Author's response to reviews

Title: The Expert Network and Electronic Portal for children with respiratory and allergic symptoms: rationale and design.

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Version: 3 Date: 8 November 2012

Author's response to reviews: see over
November 9th, 2012

Dear Dr Emily Crow,

Thank you very much for considering a revised version of our manuscript, entitled “The ‘Expert Network and Electronic Portal for children with respiratory and allergic symptoms’: rationale and design”, for publication in BMC Pediatrics.

We have incorporated the reviewers’ comments, as indicated in the detailed answer to their concerns, below. Because inclusion has continued since our first submission (April 2012), we have updated the numbers in the result section, but have also added two authors. Both authors have collected a considerable amount of data, and have contributed to the design of the EP. They have both critically reviewed the manuscript before resubmission.

We believe that these valuable comments have helped strengthen the paper. We sincerely hope that the revised text will meet the standards of your Journal.

Yours sincerely,
On behalf of all authors,

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Reviewer's report
Title: The Expert Network and Electronic Portal for children with respiratory and allergic symptoms: rationale and design.
Version: 2 Date: 8 October 2012
Reviewer: Frans De Baets

Reviewers report:

- The paper is unfortunately confined to a methodological approach of a planned study. The paper does indeed not show any study results, but describes the EP that is currently running. In the revised manuscript we describe the current rates of inclusion in the EP. We expect that first analyses of EP data will follow very soon, referring to the current paper as a baseline for all coming papers.

- The authors claim that their data will give a better insight in asthma phenotypes relying on treatment. This expectation is strange knowing that treatment of asthma especially relies on phenotypes. The current international treatment guidelines of asthma in children are based on the severity of the disease in a child, and not particularly on the phenotype. However, several recognized clinical phenotypes of severe asthma have been described in literature, but, these were defined in selected patient populations, and therefore only applicable to selected patient groups. We aim to define phenotypes in a large cohort of outpatient asthmatic patients that covers the whole unselected spectrum of asthma.

- In their conclusion the authors claim that this EP could help to support extensive data collection. Is this study mend to be an updating or extension of the ISAAC data? The ISAAC study was started with the aim to describe the incidence and prevalence of atopic diseases worldwide. As described in the previous point, our primary aims are different, focusing on asthma phenotypes in relationship to treatment responses. But of course, the data from our EP will also reveal data on incidence and prevalence additional to the original ISAAC study. We have specifically chosen to use these validated questionnaires to be able to compare outcomes and definitions with available literature worldwide.

- Reading this paper I was disappointed that only a methodology is described without any, eventually partly results. Therefore I wonder if this paper is already worthwhile to be published and publication have to be postponed until at least some results are known. See the first comment. This descriptive paper will be the basis for many upcoming manuscripts, which will all refer to BMC.

- Methodological pitfalls can difficultly be evaluated in the absence of data. Difficulties however can be expected even with the use of validated questionnaires: how to control the recognition of respiratory and allergic symptoms by parents, patients and even by general physicians. For instance exercise induced dyspnoe could be a lack of physical fitness, what do parents understand by wheezing, many parents think that red eyes after swimming in a chloride swimming pool is a characteristic of allergy (against chloride). This is an interesting point. We agree with the reviewer as far as it concerns clinical trials. However, the EP will focus on collection of patient related outcomes in real life. The large population that will be collected will – at least partially – filter out noise of differences in interpretation etc by parents. The EP also collects objective data from the treating physicians, which enables extensive comparisons of patients' and doctors' observations.

- On page 12 out of 915 selected children, 332 have completed the baseline questionnaire. On page 13 the authors mention 1485 children from which 661 have completed the first questionnaire. How can they explain those different figures?
Thank you for your comment, and our apologies for the discrepancies. It was caused by using different files (one contained patients invited for the EP, the other contained patients who had entered the EP). In the revised manuscript we have corrected and updated these numbers.

○ There is a high rate of dropouts. Are the dropout patients compared to the included patients? Couldn’t this lead to biases?
   The patients that have not filled in the questionnaire until today can not be called drop outs. Most of these patients are known asthmatic patients that are visiting their paediatrician once per year, and have been invited to fill in the questionnaire. However, we do very well understand that they will start filling in the questionnaire shortly before their next doctor visit. We will also remind these patients to fill in the questionnaire by phone. We can not describe any numbers of dropouts for the follow up questionnaires yet, because there is very limited data available on these questionnaires yet.

