Author’s response to reviews

Title: Patient information, communication and competence empowerment in oncology (PIKKO) – Evaluation of a supportive care intervention for overall oncological patients. Study protocol of a non-randomized controlled trial.

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Author’s response to reviews:

Dear Mrs. Hughes,

We are pleased to submit the revised version of our manuscript “Patient information, communication and competence empowerment in oncology (PIKKO) – Evaluation of a supportive care intervention for overall oncological patients. Study protocol of a non-randomized controlled trial.” Attached to this letter you will find our answers to the reviewers as point-to-point response. We are very grateful to the reviewers for their valuable advice. They have greatly improved our text and made it easier to understand and read. Now we hope that nothing more stands in the way of a publication in the BMC Medical Research Methodology.

Should there still be open questions or unclear facts, we would be pleased to have the opportunity to clarify these matters as well.

We wish you a stable health and all the best in these difficult times.
With kindest regards
Nico Schneider for all co-authors

Reviewer 1
1. Comment: If I have understood the work correctly, the ethics proposal was approved in November 2017, then the data was collected immediately. Less than a year later, in October 2018, the trial was registered. Why so much later? This would have to be justified. In my working world, after the ethics proposal, the trial is first registered and then the data collection is started. Why was there so much delay? This need to be justified in the work.
Reply: We can well understand this confusion. We regret even the delays back then. This study evaluates a practical health care project, which is carried out by statutory health insurances and is subject to strict guidelines (milestone plan, implementation schedule) by the governmental funder. It should also be noted that, due to the characteristics of the new funding medium (InnoFond), the project management must be independent and separate from the project evaluation. Unfortunately, the registration of the study as a clinical study (which is carried out in pure research projects right at the beginning) was neglected due to the concentration on the development of the new supportive care structures. However, data collection in the first year of the project concentrated on patients in regular care (control group), which was not influenced by any intervention. The following has been added to the trial registration in line 49: „the reason for the delay was the prioritization of the study management in the first year to establish the new approach into practice”

2. Comment: And the study protocol is only now available in February 2020, one month before the now planned end of data collection. Why only now?
Reply: The study protocol was part of the ethics proposal, is written in German and not published, but is the basis for our evaluation. At the beginning of the project we started to write an English version of the study protocol for publication. Delays in the publication of the protocol are to be justified by the workload in the first year (establishment of the new supportive care structure, development of the evaluation) and the two rejections by other journals (first submission Aug 2019).

3. Comment: The time period for the survey of the control group and the intervention group is not identical. One year versus one and a half years. Why? Again, there are open questions for the reader.
Reply: A recruitment period of one year was originally planned for both the control and the intervention group. The recruiting period for the intervention group was extended because with the entry of a fourth statutory health insurance in the summer of 2019, the prospect of transferability to standard care (main objective of the funding format) is considerably better, but patients of the new statutory health insurance should be given sufficient time to benefit from PIKKO (prerequisite for participation of the new statutory health insurance). The following has been added to the trial status in line 458: „An extension of the recruitment period of the intervention group (from one year to one and a half year) was necessary due to the entry of a further statutory health insurance (AOK Rheinland-Pfalz/Saarland) in the summer of 2019.

4. Comment: The combination of dropout rate and imputation is also not clear to me. Alpha at .05 and beta at .10 is rather unusual. Why not both the same or beta 4 times as high? On the one
hand a high dropout rate of 50% is expected for the sample calculation, on the other hand the
data is not clear to me.
Reply: Since we assume moderate to small treatment effects, we have set beta to twice the
amount of alpha and thus receive beta =.1 or power =.9. A power of .95 (or alpha=beta)
represents an unfavorable tradeoff for us (sample or costs become disproportionately large). We
agree with the reviewer that an imputation with a dropout (or missing data percentage) of 50% is
to be evaluated very critically. We have adapted our analysis strategy accordingly. We added in
line 412: “To validate our analyses, we will conduct the analyses with imputed missing data and
without imputation.”

