Reviewer's report

Title: Inflammatory phenotypes underlying long-term uncontrolled childhood asthma: Rationale and design of the PACMAN2 study

Version: 1 Date: 2 March 2013

Reviewer: anne fuhlbrigge

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Vijverberg et al present a manuscript outlining the design and methodology for the PACMAN2 study.

Major Compulsory Revisions

The primary issue that needs to be clarified in the manuscript is the definition of the subgroups and the exact information used to classify the subjects so the reader can more easily follow along;

1. Table 1 lists the inclusion criteria for PACMAN2 study. It should be highlighted that the definition of long term controlled asthma is based on retrospective data collected at baseline. Recall bias is a significant concern; the ability to accurately recall the level of control for periods that occurred months before (up to 9) is suspect. If I have misunderstood that aspect of the study design, please clarify.

2. Table 2 should include all instruments that were used at the baseline visit during recruitment for PACMAN1 and those used in PACMAN2 with notation of which information was collected at both. It is important to easily see which information was collected at both visits and which information was available at only one of the 2 visits.

On page 8 subheading Questionnaires; the text discusses that the parents and children will receive the ACT and MARS on current asthma symptoms and medication use each season. This is confusing, is there a prospective collection of level of control and medication adherence and if so over what time period. It is not possible to prospectively collect data on level of control each season between the PACMAN1 and PACMAN2 visits if they are only 6 months apart.

3. Figure 1 should include the numbers of subjects that are in each category and clearly identify the numbers of subjects excluded from each step in the diagram.

4. For the f/u visits, the subjects will again be categorized according to their level of control; controlled vs uncontrolled. Will this assessment be based on the single assessment at that visit or retrospective for the period between the 2 visits?

The authors need to be prepared to analyze the subjects as 4 groups;
Baseline long term uncontrolled – F/U uncontrolled (adherent to ICS)
Baseline long term uncontrolled – F/U controlled
Baseline long term controlled – F/U controlled (adherent to ICS)
Baseline long term controlled – F/U uncontrolled

5. It will also be important to outline the number of subjects that fall between the definitions of controlled and uncontrolled asthma as outlined in Table 1. This could be outlined in Figure 1.

6. It will also be important to clarify the exact comparison groups for the primary analysis;
   The authors will compare subjects with long term uncontrolled asthma with long term controlled asthma so I would assume that would be the subgroups;
   Baseline long term uncontrolled – F/U uncontrolled, ICS adherent
   Vs.
   Baseline long term controlled – F/U controlled, adherent to ICS

Minor Essential Revisions
1. The authors state the f/u visit was at least 6 months after the initial visit. It will be important to note the difference in time of year between these visits as this could impact the distribution of subjects between the 4 categories above.

2. Page 6; Please include a definition of the Anatomical Therapeutic Chemical code R03 medication

Discretionary Revisions
1. The authors might address why they have not included induced sputum analysis in their study design. This is unfortunate given that much of the work on asthma subphenotypes has included induced sputum in the assessment and the ability to examine EBC and compare directly to what is found in induced sputum would be valuable. Covar et al published on a substudy of the CAMP population on the safety and application of FeNO and induced sputum (J Allergy Clin Immunol 2004;114:575-82)

2. Page 6; Important to note that the original study by Green et al demonstrated a significant reduction in severe exacerbation frequency in the sputum arm with no significant difference in corticosteroid usage between the groups. However it is also important to note that Haldar et al reevaluated these results with a cluster specific analysis and noted that the benefit for preventing exacerbations occurred in the inflammation-predominant cluster.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests