Author’s response to reviews

Title: Trauma- and stressor-related disorders among hematological cancer patients with and without stem cell transplantation: protocol of an interview-based study according to updated diagnostic criteria

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Dear editors of BMC Cancer,

enclosed please find the revised version of our manuscript entitled “Trauma- and stressor-related disorders among hematological cancer patients with and without stem cell transplantation: protocol of an interview-based study according to updated diagnostic criteria” (BCAN-D-19-01067), which we are resubmitting to BMC Cancer.

We would like to thank the two reviewers for their very thoughtful and helpful comments and feedback. We believe that the manuscript has substantially improved through the revision and hope that the attached revision will address all of the reviewers’ concerns.

Below please find the point-by-point responses to the reviewers’ comments and questions. Parts in the manuscript or in the tables that have been added or revised in any way are highlighted with green lettering.

Sincerely,

Peter Esser

(on behalf of all authors)

Reviewer 1
General comment: This is a well written summary of a proposed cross-sectional study to assess trauma- and stressor-related disorders in patients undergoing auto or allo transplant for hematologic malignancies. It will answer important questions and set bench marks for interventions. The sample size is commendable.

Response: We thank the reviewer for the positive feedback and the detailed and helpful comments. Below please find our point-by-point-responses.

Comment 1: According to the editors´ comment, we do not respond to this question.

Comment 2: 300/600 patients will be patients with hematologic malignancies who are not undergoing transplant. How will they be chosen? Are they to be matched to the transplant patients? Sequentially approached? Or some other method?

Response: Thank you for mentioning this. The patients without SCT need to meet the same inclusion criteria than those with SCT. Differences in sample characteristics between the final samples will later be controlled statistically. Eligible patients are consecutively approached, i.e., the recruitment procedure is identical with the procedure for recruiting patients undergoing SCT.

We now have clarified all these issues in the manuscript in the paragraph on “study participants” (page 7, lines 147-153), “recruitment” (page 7, line 155) and “statistical analyses” (page 13, lines 310-313).

Comment 3: Including gender and age matched controls without malignancy seems reasonable, but then there are really three comparisons. No malig to transplant, No malig to malig without transplant, malignancy with or without transplant. How will all these comparisons be handled statistically?

Response: Thank you for your comment. We now have explicitly defined the comparison within the group of patients in the research objectives (page 6, lines 114-115) and the statistical analyses (page 13, lines 310-313). For multiple testing among the same samples, the alpha-level will be Bonferroni-adjusted, which is now explicitly stated in the analyses section (page 14, line 318-319). Furthermore, for all comparisons, we will calculate effect sizes, which are investigating the practical relevance of significant findings (page 13, lines 313-314).

Comment 4: 600 patients over two years is a large number. Does the center see this many patients (including an portion who will decline participating)?

Response: Our estimation regarding the feasibility of the sample recruitment is based on our experience with a previous, methodologically similar study as well as the information of our cooperating clinic for hematology.
1. Expected response rate: A member of our working group has successfully conducted a study with similar recruitment and assessment (Mehnert A, Brähler E, Faller H, Härtel M, Keller M, Schulz H et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. J Clin Oncol, 2014;32(31): 3540–3546). In this study, they reached a response rate of almost 70%. Based on this experience, we assume that it will be necessary to contact about 429 patients for each group (SCT and non-SCT) to end up with the minimum number of 300 participants for each group.

2. Available patients: The cooperating clinic for hematology is treating about 220 patients with SCT as well as about 800 patients without SCT annually. Given that we will recruit over 2 years, we will be able to contact about 440 patients with SCT and about 1600 patients without SCT, which is supposed to be enough to end up with the minimum number of participants (see above).

3. Additional actions in case of low response rate: We have planned additional six months in case the response rate will be too low (i.e., another 110 with SCT, and about 400 without SCT).

We now have included a short paragraph on “feasibility” summarizing the most important information of our response (page 8, lines 178-185).

Comment 5: "we have original data for cancer-specific quality of life measured with the EORTC QLQ-C30" - Does this mean the randomly selected German population without cancer answered the cancer-specific survey? Is this survey validated in a cancer-free population?

Response: Indeed, this questionnaire has been answered by participants drawn from the general population. Even though the EORTC QLQ-C30 is designed for symptoms normally associated with cancer and its treatment, the questionnaire is generally enough to be answered by non-cancer populations as well in order to assess health-related quality of life and functional status. The article we cite in the study protocol shows good psychometric properties (internal consistency) for this questionnaire in the general population.

To avoid further confusion, we deleted the term “cancer-specific” in the respective sentence.

Comment 6: These are a lot of questionnaires to be filled out at one time. How long do you feel this will take? What if patients do not want to complete all of them? Will they be on paper or electronic? Will they always be done in the same order?

