Author's response to reviews

Title:A complex nursing intervention on Complementary and Alternative Medicine (CAM) to increase quality of life in patients with breast and gynaecologic cancer undergoing chemotherapy: study protocol for a prospective partially randomised patient preference trial (CONGO study)

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Author's response to reviews:

Reviewer #1 Everardo Saad

Major Compulsory Revisions
1. It is not clear from the text whether eligible patients, who are starting a new chemotherapy regimen, are about to start their first ever chemotherapy. It is conceivable that this is not the case, i.e., that patients with prior regimens different from the current one are also eligible. I believe authors should make this clear. Moreover, if prior (different) regimens are allowed, authors should explain why this has not been used as a stratification factor before randomization, as prior experience with chemotherapy is likely to influence the outcomes of interest.

Minor Essential Revisions
1. Since patients undergoing palliative treatment are clearly eligible (and rightly so), authors should modify the text on page 9 (‘All patients registering for a new adjuvant or neoadjuvant chemotherapy regimen will be informed about and invited for study participation, irrespective of their participation in other studies’) to include such patients, whose chemotherapy is neither adjuvant nor neoadjuvant.

We thank the reviewer for these important suggestions. Patients are clearly eligible to participate in the current health services research study irrespective if
this is their first ever chemotherapy or a subsequent chemotherapy. This study aims to represent everyday care conditions, therefore we want to consider a heterogeneous sample including patients starting their first ever chemotherapy or a follow-up chemotherapy. If patients have already undergone a chemotherapy regimen, they may be more aware about the spectrum of side-effects, particularly in the palliative setting. We hypothesize that these patients may be more willing to participate in the observational part of the study, so that they have the assurance to receive the testing CAM care intervention. Therefore, we have not decided to not include the factor “prior experience with chemotherapy” as a further strata in the randomised part of the study. The sample will only be stratified according to cancer centre and the type of chemotherapy, namely curative or palliative.

We thank the reviewer for making us aware to include essential details on the patients’ treatment plans, including adjuvant, neoadjuvant, and palliative chemotherapies, so that it will be unmistakably represented that both patient groups, curative and palliative, are eligible for study participation.

We have changed and improved the text describing the study participants and setting as follows:

Participants and setting
To represent everyday conditions, and for obtaining a high external validity and generalizability, female cancer patients will be recruited under broad inclusion criteria from different levels of care (university hospital and community hospital). All adult women diagnosed with breast or gynaecologic malignancies starting a new adjuvant, neoadjuvant, or palliative chemotherapy regimen will be informed about and invited for study participation. Some of these women may have experienced prior chemotherapies which does not exclude them from study eligibility. Patients are also allowed to participate in other clinical or health services research studies; the only exclusion criteria of the current study are insufficient knowledge of the German language, cognitive impairment, and inability to give informed consent.

Reviewer # 2 Elisabeth Coart

Minor Essential Revisions
1. The manuscript lacks a clear definition of the primary endpoint.

It is stated that the primary outcome is the HRQoL and primary analysis will be performed with a linear mixed model. I assume the primary endpoint is the difference in HRQoL over time but this isn’t clear from the text. The latter endpoint would correspond to the significance test of the interaction term of treatment and time and not, as indicated, to the main treatment effect. The main treatment effect represents the difference in HRQoL at baseline and is not related to the administered treatment. If the primary endpoint is the difference in HRQoL at a specific timepoint (e.g. at the end of FU, T4), this should be clearly indicated as this involves evaluation of a different statistical test (although based
1. The revised manuscript now explicitly states the primary endpoint and the details of the statistical analysis (p. 12/13 and p.17/18). The primary endpoint is assessed before randomization (baseline, T0) treatment onset (T1), mid-term (T2), end-of-study (T3), and long-term follow-up (T4). We consider quality of life to be of equal importance at all these time-points. Therefore, the main study objective is reflected in the main effect of treatment group, thereby giving equal weight to all post-randomization measurements. On the other hand, the interaction of group and time is a secondary question, it mainly serves to assess whether the time course of HRQoL differs in the two groups. Please note that HRQoL before randomization (baseline, T0) is included in the model as a covariate only.

2. Because the time points T1, T2, T3, T4 are not equidistant, an unstructured covariance matrix will be estimated. Model fit will be assessed using residual plots and sensitivity analyses as described on p. 17/18.

3. In the revised manuscript, we only state now: “A total of 590 patients (236 patients in the randomised part of the study and 354 patients in the observational...
part of the study) have to be recruited in the two outpatient clinics.” (p. 3).

Editorial requests

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format “___________: study protocol for a randomized controlled trial.”

Thank you for the suggestion.

We have changed the title to fit the journal style for study protocol articles:

“A complex nursing care intervention on Complementary and Alternative Medicine (CAM) to increase quality of life in patients with breast and gynaecologic cancer undergoing chemotherapy (CONGO study): study protocol for a partially randomized controlled trial.”

2. Please include the date of registration with the trial registration number at the end of the Abstract.

Thank you for the suggestion. We have included the date of registration at the end of the abstract.

Trial registration:
German Clinical Trials Register (DRKS), DRKS00006056 (15/04/2014)

Since the trial registration, we have changed one assessment instrument measuring spiritual well-being in our sample. During the phase of study preparation, which was marked by many discussions and consultations by the authors and other CAM researchers, we came to the conclusion that the SpREUK-15 will be better suited for measuring spiritual well-being than the FACIT-Sp. While the FACIT-Sp does not differentiate between patients’ spiritual and religious practices (ref), the SpREUK takes more accurately account of the fact that the spiritual wellbeing in chronic patients is embraced by search (for support /access), trust (in higher guidance/source), and reflection (positive interpretation of disease) (Bussing et al. 2005).

We have changed the passage under Methods/Design -> Instruments accordingly.

We have also modified this assessment instrument within the registered trial registration.

3. Please mention each author individually in the Authors’ Contributions section. Currently, ‘HJS’ is missing.

Thank you for the suggestion. We have now included the author HJS in the authors’ contributions section.

Authors’ contributions

SJ, CM, CvH, JR, HJS conception, design, trial protocol, and initiation of the project. NK contributed to conception and design of the study and drafted the
manuscript. AS and AM contributed to the trial protocol and initiation of the project. All authors read and approved the final manuscript.