Reviewer's report

**Title:** Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries. What size of data platforms do we need to assess safety issues? The SOS project

**Version:** 2 **Date:** 25 September 2013

**Reviewer:** Joseph A Delaney

**Reviewer's report:**

This report is an interesting exploration of the issues of statistical power in the SOS project seeking to look at the safety of NSAID class medications in children. These databases are European and cover nearly 8 million children and adolescents. The report is well written by thoughtful scientists who have carefully thought through some key methodological issues.

**Discretionary Revisions**

1. With roughly 70% of the exposure being to ibuprofen (making it the clear drug of choice) and it being an OTC medication, would not the primary contrast for comparative safety be ibuprofen versus not ibuprofen? It would be useful to see how the power in table 3 looked for non-ibuprofen NSAIDs.

2. Was there any way to determine a dose-response element for ibuprofen or was sample size and/or data capture inadequate.

3. The suggestion that a case-only design would make sense is interesting and, I believe, correct. However, would the self controlled case series design be appropriate or would post-event exposure time be different than pre-event exposure time? Would any of the events be fatal? These are tricky issues with the SCCS (which is the gold standard in the world of vaccines) that might be considered (I think that there are advanced versions of the SCCS that can handle these issues but it might be useful to get a data driven insight). Similarly, would a case-crossover approach make sense or could there be secular trends in prescribing of NSAIDs that would make a case-time-control design appropriate. These sorts of questions naturally arise from a read of the discussion and it would increase the impact of the paper to provide some guidance on these issues in the context of European prescribing databases.

**Statistical Comments**

4. The authors employ a purely frequentist approach to drug safety, seeking to establish testing threshold to estimate power to detect an association of size X. They have appropriately used one sided tests of statistical significance (as there is no plausible biology behind NSAID class medications protecting against many of the side effects mentioned.)
However, I would encourage the authors to consider if there is a less stringent testing threshold that might make sense in this context. I would suppose that most of the interest in NSAIDs here would be in comparative safety (as it seems unlikely that paracetamol or opioids would be alternatives and the absolute risks are small). It would be interesting if the authors might propose a threshold where a safety signal might be tentatively proposed, given the vulnerability of the underlying population.

Overall

Excellent paper and it was an enjoyable read. It is a very hard problem, here, and I look forward to seeing continued work from the SOS project.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests