PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The role of rehabilitation measures in reintegration of children with brain tumour or leukaemia and their families after completion of cancer treatment - A study protocol
AUTHORS	Peikert, Mona; Inhestern, Laura; Bergelt, Corinna

VERSION 1 - REVIEW

REVIEWER	Emma Hovén Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
REVIEW RETURNED	02-Nov-2016

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol. The authors have described a study with an overall aim of bringing understanding of the process of reintegration of childhood cancer survivors and their family members and the role of rehabilitation measures in this process. This purpose has value in a public health perspective with regard to planning of health care measures aiming to facilitate patients' and their families' reintegration to daily life after the end of treatment. Overall, the protocol is logical and describes the process quite well. However, there are some issues that could be clarified concerning core concepts, selection of participants, and outcome measures. These are: TITLE The title is long, could be more succinct. INTRODUCTION The term 'acute treatment' is not clear to me. It would be useful in the Introduction to have a definition of 'acute treatment' and operationalization of 'daily life' as these concepts are key to the purpose of the study. Also, could the rehabilitation measures used in the two rehabilitation concepts be described in short to provide the reader with a better understanding of the study concept and design. In the first paragraph (page 4) the authors mention that children and adolescents are torn out of their daily life for months. For some, the daily life is disrupted for a longer time, even years, which could be mentioned as well. Second paragraph (page 4): Please add relevant references to the first statement of the second paragraph, concerning parents and siblings.

Third paragraph (page 4): Clarify that the overall survival rate of about 80% pertains to high-income countries.

First paragraph (page 5): The focus of reference number 17 could be specified. Reintegration into what is impeded by familial conflicts or high emotional burden.

Third paragraph (page 5): Among several factors, the importance of the study relates to the lack of longitudinal studies that focus mainly on aspects like quality of life in the context of family-oriented rehabilitation programmes. I would suggest that the authors rephrase the sentence, omitting the word ‘mainly’.

Research questions (page 6): Omit the word ‘do’ in research question 1 and 2. Research question 4 could be clarified; is “during the rehabilitation measure” the correct wording?

METHODS AND ANALYSIS
Following the SPIRIT recommendations, the manuscript would benefit from a schematic diagram of study enrolment. As written now, the selection of participants is somewhat difficult to follow.

If correctly understood, only one rehabilitation clinic offering family-oriented rehabilitation is involved. The study would be strengthened by a nationwide approach throughout, now only applied in study arm 1. Why are not additional cooperation partners/rehabilitation clinics engaged in the study?

When and how are the exclusion criteria physical and/or mental burden, cognitive limitations and insufficient language skills assessed?

Outcomes and measurements section (pages 10-13): The outcomes are separated for ‘Children¨’ and ‘Adults’. Are the outcome measures for ‘Adults’ referring to outcomes reported by parents and/or also adult survivors. Please clarify.

As described in the paper on page 8, the age range for inclusion (11 years or older) apply only to siblings, but in Table 1 the age range seem to apply to children overall. This needs to be clarified.

To clarify the clinical relevance of outcome measures it would be helpful if the presentation of these included a description of available age-adapted versions of the measurements, and which version(s) that will be used in the study .This is done for some measures but not all. Information about the psychometric properties would also clarify the relevance of the outcome measures.

Have the self-developed items been evaluated?

DISCUSSION
First sentence. Those studies that do exist could preferably be cited here so it becomes clear what ‘few studies” refer to.

REFERENCES
There seem to be formatting errors for reference numbers 19 and 20.

REVIEWER	David Bara

	University of East London, England
REVIEW RETURNED	17-Jan-2017

GENERAL COMMENTS	There are fundamental flaws with the paper. 1. Title - The title is confusing 2. Treatment – the treatment, effects and late effects for leukaemia and Brain Tumours are very different as such a. Reintegration and rehabilitation is very different b. In the introduction the word 'ill' is used, once a child completes treatment by they are cancer free as such the child and family are dealing with the effects/late of treatment not the cancer itself 3. Language - Language is emotional for example they use the word 'burden' and on p4 'cancer suffer physical changes' is that what was reported if so by who OR are the person going through physical changes as a result of Lukimea and Brain Tumours and the treatment I recommend the research be split into articles two one for the brain tumours and one for the leukaemia, the language be change to be more objective.

