Author's response to reviews

Title: What is the key issue in adherence evaluation of endocrine treatment of early breast cancer? - Methodological aspects of adherence evaluation

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Author's response to reviews: see over
POINT BY POINT REPLY

What is the key issue in adherence evaluation of endocrine treatment of early breast cancer? - Methodological aspects of the study 'Patient-reported outcomes in breast cancer patients undergoing endocrine therapy (PRO-BEth)

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Referee 1

Minor essential revisions Referee 1:

1. **Titel:**
   We fully agree with the reviewer that the second part of the title might somehow be misleading. The first part of the title should, in our opinion, be kept since it is supposed to draw the reader’s attention to the major point of adherence measurement: the neglect of methodological comparability of adherence measurement methods in the literature.
   We thereafter propose to change the title into: What is the key issue in adherence evaluation of endocrine treatment of early breast cancer? - Methodological aspects of adherence evaluation

2. **Assessment methods, self-report questionnaire: Items, response format, scoring and translation**
   Information regarding the self-report questionnaire SMAQ has been revised to clarify this issue. Please find a more detailed description in the Section Patients and Methods, assessment methods self-report questionnaire (SMAQ) (p.7).

3. **Argument for the decision on cut-offs defining a patient as adherent:**
   We implemented information on the decision for respective cut-off score in each measurement method section. Please find further details in the section patients and methods, assessment methods, separately for each measurement approach p.6-9. Please kindly note that the selection cut-offs for adherence is always a methodological challenge to the authors due to heterogeneous discussions in the literature. We comprehensively discussed this as a limitation in the discussion section (p. 15 second paragraph, p.16 last paragraph).

4. **Results: information on patients not willing to participate**
   We assent with the view of the reviewer that information on patients declining from study participation is important regarding the interpretation of adherence rates. Nonetheless, please kindly note that results on methodological aspects presented herein are derived from a subsample of a large study sample of the study PRO-BEth (described in section aims, p.5). This prevents us from providing a non-participation rate for this particular sample. Overall, we had a non-participation rate of about 10% in the whole sample of the study PRO-BEth, described elsewhere [17].
5. **Expression methodological consistency:**

We highly appreciate this recommendation and changed the term “methodological consistency” into “concordance between methods” (p. 2, 4, 10,11).

**Discretionary Revision:**

1. **Introduction**

   We appreciate the reviewer’s recommendations regarding more detailed information on methods commonly used in adherence research and thereafter implemented some sentences in the section introduction, p.3, second paragraph.

2. **Discussion**

   Please kindly note that some suggestions regarding the development of new methods/ further research in breast cancer patients receiving endocrine treatment are provided in the section, conclusion, p.17. More detailed considerations are beyond the scope of this paper and should be investigated in further research.

**Minor issue Referee 1:**

1. **Grammatical revision of sentence in the discussion, second paragraph, sentence with reference 7:**

   The sentence was grammatically corrected. Please find details in the respective section (p. 12).

**Referee 2**

**Major Compulsory Revisions Referee 2:**

1. **Abstract:**

   We reformulated the sentence on adherence rates in the result section of the abstract (p. 2) by deleting the word “strikingly” to qualify this statement (which might appear too strong in this content). Please kindly note that it is difficult to adequately discuss in the abstract the comprehensive subject of high adherence rates found herein compared with the literature in the light of modest methodological comparability.

2. **Introduction:**

   a) We fully agree with the reviewer that the ATAC trial does not provide information on OS survival and thereafter deleted this statement. Please find further details in the manuscript on p. 3, first paragraph, first sentence.

   b) We assent the reviewer that this statement (“too much to lose”) as presented in our manuscript might be misleading for the reader understanding it as a result of the study of Waterhouse at all (Ref 3). Since this is rather a consideration of the authors (please find it in their introduction on p. 1189, right column, fourth line in Ref 3) than a result of their study, we reworded the sentence in our manuscript to clarify this issue. Please find further details on p. 3, first paragraph.

   c) Since we fully agree with the reviewer that this reference does not support the respective assumption adequately, we included another, more appropriate reference.

   d) We agree with the reviewer that the paper cited is based on a previous report by Partridge et al. (Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral
antineoplastic agents. J Natl Cancer Inst. 2002 May 1;94(9):652-61), which investigated adherence to oral antineoplastic agents in general. We therefore changed the sentence on p.2, second paragraph according to this reference and added the reference to the literature section.

e) We changed the term “prevalence rates” into “non-adherence rates” to increase the clarity of this sentence.

3. Method section:

f) We assent with the reviewer that the term “applicable” might be misleading in this section and replaced it by the term “reliable” referring to the Cronbach’s Alpha found in this study.

g) We highly appreciate the reviewer’s comment regarding the lack of clarity of the frequency of physician ratings. Certainly, the cross-sectional assessment was conducted only once. Since the reader is mislead by the word “each”, we clarified the wording by replacing “each” with “the”, please find further details on p. 8, second paragraph.

h) We fully agree with the reviewer that it’s important to illustrate expert ratings to be an established method for the assessment of adherence. We revised this section, p. 8 in this regard also referring to reference 16.

4. Result section:

a) We appreciate the suggestion of the reviewer to show a distribution curve of anastrozole levels and implemented it (Figure 1, p.24). As indicated in the manuscript please note that further details on anastrozole serum concentrations are presented elsewhere [Ref. 20].

b) Patients with the diagnosis “in-situ” do not have invasive disease. We corrected table 1 in accordance with the reviewer’s comments. Please find further details in Table 1, p. 21. Please kindly note that information on the endocrine agents used in this study population (upfront anastrozole treatment) is given in detail in the section sample, inclusion criteria, p. 5.

5. Discussion section

a) Different methodological approaches (with different limitations) appeared to result in variant non-respondance rates; this cannot be explained by a single reason. For example, as not all patients have the same health insurance or more than one insurance, we were not able to obtain information on 100% of the patients.

b) Please kindly note that since the main focus of this paper was to answer the question of whether or not the methods are comparable, we are not able to reliably answer the question regarding the reasons for this modest concordance. This lies beyond the scope of this paper and should be answered by further research (as indicated in the section conclusion, p. 17).

c) Please find information on the rate of study participation above: Referee 1, Minor essential revisions Referee 1, Nr. 4, Results: information on patients not willing to participate;

c) Title
Please find corrections to the title above, Referee 1 (minor essential revisions 1)

Minor essential revisions Referee 2:

1. Title page:

Please find all changes (a, b,c) on the title page.
2. *Section assessment method:*

Please kindly note that the section “assessment method” is to be found on p. 6 below the section “procedure”.

3. *Key words*

We added the key word adherence, p.2.

**Discretionary Revisions Referee 2:**

We highly appreciate the reviewer’s comments and revised the title page.