Alternatively, a table of the model groups with examples could be provided.

Authors’ response to comment: The manuscript has been reduced in length some 25% and extensively re-arranged, condensed and revised with these comments in mind to eliminate redundancy and improve readability. In reference to the model groups applied in research, it has to be kept in mind that presently a list of generally accepted models in fracture research exists. Each major facility uses its “favored” models. The aim of this paper is to open the dialogue and contribute to eventually arriving at a consensus opinion.

2) The sentence structure is often over-long, making the text very difficult to read – even for someone with English as a first language. This report will be of international interest, and I strongly advise editing of the style of the manuscript to make it more accessible. This would also provide further opportunity for reducing it in length.

Authors’ response to comment: We have revised the entire manuscript to improve comprehension and readability. We hope this is significantly improved.

3) There are a few sections that require grammatical corrections but these can easily be addressed in the editing process.

Authors’ response to comment: Done.

4) The majority of statements made are referenced appropriately, but some quite contentious areas are not supported by references. For example, on page 12, the discussion of pain and its consequences makes many statements that are only supported by references to the IASP education curriculum. It would be far better to reference this section more fully. The whole area of analgesic use in musculoskeletal research is contentious, and it is disappointing that the document does not address this more directly. Simply stating that “concerns have been raised…..” does not provide any support for ethics committees that may be
requiring analgesic use following musculoskeletal surgery. Some more definite statements about the relative effects of analgesic use compared to other sources of variation in such studies would be of value.

Authors’ response to comment: This comment is absolutely justified, but even the reviewer must accept that there is a wide range of “point of views”. As stated above, our aim was to open the dialogue among researchers and through this eventually arrive at an acceptable consensus. There is no doubt that the administration of certain anti-inflammatory drugs reduces suffering, but at the same time it also influences bone healing. Of course in clinical practice these drugs are administered to reduce patient suffering, accepting potential disturbances in fracture healing. However in research there are the “purists” that want to find out how fractures heal without any influence of anti-inflammatory drugs and there are the more pragmatic researchers that feel there is no use to study a situation that is not encountered clinically. Who is right is very difficult to assess.

5) The statement “Unfortunately, human surgeons sometimes appear to lack compassion for their research animals… on p26 is rather contentious, and is not supported by any data. I agree that examining the reported frequency of analgesic use in papers in this field suggests a lack of concern, it may simply reflect a lack of awareness of the potential animal welfare consequences of their research.

Authors’ response to comment: Two authors have observed this problem repeatedly and we now make the statement more specific with reference to these two authors. The fact that this is contentious does not mean to us that we should not mention it. Of course, documenting this in the literature will be impossible except with equally unsubstantiated claims from animal rights advocates.

6) Although I agree that obtaining imput and advice from veterinary professionals is important, the number of veterinary anaesthesia specialists with further research qualifications is relatively low. Similarly the number of laboratory animal specialists with high levels of expertise in anaesthesia and analgesia is also limited. This imposes some practical constraints on implementing some recommendations. I support the recommendations, but the need to develop appropriate professionals to support research perhaps should be highlighted.

Authors’ response to comment: Done.

Reviewer 2 comments:

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:

Authors’ response to comment: The manuscript has been reduced in length some 25% and extensively re-arranged, condensed and revised with these comments in mind to eliminate redundancy and improve readability. We hope this is significantly improved.

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.
Authors’ response to comment: see previous response – we believe addressed this issue to your satisfaction.

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.

Authors’ response to comment: We have tried to begin each argument philosophically and get more specific as the argument is developed.

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”.

Authors’ response to comment: We have re-arranged text, eliminated complete sections and revised with an emphasis on avoiding redundancy.

It is, again from a journalistic viewpoint, not a good thing to have such a large text without a single picture.

Authors’ response to comment: We added some pictures to satisfy this demand, knowing, however that it will expand the length of the paper again.

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.

