Author’s response to reviews

Title: Pragmatic trials in primary care Methodological challenges and solutions demonstrated by the DIAMOND-study

Authors:

Gerdine A.J. Fransen (gerdinefransen@hotmail.com)
Corine J. Van Marrewijk (c.vanmarrewijk@mdl.umcn.nl)
Suhreta Mujakovic (suhreta@backus.com)
Jean W.M. Muris (jean.muris@hag.unimaas.nl)
Robert J.F. Laheij (r.laheij@mdl.umcn.nl)
Mattijs E. Numans (m.e.numans@umcutrecht.nl)
Niek J. De Wit (n.j.dewit@umcutrecht.nl)
Melvin Samsom (m.samsom@umcutrecht.nl)
Jan B.M.J. Jansen (j.jansen@mdl.umcn.nl)
J. Andre Knottnerus (andre.knottnerus@hag.unimaas.nl)

Version: 2 Date: 28 March 2007

Author’s response to reviews: see over
Dear editors,

Please find enclosed a copy of our revised manuscript entitled “Pragmatic trials in primary care. Methodological challenges and solutions demonstrated by the DIAMOND-study”. With the help of the good comments of two reviewers we improved the paper and to our opinion we addressed all issues raised by the reviewers. Therefore, we wish to resubmit this manuscript for publication in BMC Medical Research Methodology.

Our reply on the comments of the reviewers is presented at the end of this letter.

We certify that this work has not been published, simultaneously submitted, or already accepted for publication elsewhere and that submission for publication has been approved by all authors and by the departments where the work was carried out.

We hope that you will reconsider this manuscript for publication in your journal. We are looking forward to hear from you.

Yours faithfully,

Gerdine Fransen
On behalf of all co-authors
Reply on the comments of the reviewers

We would like to thank both reviewers for their useful comments. Although Martin Dawes concluded that “the article should now be published as it is”, Shaun Treweek did not think the paper was ready for publication yet. Therefore, we aimed to improve the article with the help of the suggestions of both reviewers.

Comments of Martin Dawes:

Martin Dawes suggested to explicitly quote information on the quantitative aspects of blinding. On page 6, line 12 we added one line on this subject and refer to the suggested paper by Jüni et al.

To reduce the impact of a lack of blinding in pragmatic trials Dawes suggest to explore the GP preferences for treatment and use this information as a factor in a sensitivity analysis. This is a good and useful suggestion when it is not possible to blind treatment allocation, but under the condition that the preference of treatment of GPs can be measured in a valid manner. In our trial we chose to blind treatment allocation, because we wanted to maximize the internal validity, although this might have decreased the external validity and might contrast with the purpose of pragmatic trials to reflect every day practice as much as possible. Therefore, we recommend that blinding should always be carefully considered. But, we also need to keep in mind that, as Jüni et al. state: internal validity is a prerequisite for external validity; if the internal validity is low, the question of external validity becomes redundant.

We fully agree with Dawes that researchers of pragmatic trials need to compare the distribution of severity of complaints of the recruited population with the target population. But in practice this is not easy, because information about the distribution of severity of the target population is often not available. For instance, the severity of gastrointestinal complaints needs to be measured by questionnaire and is not registered for all patients. Therefore, data on the distribution are often compared with data from other studies. But to reflect the target population as much as possible, these other studies are preferably population based studies with little patient selection. Therefore, we added “preferably population based studies” on page 12, line 17.

We agree with Dawes that we should be moving to patients helping determine outcome measures relevant to themselves. We have chosen our primary outcome (sufficient symptom relief at six months according to patients), because we thought that this reflected the patients’ opinion of effectiveness. It is a subjective outcome measuring effectiveness as perceived by the patient. It is likely that most patients base their decision on whether or not to return for a follow up GP consultation and to continue treatment on the question: “has symptom relief been adequate since the start of the treatment?” Although we tested this question in short pilot test and believe that we have used an outcome measure relevant for patients, we have to acknowledge that no patients were consulted in determining this outcome measure.
Comments of Shaun Treweek:

