Author’s response to reviews

Title: The ANTOP study: focal psychodynamic psychotherapy, cognitive-behavioral therapy, and treatment-as-usual in outpatients with anorexia nervosa: a randomized controlled trial

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Author’s response to reviews: see over
Dear Editorial Board,

Enclosed please find the revision of the above manuscript. We appreciate the reviewers’ careful evaluation of the study protocol and have addressed their comments in the revised manuscript. Please see below our detailed response to the reviewers’ concerns.

**Response to the comments of reviewer 1 (Prathap Tharyan):**

1. – 2. We appreciate the reviewer’s positive comment regarding the adequacy of the design and the adequacy of the details provided.

3. The reviewer’s comment regarding the synchronization of the registration document and the study protocol is crucial. In the design of the study as well as for the sample size calculation, the 10 month outcome was defined as primary outcome. We have clarified
this in the trial record in the ISRCTN register. We also agree with the reviewer that the expression “multi-level analysis” could be misleading. Therefore, we changed the expression “multi-level analysis” to “mixed modelling approach”. Further changes in the statistical section are discussed in the response to the comments of reviewer 2.

5. We agree with the reviewer’s comment on the Helping Alliance Questionnaire (HAQ). The HAQ is an important process measure in the ANTOP study. We had omitted the HAQ in the registration document but have added it in the meantime. The reviewer’s further criticism addresses an important aspect of the study. The reviewer is absolutely right with his assessment of the psychotherapy treatments in the treatment as usual (TAU) group as cognitive–behavioural and psychodynamic oriented therapies are the most often delivered therapies in Germany. However, anorexia nervosa patients have a reputation for being difficult to treat, with several peculiarities that complicate the treatment process. Therefore, our hypothesis is that a standardized psychotherapy according to a detailed manual specifically tailored to the symptoms and problems in the treatment of anorexia nervosa (AN) should show a better outcome than the psychotherapeutic approaches generally practiced in AN patients in Germany. In the study, we ascertain the therapeutic dosage and treatment condition of the patients of the TAU group to be able to assess the “treatment as usual”. From a clinical and ethical point of view, in a study with AN patients, it is simply not possible to create a no-treatment control group or a waiting control list. Studies that tried to implement such control groups had a drop-out rate of up to 80% in the control condition (Bergh et al., 2002).

6. We agree with the reviewer’s comment that it might have been better to randomly review the audiotapes. However, as the study is conducted in 10 different centres spread all over Germany, it was better – from an organisational point of view – to standardize the process of sending the audiotapes to the adherence control. In addition we have implemented a
number of quality assurance procedures, e.g. supervision of every 4th therapy session, intensive training of therapists and supervisors, and standardized feedback protocols.

Response to the comments of reviewer 2 (Tim Cole)

1. We inserted some further explanations in the abstract in order to clarify the points stated by the reviewer. The two intervention groups are compared separately to the control group and the patients are evenly assigned to the three groups. For a better understanding, we also inserted a sentence describing the TAU group and changed the final sentence of the abstract. The other unclear points are explained in the later text. In the revised manuscript, we also gave an explanation for the length of the treatment period (page 6). The sample size of 237 patients is explained in the sample size calculation (page 9). A three-month follow-up is included in the first funding period of this study. Funding for a one-year follow-up has been applied for (page 8).

2. To be more precise in the description of the TAU condition, we inserted a new paragraph on page 7. The reviewer’s comment is crucial because some of the patients are not happy to be randomized to the TAU group. However, here are also certain advantages of TAU: the patient is able to freely choose a certain therapy approach and to choose or change a therapist, and the therapy can be arranged far more individually in time and content as it is the case with a standardized manual. To avoid early drop-outs, at all centres, detailed information about the study is given before a patient is included. Also, patients of the TAU group are grateful to get some support for their further therapy planning. Preliminary data shows that the drop-out rate in the TAU group is not greater than in the two intervention groups. However, the reviewer is correct in the statement that it is possible that some patients may not receive treatment. It could also happen that some patients of the TAU group are referred to inpatient treatment. The TAU arm reflects the standard procedure of allocation of patients to treatment in the German health care system.
3. We agree with the reviewer’s comment. Unfortunately, in the former manuscript the hypothesis was not exactly formulated by mistake. In the revised manuscript, we explicitly separated the primary hypothesis into two parts (see page 7) (as a matter of fact, before the beginning of the study, in the original German study protocol, we did formulate two separate hypotheses). We also changed the description of the primary outcome without changing the primary outcome itself. That is, due to the reviewer’s comment about the necessity of adjusting the analysis of change in BMI for the baseline BMI, we now describe the primary outcome as “BMI at T2” and adjust in the statistical analysis for the BMI at T0.

