Author's response to reviews

Title: Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin creme rinse for treatment of head louse infestation: a randomised controlled trial.

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Dear Editors

First I would like to thank my three reviewing colleagues for their very helpful suggestions and comments. I have made a number of revisions to the manuscript. Some of them were simply removal of duplication of wording or simplification of the presentation, achieved by rephrasing in a few places; others were specifically in line with those comments from the reviewers as follows:

Review by Rémy Durand


2. The last two sentences starting from “In those who did have lice...” have now been moved into the Discussion section and the order of words changed to suit that position.

3. As suggested I have entered an estimated cost figure per individual for both treatments. However, I was not sure which currency unit to use so I have selected the Euro, mainly because Hedrin Once is available widely in the European Union but not in North America. Please advise if you would prefer another currency.

4. I have restructured part of the Discussion section dealing with use of permethrin to explain why the material was selected (widespread use, familiarity with regulatory authorities) and why malathion was not selected (diversity of formulations making them not comparable and non-availability of the only product still listed in the UK).

Review by Ariel Toloza

The comment/question by Dr Toloza is not easy to answer within the manuscript. For estimation of sample size a reasonable balance need to be retained between minimising exposure of participants to investigative procedures and obtaining
adequate data to fulfil the purpose of a study. In this case the estimation was based on a “potential” efficacy for the permethrin comparator that, although optimistic, was not outside the bounds of possibility, in a similar manner to the way the estimation of efficacy for the dimeticone preparation was based on what the sponsor would have anticipated should all aspects of the study proceeded as they may have hoped. The other aspect of the balance is to obtain an estimate of numbers that is consistent not only with demonstrating the level of difference between treatments but also demonstrating the safety of the treatment regimen in use. This necessarily requires adequate numbers per group to satisfy the perceptions of the statistician advisors to both the ethics committee and the competent authority (MHRA). Given the sponsor estimate of how well they expected their product to perform (around 90% success) and the realistic view of how permethrin might fail to perform (15-20% success) and using standard approaches to confidence (95%) and power (80%) the numbers per group would have been 8 participants, clearly so open to statistical noise that almost nay result would have been meaningless. Even increasing the both levels of confidence and power to 99% the numbers per group would only have increased to 18 participants. Had we had prior knowledge of the outcome and used a true estimate, i.e. 70% success for dimeticone and 15% for permethrin, with 95% confidence and 80% power, the numbers would have only been 15 per group increasing to 36 per group for 99% confidence and 99% power. Thus, in satisfying the anticipated estimated bottom end number acceptable to the statisticians involved (of 40 based on previous experience) this somewhat artificial estimate was derived, which would address all possible eventualities of unprecedented outcomes, including drop out and unexpectedly high rate of failure for the dimeticone, and provide sufficient data to be confident of a true outcome that would be acceptable for regulatory purposes in those territories in which the dimeticone product was seeking regulatory approval.

Review by John Clark

1. I have now ensured consistency in the order of placing reported data for the two treatments as requested.

2. The Odds Ratios have been included for outcomes primarily because the current trend in presenting comparative data for treatment outcomes in clinical evidence reviews employs ORs more frequently than other measures (e.g. Absolute Risk/Rate, Relative Risk/Rate, etc). I can understand Dr Clark’s question as to the value but the primary justification for including them is that in the absence of quoting such data it has been a trend in some CE reviews to “mark down” in quality studies that do not contain them so essentially we are following a convention set by someone else.

3. I can fully understand Dr Clark’s puzzlement over the difference between “ovicidal activity” and “inhibition of egg hatching”. I apologise for omitting to qualify these two criteria. Primarily they were the product of a statistical algorithm to make distinctions between a single treatment regimen and a double treatment application regimen in that “inhibition of egg hatching” referred to prevention of eggs hatching/nymphs emerging at any point during the post treatment
assessment period and “ovicidal activity” referred specifically to no eggs hatching after the completion of treatment. I appreciate that this distinction was one of statistical semantics and unnecessarily confusing for any reader. Therefore, I have rationalised the information to only state “inhibition of egg hatching”, which actually covers both and makes the information a lot easier to understand. Just for information, the reason I have not used “ovicidal activity” is that in my opinion ovicidal activity generally implies some physiological mechanism, which in the case of physically acting preparations is probably not strictly correct, so I have opted for the slightly lengthier but probably scientifically more accurate description.

Regards

Ian F Burgess