The main concern of Shaun Treweek is that the “paper aims to provide general guidelines for designing and running a pragmatic trial in primary care, using DIAMOND as an example, but what it really does is explain the rationale behind the decisions made in the DIAMOND trial”. We apologize for this misunderstanding. We did not want to pretend to provide general guidelines; we merely wanted to provide a short introduction or brief reflection on possible issues in designing or conducting a pragmatic trial. The focus of the paper was indeed to explain the rationale behind the decisions made. We agree with Treweek that providing general guidelines, which is indeed a very ambitious scope, surely needed a much more systematic review of the literature than presented. To avoid misunderstandings or unfulfilled expectations among readers, we adjusted the “Background” to make sure the reader knows that each section will first present a brief introduction on the challenges we faced (instead of giving a general guideline). Then we discuss how we dealt with these challenges, why we made the choices we made and what can be the consequences of our choices. We did make several small changes (different choice of words), and at the end of the “Background” (page 4 last paragraph) we will explain the structure of our paper and the subjects we present in this paper.

As Shaun Treweek suggested we changed the structure of our paper. He suggested to present a “brief introduction on the sorts of issues faced by trialists”. The beginning of each section aims to be a brief introduction on one specific challenge we faced. Furthermore, Treweek suggested to use subheadings like “The rationale behind our choices”. We added this subheading to each section, followed by a discussion of the choices we made and the motivation of these choices. We think that for trial results to be relevant and useful for patients, general practitioners and policy makers, both the internal and external validity need to be optimal. Therefore we clearly explain in each section what we have done to optimize the internal and external validity, to make DIAMOND more relevant and useful for patients, general practitioners and policy makers. We decided to end the paper with a section “The consequences of our choices for the usefulness and relevance of the DIAMOND results”. In this section the most important findings concerning the relevance and usefulness of our results as discussed in the paper are summarized.

Based on the previously discussed comments we made changes. Since most changes concern different choices of words, we will not discuss all changes here. The most important changes are:

- In the abstract (page 2 line 7) we changed “using our experiences in the DIAMOND-study as an example” in “based on our experiences in the DIAMOND-study”. To our opinion the new sentence explains more clearly that the paper is mostly based on our experiences instead of systematically reviewing all relevant publications on how to design and conduct a pragmatic trial and presenting a general guideline.

- The discussion-section of the abstract (page 2, beginning at line 10) is rewritten. In the old version it discussed the challenges faced more in general and gave the impression that our paper presented general guidelines how to design and conduct a pragmatic trial. Since we did not want to present a general guideline but we wanted to present the challenges we faced, our experiences and rationale behind our choices, we decided to rewrite this part. The new version presents the most important challenges we experienced and how we succeeded in facing these challenges.
- In the old version we addressed “choosing the right intervention” and “When to disclose treatment allocation” separately. In the new version we combined these sections into “Choosing the right intervention and blinding treatment allocation” because the sections were very much related and combining shortened our paper.

- In sections discussing the “rationale behind our choices” we tried to explicitly state which choices we made and motivate these choices. This resulted for instance in changing “DIAMOND focused on “adult patients with a new episode of dyspepsia”, in “We chose to focus on “adult patients with a new episode of dyspepsia”, because the most effective treatment for these patients was unknown.” (page 11, line 13).

Minor essential revisions:
As Shaun Treweek suggested, the subheading “The DIAMOND trial” is added in the “Background” section on page 5.

The question on page 19 in the old version (page 21 line 12 in the new version) is changed into “has symptom relief been adequate since the start of the treatment?”, since this was closer to our earlier choice of phrase on page 13 line 22.

We indeed try to emphasize that researchers always have to make a choice where on the explanatory-pragmatic spectrum they want their trial to be. Therefore, we added this to our summary on page 23, beginning on line 9.

We changed in- and exclusion criteria into inclusion and exclusion criteria in Box 2 and 3.

Discretionary revisions:
Concerning our arguments regarding blinding and generalisability, we agree with Treweek about the importance of blinding treatment allocation. As discussed before, blinding is often necessary to get a high internal validity, and without a internally valid trial, the external validity becomes redundant. Therefore, we chose to blind treatment allocation in our trial. Indeed if one treatment strategy is more effective than the other, then it is our job to implement this treatment strategy into practice and address any prejudice against the intervention among stakeholders. In our paper, we just want to point out that although blinding is needed when dealing with prejudices, one should always be aware that blinding does contrast with the purpose of pragmatic trials to reflect every day practice. Therefore, researchers should carefully decide whether or not to blind treatment allocation.