Author's response to reviews

Title: Flaws in design, analysis and interpretation of Pfizer's antifungal trials of voriconazole and uncritical subsequent quotations

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Version: 4 Date: 12 January 2006

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Response to comments by John Ioannidis

General comment: We have modified the tone of our language while retaining our criticism.

1: Our requests to the corresponding authors of the voriconazole trials consisted of 5 rather simple questions (e.g. was allocation concealment ensured?). Yet the first authors declined or were unable to answer our questions and referred to Pfizer. Pfizer provided a lengthy and thorough response, which we have incorporated in our Cochrane review of the trials, but it was not useful for the analysis we have provided in our comment to Trials.

2: We don't think we have blamed any particular party in our paper. There exists a mutually beneficial relationship between companies, journals and authors, which we attempt to outline in our discussion. We believe it is unreasonable to expect drug manufacturers to be able to provide unbiased evaluations of their own products (and the literature so amply shows they don't), to expect authors to be uninfluenced by the prospect of publications in prestigious journals and possibly further research money from the companies, and journals to be immune to the income and numerous references that follows acceptance of these trials. However, it is clear from the literature that the dominant force behind all this is earning money on part of the drug companies. We have chosen to describe what we found and avoid getting into a detailed account of the underlying driving force, but in response to the reviewer's questions, we have changed our conclusion into two suggestions that should be easy to implement for journal editors.

3: We have added data on creatinine, as suggested.

4: The instruction to participating units was to administer amphotericin B "as usual". Since numerous departments participated, many from third world countries, it is extremely unlikely that the drug was given under optimal conditions. It demands careful planning to use pre-medication to reduce infusion related toxicity and substitution with electrolytes and fluid to reduce nephrotoxicity. This just doesn't happen without being described in a trial report, and the results also show very clearly that it could not have happened. Furthermore, if a requirement for supplemental therapy had existed, it would have appeared in the article for the very simple reason that this would have strengthened the conclusions; it would therefore have been highly attractive for the company to state this.

5: We are most thankful for this suggestion. We have elaborated on this point and believe it has improved our paper. We have now analysed a random sample of 50 references to the two trials.

Response to comments by Rodrigo Martino

The reviewer writes that the specific problems with voriconazole have been extensively recognised in the literature. We are not convinced this is the case and have now added an analysis of 50 articles that quote the voriconazole trials and which shows that there are problems with the recognition of the shortcomings of the trials.

The reviewer also suggests that we don't focus all our complaints against voriconazole and recognise that most other trials suffer similar, if not even greater defects. In response to this, we have extended our discussion section.