Authors’ response to comment: Two authors have observed this problem repeatedly and we now make the statement more specific with reference to these two authors. The fact that this is contentious does not mean to us that we should not mention it. Of course, documenting this in the literature will be impossible except with equally unsubstantiated claims from animal rights advocates. The list you referred was commented as being redundant, because it was mentioned in the summary at the beginning and at the end as conclusion. To address the request of shortening the manuscript and remove redundancies, we omitted the conclusions. We hope you accept our response to the different requests.

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.

Authors’ response to comment: By completely rewriting, shortening and changing the style of the
manuscript we feel we responded positively to your request.

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.

Authors’ response to comment: See above comments. We hope we satisfy your request.

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

Authors’ response to comment: Thank you, we appreciate it indeed.

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

Authors’ response to comment: Eliminated.

Defining “a justified” animal study: This section uses 21/2 pages to make clear why animal models are so terribly inadequate, and 1/2 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.

Authors’ response to comment: We have eliminated a large part of this section and tempered our views.

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.mrmcmed.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.

Authors’ response to comment: Thank you for this comment. This importance of this citation has been changed

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

Authors’ response to comment: Done.

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.
Authors’ response to comment: We have re-tooled this section and condensed it quite a bit.

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.

Authors’ response to comment: We have added comments about animal behaviour twice now.

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.:

Authors’ response to comment: We have re-done this section as well, attempting to address these comments.

· P17, line 9 from bottom: the three R’s are explained (and were already at the start of the anaesthesia-section).

Authors’ response to comment: Eliminated.

· P19, last paragraph: in part repetition of limiting factors of animal models as listed in the introduction.

Authors’ response to comment: Redundancy eliminated.

Minor remarks:
P15, line 10 from bottom: remove double dot after “bone”.

Authors’ response to comment: Done.

P21, line 5: …of critically sized..

Authors’ response to comment: Done.

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)?

Authors’ response to comment: You raised an valid point. The authors feel that we have to start somewhere and go from there according to the answer of the following question: “How do you eat an elephant”? Answer: “One bit at the time”!

The somewhat challenging statement on the compassion of human surgeons for their research animals (P26, 2nd paragraph) has been mentioned earlier.
Authors’ response to comment: Two authors have observed this problem repeatedly and we now make the statement more specific with reference to these two authors’ experiences. The fact that this is contentious does not mean to us that we should not mention it. Of course, documenting this in the literature will be impossible except with equally unsubstantiated claims from animal rights advocates.

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

Authors’ response to comment: Fixed.

Model standardization: This section is largely a repetition of what has been said earlier. Fixed.
Minor remark:
P26, line 7 from bottom: ..number of animals used,…

Authors’ response to comment: Done.

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.

Authors’ response to comment: These comments are very valid and we addressed them in the revised manuscript.

Minor remarks:
P28, line 3: Phrase does not sound well, probably:…drugs, as well as with the wound healing…

Authors’ response to comment: Eliminated.

P29, line 8: Where does superscript “c” refer to here?

Authors’ response to comment: Corrected

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 acceptation 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.

Authors’ response to comment: You hit the nail on the head with this comment. As we stated initially, we want to open the dialogue among experts and through this we also hope to attract Bio-ethics specialists that contribute constructively to this issue. Presently there is very little to put your hands on. Hopefully we can change this in the future. But this paper cannot suffice all aspects.

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.

Authors’ response to comment: This has been reduced, focused and internationalized.

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

Authors’ response to comment: This was eliminated.

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

Authors’ response to comment: Fixed.

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

Authors’ response to comment: Done.

Reviewer 3 comments:

I suggest to combine parts of the introduction, the chapter on “defining a justified animal study” on page 7, the chapter on “the role of in vivo models in bone repair research” on page 17, and the chapter on “model standardisation” (pp 26), since all three chapters address similar issues with respect to the choice of animal model and therefore repeat each other.

Authors’ response to comment: Authors’ response to comment: The manuscript has been reduced in length some 25% and extensively re-arranged, condensed and revised with these comments in mind to eliminate redundancy and improve readability.