○ Doesn’t the high rate of dropouts already after completion of the first questionnaire put a mortgage on the further compliance to the study, especially if the study needs many different questionnaires?
   As described above, dropouts are not a problem at this moment. The follow up questionnaire is short, as described in table 1, and the different questionnaires are presented as one set of questions to the patient. Patients do therefore not notice the different parts of the questionnaire but do only notice the different length (about which they are informed on forehand)
Reviewer's report
Title: The Expert Network and Electronic Portal for children with respiratory and allergic symptoms: rationale and design.
Version: 2 Date: 26 September 2012
Reviewer: Anders Bjerg

Reviewer's report:

Major compulsory revision:
- As of now, it is not clear why there are discrepancies between the numbers given under "Findings" and those detailed in Discussion, 2nd paragraph. I suggest that all results/findings are collected in one place, and discussed subsequently. E.g. in "Findings" it is stated that "915 children have been invited to participate"; yet the Discussion reads "since the start of inclusion (...) 1485 patients were invited to participate". Since this is the only original data presented in the paper it needs to be crystal clear.

Thank you for your comment, and our apologies for the discrepancies. It was caused by using different files (one contained patients invited for the EP, the other contained patients who had entered the EP). In the revised manuscript we have corrected and updated these numbers.

Minor essential revisions:
- Background, paragraph 1, 2nd last sentence: "are common approaches to mitigate/avoid" would be a more precise wording. Control usually refers to medications. Thank you for your suggestion. Indeed asthma control refers to medication effects, and the word ‘avoid’ would be more suitable here. We have adjusted this in the text.

“The impact of asthma on daily activities is substantial; avoiding exertion (47%) and staying inside (37%) are common approaches to avoid asthma symptoms.”

- Methods, study design, line 7: “potential toxins”
We have adjusted this in the text.

potentially toxins has been changed into potential toxins

- Methods, The Expert Network: Sentences 1 and 2 seem to overlap, please revise
Thank you for your comment, I have deleted the double information and shortened the sentence.

“The EN consists of caregivers in the…”

- Methods, The Expert Network, para 3: Parents of patients who do not understand Dutch: a) at what age do the participants complete the data themselves, and b) commonly, e.g. for 2nd generation immigrants the children may have better language skills than their parents. Could this be taken into consideration, leading to less loss of non-Dutch speaking patients?
Patients are selected based on the reason of referral. At that time it is unknown whether they do understand the Dutch language. Therefore they are invited to participate, but when the questionnaire is not completed at the time of the hospital visit they are asked what the reason for non-response was. Children are asked to fill in the questionnaires themselves from the age of 12 years and older, and children of 2nd generation immigrants above the age of 11 years are eligible to participate. We describe this more extensively in the revised manuscript.

- Methods, Diagnostic tests, Respiratory function, 1st line: "..asthma, lung function and allergy tests"
We have adjusted this in the text.

- Methods, Diagnostic tests, Respiratory function line 4: "three correctly"
Thank you for your comment. We have adjusted this in the text.

- Methods, Follow up, line 1: "each season", does this mean that patients are followed up at even 3-month intervals? And how about exacerbations/other unexpected events? The structure of follow-up could be clearer in the paper.
  Yes, this is indeed what it means. Each patient is sent an email notification to fill in the questionnaire every 3 months. We are currently creating the possibility to fill in the questionnaires also in between, as prior to an extra doctor visit, exacerbation, etcetera.
  We have described this more in detail in the manuscript.

- Methods, Follow up, last sentence: If medication use is registered exclusively by the patients large discrepancies may exist from how much medication the patients actually take.
  We indeed ask parents to fill in the used medication (which medicine, how often used, in which dose (or only in case of complaints) as well as the way they use the medication (through the MARS questionnaire). Because the EP is also used by the treating physicians, there is a check of medication and this offers the opportunity to detect discrepancies by the doctor.

- Discussion, para 3, line 3: "treatment related asthma phenotypes": I am well familiar with the discussion of phenotypes, but not with any treatment-related phenotypes. Please either explain this, or omit from the paper.
  What we mean is that we want to study correlation between asthma phenotypes and responses to therapy. Eg: do patients with asthma AND eczema respond better to inhaled corticosteroids compared to patient with asthma without eczema. Or: do patients with asthma AND marked airway reversibility respond better to long-acting beta-agonists compared to patients with asthma without or with minor reversibility. We have explained this more clearly in the revised manuscript.

- Figure 2, "Patient inclusion" not patient
  Thank you, we have adjusted this into patient.