Response: The questionnaire battery will be paper-pencil and will take around 30 to 60 minutes. The single instruments are formatted into one single document (labelled as “study questionnaire”) so that the order of the questionnaires is supposed to be the same for each patient. The questionnaire will be mailed to the patients so that they have enough time to complete the questionnaire. Of course, patients are free to refuse their response to certain questions. Missing data will later be compensated by imputation techniques.
We now have incorporated the information above in the paragraph on “assessment” (page 9, lines 196-207). Information on imputation can be found in the analyses section (page 13/14, lines 316-318).

Comment 7: Likely should add in the disease risk index (DRI) as a variable in analysis beyond just disease status.

Response: Thank you for bringing this up. In fact, the DRI is very advantageous for studies investigating patients undergoing allogeneic SCT. Given that this population forms only one subgroup in our study (besides autologous SCT and non-SCT), however, we think that the other medical variables we assess (including disease status, history of relapse, comorbidity etc.) will be sufficient and even more relevant in order to control for confounding factors between the subgroups.

Comment 8: Typo in line 321: Patient recr13uitment

Response: Thank you for this comment, we have addressed this issue (page 16, line 356).

Reviewer 2

General comment: This manuscript is a protocol paper describing the authors' plans to determine prevalence rates of trauma and stressor-related disorders among hematologic cancer patients (with and without stem cell transplant) using differential diagnostic interview methods, assess for sociodemographic and medical risk factors for these disorders, and compare patient values with normative values. Further understanding of rates of and risk factors for PTSD and other disorders in this population is justified given updates to diagnostic criteria within the DSM-5 and medical advances that may impact the experience of and emotional reaction to transplantation. The manuscript however raises a number of questions that limit my enthusiasm for the project in its present form.

Response: We thank the reviewer for her important and thorough comments. We hope we could satisfactorily deal with all of the issues raised.

Comment 1: In general, I found the justification for the study to be well-reasoned. However, while the authors spend considerable space describing study aims, the wording is vague and confusing in places. For example, the authors state that aim 3 is to "run comparisons between patients and norm values matched by age and gender." It's not clear to me what will be compared. Does this refer to PTSD, trauma- and stressor-related disorders, or all disorders assessed more generally, or to something else entirely? Please specify.
Response: Thank you for this advice. We have specified this issue in the research objectives (page 6, lines 113 – 115).

Comment 2: Consider revising statistical/methodological verbiage used in the study aims (e.g., "analyze" in line 116 (the first study aim) and "extract" on line 125 (in the second study aim)) to language that is more conceptual such as "investigate" or "examine."

Response: Thank you for this comment, we now have changed the objectives into research questions (page 6, lines 109 - 115).

Comment 3: What are the hypotheses for the three study aims? Please specify.

Response: Thank you for bringing this up. We have incorporated a statement on hypothesis in the research objectives (page 6, lines 116 – 119).

Comment 4: The ability to draw meaningful conclusions from this study, which proposes a cross-sectional design including a one-time post-transplant/post-treatment assessment, is somewhat concerning. For example, there will presumably be considerable variability with time since diagnosis and number and type of cancer treatment even prior to transplantation. Will these past treatments not also be relevant to trauma and stressor-related reactions? How will this be accounted for? It would be helpful for the authors to provide further justification for why this will not interfere with their ability to draw conclusions from their data.

Response: Thank you for your comment. Regarding the variability of medical characteristics such as time since diagnosis, we note that the general inclusion criteria are the same for both groups (SCT and non-SCT). Nevertheless, certain variability will definitely occur: Therefore, comparisons between the two groups will always be controlled for central characteristics by applying analysis of covariance. We now have clarified this in the manuscript, both in the section for bias control (page 15, lines 344-346) and the statistical analysis (page 13, lines 310 – 313). Furthermore, we will assess in detail to which event the stressor-related symptomatology is referring to: That is, we will have a general trauma list. In case the patient confirms that he/she has experienced a cancer-related distressing event, we will ask further to assess the most severe event within the period. For this event, the symptomatology will be assessed. With this procedure, we will know in the end which PTSD cases are in fact related to the SCT and which cases are attributable to other cancer-related events (e.g., a treatment prior to the SCT). To clarify this issue, we now have focused all relevant information on that topic in a new paragraph named “Differential-diagnostic Analyses” (page 14, lines 322-336).

Comment 5: I have some questions about several transplant-specific issues. As stated above, how will the authors determine that symptoms arise from the transplant/hospitalization versus previous treatments (for those patients who have had previous treatment's)? It appears that the authors have plans to control for comorbidity and remission status, but how will readmissions be
managed? What about transplants performed for curative intent versus performed for delaying disease progression, since it would be reasonable to speculate that this may impact stress-reactions? All of these factors could have important implications for the conclusions the authors are able to draw from the data collected. It would be helpful to understand how these key transplant specific factors will be thought about, accounted for, and used within the study.