Although the paper discusses the role of in vitro and computer-based studies in fracture research, it does not deal with the human patient as best study object and alternative to animal experiments. What opportunities do we have nowadays, or are we missing, to directly study fractures in men?

Authors’ response to comment: You mean humans? We assume you are aware of the present kick to have prospective studies to address this issue. It is the view of the first author that effective prospective randomized studies on this issue are unethical. If you are convinced that one type of treatment is the best, how can you justify to apply a second-, or third rated treatment to patients – and this not just to humans (and just to men)? That’s all we can say.

Pp3 halfway: “a database should be established to facilitate selection of anesthesia and pain management protocols”. On http://altweb.jhsph.edu/ is a database on anesthesia and analgesia. Furthermore there is a large links section to links dealing with pain and distress (http://altweb.jhsph.edu/pain.htm). These should be mentioned.

Authors’ response to comment: This reference has been added. However to retrieve some meaningful information is very difficult.

PP5 last sentence 1st paragraph: The authors state “as the limitations and inaccuracies inherent in translating in vitro models results to in vivo equivalence”. The authors should substantiate this assumption, since this may be true in orthopaedic research, but is certainly not true in all research areas. The same holds for the statement on pp7: “Many past and on-going research efforts seek to establish new
and innovative approaches to in vitro modeling of in vivo complexity without clear progress or improved relevance”. The authors totally ignore recent progress. Although complex processes can yet not be totally replaced by in vitro methods, part of the results can be obtained by in vitro studies, although results have to be confirmed in in vivo studies.

Authors’ response to comment: We are not as convinced as you are that in vitro studies, while acknowledging the progress that has been made on this front, can replace in vivo studies. Can you help and convince us?

PP29. Termination criteria. Termination criteria are also named “Humane endpoints”. For humane endpoints several reference sources are available:
• The CD Humane endpoints in laboratory animal experimentation (http://www.vet.uu.nl/nca/documents/humane_endpoints)
• Several links to humane endpoints sources (http://altweb.jhsphs.edu/humane-endpoints.htm). These should be mentioned.

Authors’ response to comment: We added these references in the text. Thank you we were not aware of this web page.

Conclusions: Although the authors spend many words on animal models, and urge to formulate appropriate selection criteria for animal models, this is not returned in the conclusions. This important recommendation should be listed as well.

Authors’ response to comment: We omitted the conclusions to shorten the length of the manuscript. As stated several times we intend to open the dialogue among researchers and develop standard guidelines in a second step.

I also miss the important recommendation that Termination criteria (Humane endpoints) should be defined before each animal study starts.

Authors’ response to comment: Good point – done.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
PP8. (e.g., anti-inflammatory drugs, antibiotics19, anti-cancer20 and anti-osteoporetic therapies21. Missing closing bracket.

Authors’ response to comment: Fixed.


Authors’ response to comment: Fixed.

PP20. “fractional power law, approximating (body mass)0.67.” Delete brackets. Fixed.
3rd sentence: replace “euthanazed” with “euthanized”.

Authors’ response to comment: Fixed.
Discretionary Revisions (which the author can choose to ignore)
From “defining a justified animal study” (pp7) it is not clear whether this deals with research animals in
general or research animals in fracture research. In my opinion, it should focus on research animals in
fracture research.

Authors’ response to comment: We have focused on fracture research now with our revisions and have
eliminated large parts of this section. In some cases, defining a general animal study applies the same
criterion whether fracture focused or not.

PP 11. In the chapter on anesthesia and pain management, I miss a discussion on proper anesthesia
regime. The chapter focuses mainly on pain management.

Authors’ response to comment: Good point, but in view of the request to substantially shorten the
manuscript, there is no chance to include proper anesthesia protocols, because there are several to
mention and this goes beyond the scope of this paper.

PP23 and 26: the chapters on “fracture model standardisation” and “model standardisation” could be
combined.

Authors’ response to comment: Done.

PP30, top sentence. Judgement of termination should be made by a veterinarian or qualified animal
caretaker.

Authors’ response to comment: Done.

Submitted with honest respect.

Prof. J. Auer, Representative of the authors