5. Comment: 338 per group, that makes 676 in total and not 667 as in the text (typos?). If one
assumes a dropout rate of 50% here, 676 people would have to be collected per group. This
makes 1352 in total and not 1014 as described in the text. As a result, the project is overfinanced
here, or the sample size was calculated incorrectly.
Reply: Yes, 667 was a typos. We fixed it. We changed 667 to 676 in Lines 301 and 305. The
50% is actually somewhat misleading. We expected 338 dropout patients which represents 50%
of 676 primary outcome respectively 33.3% of included patients (1014). Nevertheless, we would
like to briefly point out that we firmly reject the idea of overfinancing. In your calculation 1352
should be included. In our study we included a smaller number of patients (1014). This would
mean an underfinancing in your logic. We changed text from line 305-307: “We assumed that
338 patients would drop out and added this amount to the total number of included patients. As a
consequence, the recruiting aim was N=1014=676+338 patients (per group 507 = 338 reaching
the end point + 169 dropout). The expected dropout rate was 33.3% regarding the baseline (338
of 1014) or respectively 50% regarding the patients reached the endpoint (338 of 676).”

6. Comment: The statistical procedure is also not clear to me. Surveys over five measuring
points: But the primary analysis is only on t2 and „only“ a t-test on one variable. But the design
should analyze over several measurement times and has several dependent variables. Or why else
were all these measurement points and variables collected? In my view, the study and the data
set require a latent growth model. Here one could take into account several dependent variables
and also introduce covariates.
Reply: According to your suggestion we revised the method section / sub section statistical
analysis. We changed the following from line 398: “Characteristics of control and intervention
groups (e.g. age, sex, education, family situation, partner situation) will be analyzed with
descriptive statistics. Since no randomization is made for ethical and research practical reasons,
univariate tests are used to determine which of the above mentioned characteristics differ
between the two groups. Ideally there are no significant differences between the two groups. In
the case of significant differences we will compute propensity scores using the corresponding
pre-treatment variables. Then, we will apply in the subsequent analyses propensity scores as
stabilized regression weights to reduce bias caused by different group characteristics. The main
hypothesis of an intervention effect on psychological and physical health, self-efficacy, health
care costs etc. will be proofed by the comparison of averages of intervention and control group
(resp. t-tests). To estimate the corresponding regression adjusted group means we will use
growth curve models. Furthermore, we will conduct subgroup analyses to identify conditional
treatment effects. For dropout analysis we will conduct a logistic regression with dropout as
criterion and group assignment and baseline variables as predictors applying the regression
weight mentioned above. For the time-to-event analysis we will conduct a Cox regression. The level of significance will be \( \alpha = 0.05 \). To validate our analyses, we will conduct the analyses with imputed missing data and without imputation.”

7. Comment: The lack of randomization is not good from the evidence. A more detailed explanation would be desirable.
Reply: The lack of randomization was already addressed at page 6 line 129. However, we agree that this is a very critical point. In the revised manuscript we discuss this point more in detail. We changed the text from line 127 to 136: „A non-randomized design with two recruitment periods, starting with the (first) control group, was chosen due to the following reasons: 1) randomization on a test person level was not possible for ethical reasons and for reasons of the statutory basis of the German health care system. 2) It is also not reasonable from a CRM (Customer Relationship Management) perspective to withhold an existing service from needy persons on the part of the statutory health insurances. 3) In a medical facility (practice, clinic), intervention and control cannot take place simultaneously to the extent required by this study (control patients could still contact PN). 4) Cluster randomization was not feasible for a project of this size and kind due to the medical infrastructure in the small state of Saarland.”
Reviewer 2

8. Comment: The aim of the study needs to be clarified at the end of the Background section of the Abstract. The aim needs to clarify that this manuscript is a methodological manuscript to illustrate how this study was planned, implemented, and evaluated.
Reply: This point is connected with point 11. We moved the following from line 44 to line 31: “PIKKO is designed to improve quality of life, self-efficacy, health literacy and patient satisfaction and to reduce psychological distress, related health care costs and the days of inability to work. This methodical work presents the process and analysis planning of this evaluation.”

9. Comment: The study participants need to be in the first sentence of the Methods section of the Abstract.
Reply: We moved the following from line 42 to line 32: “The study population includes all cancer types, both new and existing diseases.”

10. Comment: The Methods section needs to mention briefly the statistical methods used to evaluate the study.
Reply: We added the following to line 43: “Among other statistical procedures, we use t-tests, univariate tests and growth curve models.”