Response: Again, thank you for your thorough thoughts. Regarding the first question, please refer to our response to comment 4. With respect to re-admission, we note that patients will assessed only if they are 6-8 weeks after treatment and are not scheduled for any further re-admission (we now have added this information in the section for study participants, page 7, lines 150-151). Concerning the potential effect of treatment intention (curative vs. delaying progress), we plan to conduct additional analyses for patients with chronic forms of hematological diseases (e.g., CML, CML as well as multiple myeloma) to see if they differ in their reaction to certain stressors.

In general, we have thoroughly selected transplanted-related variables which in our opinion might have the largest impact on stress response symptoms. These are:

- the total time spent in hospital for the (current) hematological disease
- history of relapse or another malignancy in the past
- previous treatments (including previous SCT) and their respective dates
- total time in isolation in the course of the SCT
- suffering from acute GvHD

All these variables will be descriptively presented to provide the reader a better overview of the final sample. Variables such as time in isolation or the occurrence of acute GvHD will be used as covariates in any inferential analyses. Additionally, we plan sensitivity analyses for subgroups provided that sample sizes will be large enough. We now have added this information in the section for “description of assessment instruments” (page 10, lines 233-238) and bias control (page 15, lines 346-347).

Comment 6: I also have some questions about the timing of the clinical interview and validated questionnaires. Why 6-8 weeks after discharge for those patients receiving inpatient treatment? And why at the "end of treatment" for those individuals receiving outpatient treatment? Do the authors propose that these are windows that are directly comparable? Also, some centers perform autologous transplants largely or completely outpatient. Will all patients receiving transplant who are enrolled in the study have had an inpatient transplant?

Response: We were not clear enough about that: “6-8 weeks” refers to both the inpatients and the outpatients – we now have modified this sentence accordingly in the study design. This time
point (6-8 weeks after treatment) was thought to be as close as possible to the potentially traumatic events but at the same time long enough after treatment to ensure that the (majority of) potential stressors in the course of the therapy has already ended, so that a potential PTSD might have developed (in the first 4 weeks of symptomatology, patients would be diagnosed with acute stress disorder). We now have added this information in the section on study design (page 7, lines 141-143). In the department for hematology, in which our participants are recruited, all transplantations are performed as inpatient treatment.

Comment 7: With regard to the clinical interview, the Clinician-Administered PTSD Scale is the gold standard for PTSD assessment and I'm curious why the authors have chosen not to use this interview?

Response: Given that we also assess not only PTSD, but a variety of mental disorders, we decided to use only one diagnostic instrument for all mental disorders. Furthermore, the SCID-5 is the interview which is mostly applied in PTSD studies among cancer populations (Abbey G, Thompson SBN, Hickish T, Heathcote D. A meta-analysis of prevalence rates and moderating factors for cancer-related posttraumatic stress disorder. Psychooncology. 2015;24(4):371-381), an thus the use of this assessment improves the comparability with other studies.

Comment 8: Some of the physical symptoms that are normative after a transplant (even 6-8 weeks out) are part of the criteria for a PTSD diagnosis (e.g., trouble falling or staying asleep, difficulty concentrating, being watchful or on guard, feeling distant or cut off from others). Could the authors describe more fully how they intend to manage this?

Response: Thank you for bringing this up. We are aware of the difficulty in differentiating some physical side effects of the treatment with psychopathological symptomatology. Nevertheless, the use of clinical interviews and the thorough investigation of the stressors are the best methodological way to deal with potentially confounding symptoms (Gurevich M, Devins GM, Rodin GM. Stress response syndromes and cancer: conceptual and assessment issues. Psychosomatics. 2002;43:259–81). Additionally, we will conduct sensitivity analyses, i.e., we will investigate the prevalence of PTSD excluding all symptoms that may be directly affected by the therapy, i.e., cognitive symptoms (memory, concentrating) and sleep problems. We added this information on the section on differential-diagnostic analyses (page 14, lines 333-336).

Comment 9: The authors also propose collecting data via a battery of questionnaires. Do the questionnaires described have cutoffs for clinically-meaningful symptoms, and, if so, would those be appropriate to report in addition to absolute percentages from the clinical interview?

Response: In fact, there are cut-offs for the questionnaires assessing PTSD symptomatology, adjustment disorder symptomatology, depressive symptomatology and anxious symptomatology, which can be used as additional information on prevalence of clinical symptoms. Even more important, we will also use the normative values for comparisons between patients and norms: Thereby, we can investigate if patients are clinically meaningful impaired (e.g., if the effect size
d is > 0.5) (see page 13, lines 313-315). Other assessments such as experiential avoidance or fear of progression will be used as potential risk factors for stressor-related symptomatology.

Comment 10: General comment that the manuscript focuses quite heavily on those patients who received transplant at times to the detriment of the other 300 patients with hematologic cancers who are not receiving transplant.

Response: Thank you for this comment. We have incorporated additional information on hematological cancer patients in general in the abstract and the introduction.

Comment 11: English-language and grammatical editing needed throughout manuscript.

Response: We re-checked the whole manuscript for linguistic and grammatical errors.