Author's response to reviews

Title: Cyxlo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk

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Author's response to reviews: see over
Dear Editor

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Cytlo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk
R Andrew Moore, Sheena Derry and Henry J McQuay

Firstly we would like to thank Angel Lanas and Leslie Cleland for their detailed and insightful comments. We understand the frustration with the issues of risk calculation and presentation, which brings with it an imperative to strive for clarity, but with the danger of losing some precision. Moreover, we struggle with averages from studies when patients are never average and expect better than average from their carers.

Angel Lanas

1. We have addressed Angel’s first point in two ways. Firstly, throughout the manuscript we speak of complicated GI events and serious CV events. Secondly, we have altered the Methods section to bring descriptions of events together. The first paragraph describes them, we think adequately. We also point out here for clarity that our analyses were eventually based only on meta-analyses of RCTs and RCTs, despite our intent being to seek observational data also. We point out in Results that almost all the events had independent adjudication apart from GI events with celecoxib, chosen because it was the largest and the most conservative estimate. The information used for GI and for CV events was therefore very similar. Observational data were lacking, and they were the ones with different outcomes, GI and CV. They are described in results, but are not used in analysis. This should not now be a problem.

2. The term “closest equivalent” has been removed. It was originally included for observational studies, but where cohort studies are referred to the exact outcome used is given, so it was redundant.

3. We have changed the wording in methods to explain that we obtained both the number of events and the number of patient years of observation from papers. The calculation of event rates was therefore simple arithmetic.

4. The abstract has been changed to reflect journal standard.

5. We have kept the rates as per 100 and per 1000, but have explained this in methods. The point is that per 100 is useful for calculations of risk frequency, but leads to fractions of a person. Using the 1000 base means one can deal with whole persons. No one knows which is best, or even if there is a best; until that time we would crave a little indulgence on this point.

6. Like Angel we would like to see information available for particular drug/dose combinations. It often is not available, and when it is it often has rather small numbers of events because already limited data are then subdivided. We have not extolled on the dangers of sub-group
analysis in the paper (see Journal of Clinical Epidemiology 2006 59:964-969), but it is well known.
1. While we did have sponsorship from Pfizer, we work to our own clear guidelines. The bottom line is that we have an absolute right to publish what we want, without let or hindrance. We have been working to improve issues of independence for over 30 years, and find many others rather unclear on the subject. As one example, we have investigated some of the issues of industry funding in acute pain trials (Barden et al. Bias from industry trial funding? A framework, a suggested approach, and a negative result. Pain 2006 121 :207-18), and it also has a useful discussion on the limitations of other studies of industry bias. As a group that has also published on other sources of bias, and on the understanding of evidence, we are mindful of the problem, perhaps more than most. While we understand that our work may be dismissed, we would like to point out that it was we who had the idea and sought the funds, and not the other way around.

2. We cannot see how the selection of studies was unclear. The supplementary files provide information on studies available that were available, and as most were case-control with no information as to incidence, and the amount of cohort data was limited in number and outcome definition, we were left with no choice but to use RCT data for absolute risk comparisons. We then chose meta-analyses or large RCTs with the largest, and best, amount of information.

3. We have a certain sympathy about how to give perspective to risk. If referencing is considered selective, we thought we were being conservative. For instance, we did not reference any of the growing body of evidence linking use of PPI and H2A with increased fracture risk, and especially hip fracture. In older people, the ones most likely to need analgesia, the additional effects are devastating and much more frequent than GI bleed or CV event.

4. We have presented these analyses to a number of audiences, including those with primary care, rheumatology, gastroenterology, cardiology, and prescribing policy interests. They seemed to provoke much interest and discussion. Moreover, if we are to try and get some sort of grip on risk and risk presentation as a whole, we need to consider various ways of doing so. Diane Berry’s 2004 book on risk is a useful start to explain the many complexities.

5. The second paragraph of our discussion goes to the heart of the point about lack of discussion on alternatives. Let’s face it, we could write a book on alternatives to NSAIDs for arthritis. But this paper is about looking at risk differences for two outcomes for these alternatives, and does not set out to look at every possible treatment. If we were to include evidence on CV risk with paracetamol, the dangers of acupuncture, and the unknown dangers from therapies without any good safety data about rare but serious adverse events, then we would need many, many pages. We limited ourselves the one task, the one brick in the much larger wall.
And, finally, we have taken the opportunity to include a large additional amount of information from the MEDAL program, published in the last few days. This amounts to a major increase in the amount of information available on both coxibs and NSAIDs for CV events. Unfortunately the GI results from MEDAL have not yet been published, though they too apparently show reduced GI bleeding with etoricoxib. We understand that these will not be published until 2007.