11. Comment: The first sentence in the Discussion belongs to the aim of the study, not Discussion.
Reply: See Point 8.

12. Comment: The future direction in the Discussion in unclear. The future direction needs to be clear in terms of future evaluation and having results, modifying the study based on the findings of the first stage, expanding the study to other regions in Germany, or guidelines for other researchers who would like to benefit from this study for other regions, settings, or countries.
Reply: We changed the discussion from line 44: “If PIKKO proves to be effective, recommendations can be made to health organizations, which should lead to the concept being rolled out throughout Germany and included into oncological guidelines. We expect PIKKO to be a useful addition to usual cancer care, helping to improve the quality of life of cancer patients and reduce healthcare costs.”

13. Comment: The funding source needs to be takes out of this section. This could be part of the Acknowledgement.
Reply: We deleted the funding in line 97 and insert the period into line 479.

14. Comment: This section needs to end with the aim of the study.
Reply: We added to line 103 the following: „The evaluation aims to measure the effect of PIKKO on a patient level (better quality of life, less psychological stress, better self-efficacy, better health competence, more satisfaction with the practitioners), as well as on the level of health care costs which should provide information on the implementation of the care concept and the transfer to other diseases. This paper describes the evaluation concept.”

15. Comment: Would selecting from three health systems, 25 cities, and 80 providers create a selection bias for future generalization of the results?
Reply: Yes, that’s right. A selection, which is based on voluntariness, is always a problem for generalization. Nevertheless, we cover representative areas of the health system in Saarland for oncological care. Especially the participation of initially three, later on four, statutory health insurances, which have a total of 50% market coverage in Saarland, shows how extensive the recruitment is. Later generalizations and implementations can only be made from federal state to federal state, a characteristic of the federal system in Germany. We will add this limitation in the "Limitations" section starting at line 433: “The voluntary and selective participation of hospitals (respectively individual departments), clinics and practices could lead to a selective clientele of patient e.g. disproportionately many breast cancer patients. However, this could also make the study more comparable to the many studies that have been pre-determined for certain groups, e.g. specialized in breast cancer patients.”

16. Comment: How would the wide age range be a problem for different needs of different age groups?
Reply: The age range appears to be very wide, but it decreases due to the fact that most cancers are correlated with higher age. Apart from the fact that PIKKO was designed for all age groups (counselling services, website), the age range also allows comparisons between age groups regarding their use of different counselling options. We see this as an advantage rather than a problem. It remains to be seen whether the analysis will reveal age group differences. We will address this as strength of the study in the discussion starting at line 432: “The study is designed to evaluate the effect of PIKKO interventions under naturalistic conditions. The according heterogeneity of the sample (age range, all cancer types, all sexes) tries to reflect the reality of oncological care. Due to the heterogeneity of the sample, subgroup analyses are planned to show which module of PIKKO works best for whom.”
17. Comment: Same for all cancers. Different cancer sites would have different needs and information requirements. Would focusing on a specific and limited number of cancer sites make the study more under control?
Reply: Right. The focus on one or less cancer types would possibly strengthen the statements for this entity; this has already been done in other studies. It is the declared goal of the new, supportive care concept (and a goal of the funder and so a reason for state funding) to establish an offer for all cancer patients. The website, for example, offers both specific and general information. The broad further training of the patient navigators also ensures their comprehensive commitment. We will address this as strength of the study in the discussion starting at line 432: “This new supportive care concept is intended to establish an offer for all cancer patients. Low barriers for the procurement of information such as the website, which offers both specific and general information, are just as much a part of the concept as the broad further training of PN, who can thus advise all cancer patients.”

18. Comment: How would the heterogeneous sample affect the interpretation and generalization of the results?
Reply: We also see heterogeneity as strength of the study, as it better reflects the reality of supply than a population selected in advance (see point 22). Subgroup analyses allow differentiation of the results. Adjustments are made to test the hypotheses. We will address this as strength of the study in the discussion starting at line 432: “The study is designed to evaluate the effect of PIKKO interventions under naturalistic conditions. The according heterogeneity of the sample (age range, all cancer types, all sexes) tries to reflect the reality of oncological care. Due to the heterogeneity of the sample, the study can use subgroup analyses to show which component of PIKKO works best for whom.”