4. The reviewer suggested a slightly different statistical approach that may have been motivated by the fact that the main hypothesis was mistakenly described in the former manuscript. In the revised manuscript, we stated more clearly that the main objective of the study is to test the two null hypotheses $H_0^{FPT} : \mu_{FPT} = \mu_{TAU}$ and $H_0^{CBT} : \mu_{CBT} = \mu_{TAU}$, where $\mu$ denotes the expected values of the BMI at the end of treatment (T2), adjusted for the pre-randomisation baseline BMI at T0. In the study protocol, for the simultaneous test of these two hypotheses controlling the family wise error rate at $\alpha = 0.05$, we defined two-sample t-tests each at a two-sided significance level of $\alpha = 0.025$. The reason for this choice was the robustness of this approach with respect to the unknown true parameters $\mu_{FPT}$, $\mu_{CBT}$, and $\mu_{TAU}$. It is true that the contrasts that were proposed by the reviewer could give a more powerful test for testing the intersection $H_0^{FPT} \cap H_0^{CBT}$ (as the first step of a closed testing procedure) provided that both experimental treatments are superior to TAU. However, when we designed the study, we did not want to make this assumption. If only one of the treatments should be superior to TAU, the primary test procedure should have power to reject the null hypothesis for the other treatment. Motivated by the request of the reviewer, we performed some power comparisons.
The power comparisons were done under the simplified model of normal distribution with known equal variance in all three groups. The objective was to compare the power of the following three tests for testing the joint null hypothesis \( H_0^{FPT} \cap H_0^{CBT} \):

- **(D)** Dunnett–like, i.e., test statistics \( \max|X_{FPT} - \overline{X}_{TAU}|,|X_{CBT} - \overline{X}_{TAU}| \)
- **(B)** Bonferroni with test statistics \( |X_{FPT} - \overline{X}_{TAU}| \) and \( |X_{CBT} - \overline{X}_{TAU}| \)
- **(M)** Mean treatment effect, i.e., test statistics \( \frac{1}{2}(X_{FPT} + X_{CBT}) - \overline{X}_{TAU} \)

We used \( n=3 \times 55, \alpha = 0.05 \sigma = 1, \mu_{TAU} = 0 \) and three parameter constellations:

- **(P1)** \( \mu_{FPT} = \mu_{CBT} = 0.59 \)
- **(P2)** \( \mu_{FPT} = 0.295, \mu_{CBT} = 0.59 \)
- **(P3)** \( \mu_{FPT} = 0, \mu_{CBT} = 0.59 \)

and for control

- **(P0)** \( \mu_{FPT} = 0, \mu_{CBT} = 0 \)

**Results: Power** (probability that \( H_0^{FPT} \cap H_0^{CBT} \) is rejected)

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunnett (D)</td>
<td>0.91970</td>
<td>0.82269</td>
<td>0.82026</td>
<td>0.05</td>
</tr>
<tr>
<td>Bonferroni (B)</td>
<td>0.91476</td>
<td>0.81470</td>
<td>0.81179</td>
<td>0.04647</td>
</tr>
<tr>
<td>Mean effect (M)</td>
<td>0.94659</td>
<td>0.76409</td>
<td>0.43116</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Regarding the linear contrasts, we decided to stay with our previously defined approach – the Bonferroni procedure. However, motivated by the comments of the reviewer, we did change the main modeling approach. We now define the primary statistical analysis as a mixed model analysis (see point 7 of this letter and page 10 of the revised manuscript).

5. The reviewer is right with the statement that the point of the intervention is long–term improvement and that T3 is only three months after the end of the treatment. In the proposal, we had to choose this T3 time point for the follow–up measurement because the funding period was limited to three years. Currently, we are applying for a prolonged funding period with a one–year follow–up. We appreciate the reviewer’s comment that the different time–points in the hypotheses are distracting. We therefore maintained only the
secondary hypotheses linked with T2, as the primary endpoint in this study is measured at T2 (see page 7).

6. We addressed this point by giving a further explanation in the legend of figure 1 (see page 20).

7. We agree with the reviewer’s comment that the analysis of the primary outcome should be adjusted for baseline BMI. The reviewer’s comment motivated us to carefully re-check the model for the confirmatory analysis. After a serious discussion we decided to change the primary statistical analysis approach. In the revised manuscript, we specified the mixed model approach that we will use for the confirmatory analysis (page 10). We defined the BMI at T2 as primary outcome, and adjusted the statistical analysis for the baseline BMI. In addition, we wrote an amendment for the ethics commission that describes the changes we made in the statistics section of the study protocol.

8. We appreciate the reviewer’s advice and added the definition of improvement (BMI ≥ 14) to the paragraph of medical complications. We also inserted a paragraph regarding medical complications in the control group (see page 13).

9. We corrected the name “Morgan–Russell” in the table.

We trust that these changes meet with your approval. Should you require further adjustments, please do not hesitate to get in touch with us. Thank you very much for your time. We are looking forward to hearing from you.

Yours sincerely,
Beate Wild, PhD