19. Comment: The recruitment needs to be in the beginning, not the end of this section.
Reply: After the SPIRIT checklist the item "Recruitment" comes after “Study setting”, “Eligibility criteria”, “Interventions”, “Outcomes”, “Participant timeline” and “Sample size”. (Chan et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013 Jan 8;346:e7586. doi: 10.1136/bmj.e7586.) But okay, if their desire is to move “Recruitment” further forward, we move it behind the inclusion and exclusion criteria. Even further forward we think it is illogical, but we are still prepared to do so, should this be a wish of the journal. Nevertheless, we would like to point out once again that we have followed the rules of the SPIRIT checklist. We moved it behind the inclusion and exclusion criteria.

20. Comment: What is the response rate of participants?
Reply: We cannot give results or process numbers (e.g. the response rate) at this stage. This paper is a study protocol and only describes the procedure and methods. (see editor comments)

21. Comment: What is the difference between respondents and non-respondents and how would that affect selection bias and generalization of the results?
Reply: We cannot give any result details here yet, if this was desired. (see editor comments). However, we expect respondents to be more motivated, less burdened patients, while patients who are heavily burdened with cancer have no strength to participate, have less patient activation, less self-efficacy, less social support or more depression, and therefore are not willing to participate. However, we try to lower the participation barrier by addressing all patients in the
oncology centers (through patient navigators on site) and by directly involving the statutory health insurances. We added this point to the limitations from line 433: “In general, less burdened patients, patients with a stronger self-motivation, patients with higher self-efficacy or patients with more social support could preferably participate, leading to a selection bias. Related with this bias can be an overestimation of treatment effects when the treatment is especially effective for less burdened patients. Also an underestimation of the mortality or patient’s withdrawal is possible. To examine the selection bias, we included a second control group which is a random sample of eligible patients based on health insurance company data. We expect that the selection bias is small so that the generalizability of study results should be high.”

22. Comment: The strengths, not just the limitations, need to be included in this section.
Reply: We added the part „Strengths“, starting at line 432. Implications of point 16, 17 and 18 have been included here: “This new supportive care concept is intended to establish an offer for all cancer patients. Low barriers for the procurement of information such as the website, which offers both specific and general information, are just as much a part of the concept as the broad further training of PN, who can thus advise all cancer patients. The study is designed to evaluate the effect of PIKKO interventions under naturalistic conditions. The according heterogeneity of the sample (age range, all cancer types, all sexes) tries to reflect the reality of oncological care. Due to the heterogeneity of the sample, subgroup analyses are planned to show which module of PIKKO works best for whom. Furthermore, the longitudinal design with five measurement points allows the investigation of long-term effects. Last, the telephone interviews with participating PN and physicians can show experiences in the implementation that help to make PIKKO a common part of cancer care.”

23. Comment: Comparison with similar studies from other countries needs to be included in this section.
Reply: A comparable study combining patient navigator, database and specialized counseling cannot be found nationally or internationally. Nevertheless, at the beginning of the “Discussion” we refer to studies on comparable individual elements from Germany. We added from line 432: “So far, there is no other project in Germany that offers cancer patients such a wide range of possibilities as PIKKO. There is also no known international study that combines PN, technical applications and course offerings. There are many technical applications, from websites [50] to apps [51, 52]. Patient navigators are also being tested [53, 54]. There are also numerous cancer advice centers [55, 56] and courses for cancer patients [57]. To bundle all these services and offer them together is an innovation of this study. Finally, the strengths and limitations of such an extensive project should be noted.”

24. Comment: The manuscript is too long and readers will lose interest in reading it because of its length.
Reply: We shortened the text by a few sentences, which contained less relevant information. We hope to increase the reading pleasure by a more catchy text. Unfortunately, the number of words did not decrease visibly, because in other places additions were made according to the reviewer comments.

25. Comment: Please ensure not to add any results related to this study into the manuscript, even if associated details are queried by the reviewers. As this is submission describes a study
protocol, details such as the recruitment rate, should not be stated here. Please consider adding such a statement in the point-to-point response letter, where appropriate.

Reply: yes, thank you.