REVIEWER	Katie Devine Rutgers Cancer Institute of New Jersey, USA
REVIEW RETURNED	24-Mar-2017

GENERAL COMMENTS	Overview: This is a study protocol of a prospective observational longitudinal study of childhood cancer patients and their families as they transition from the end of treatment and reintegrate into "normal" life. The study proposes three "arms": (1) survey of patients recruited from cancer registries, (2) survey of patients recruited from a cooperating rehabilitation program, and (3) a qualitative interview study of the reintegration process. The protocol explains the major aspects of the study, but there are a number of minor issues to address that would improve the clarity of the methods and planned analyses. 1. For readers unfamiliar with the German rehabilitation system, please clarify the timing of entry into the rehabilitation program. Does it overlap with acute cancer treatment since it is an inpatient program? Are there other rehabilitation programs besides the one cooperating in the study (and will this be accounted for in study arm 1)? 2. Please clarify why the timing of assessments was chosen and why the timing does not match between study arm 1 and 2? (My understanding was that the rehabilitation program is 4 weeks, so the difference pre/post will be 4 weeks in arm 2 but the difference in arm 1 will be 4-6 months). 3. For recruitment, how many siblings will be enrolled per family? Also, how do the registries know that a patient is at the end of acute treatment (and how quickly are the registries updated to allow for your recruitment window)? 4. For arm 3, how will parents be selected for interview (e.g., the first consecutive 20-25 that agree or a purposeful sampling of particular characteristics?). Please clarify whether multiple members of the same family will be interviewed. 5. There are multiple outcomes per reporter. Please clarify if any are

	considered primary outcomes vs. secondary outcomes, or if all will be analyzed. 6. The proposed data analyses do not account for non-independence of the data (i.e., there will be multiple reports from the same family and these data may not be independent). How will this be accounted for in the analyses? 7. In the sample size/power calculation section: please clarify if the sample in arm 2 will come from the same pool as the sample in arm 1? Also, please clarify if 142 total or per group is needed.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Emma Hovén

Comment: TITLE The title is long, could be more succinct.
Response: Thank you for this comment. We reworded the title to make it more concise.
Changes in the manuscript: p. 1: The role of rehabilitation measures in reintegration of children with brain tumour or leukaemia and their families after completion of cancer treatment - A study protocol

Comment: INTRODUCTION The term ‘acute treatment’ is not clear to me. It would be useful in the Introduction to have a definition of ‘acute treatment’ and operationalization of ‘daily life’ as these concepts are key to the purpose of the study.
Response: With "acute treatment" we mean intensive cancer treatments such as chemotherapy, radiation, surgery and stem cell transplantation or bone marrow transplantation. "Acute treatment" seems to be an unclear term. Therefore, we replaced it with "cancer treatment" and gave a definition in the introduction. According to your suggestion, we adapted the manuscript and specified "daily life".
Changes in the manuscript: We replaced "acute treatment" with "cancer treatment" in the manuscript.
p. 4: In this study, the end of cancer treatment is defined as the end of intensive cancer treatments such as chemotherapy, radiation, surgery and stem cell transplantation or bone marrow transplantation.
p. 4: Depending on diagnosis and treatment, children and adolescents are torn out of their daily life such as family and social life as well as school for months or even for years.

Comment: Also, could the rehabilitation measures used in the two rehabilitation concepts be described in short to provide the reader with a better understanding of the study concept and design.
Response: We only described the family-oriented rehabilitation programme in detail (p. 5) because in study arm 2 we only survey families using this rehabilitation measure.
We added further information on the rehabilitation programme for adolescent cancer patients. Thank you for your comment.
Changes in the manuscript: p. 5: For adolescent cancer patients (>15 years) a rehabilitation programme in small groups was developed to adapt to the specific developmental needs of adolescents (e.g. support with development of autonomy).[22] In this rehabilitation programme adolescents are not accompanied by their family members.

Comment: In the first paragraph (page 4) the authors mention that children and adolescents are torn out of their daily life for months. For some, the daily life is disrupted for a longer time, even years, which could be mentioned as well.
Response: Thank you for your comment. We changed the manuscript accordingly.
Changes in the manuscript: p. 4: Depending on diagnosis and treatment, children and adolescents are torn out of their daily life such as family and social life as well as school for months or even for years.

Comment: Second paragraph (page 4): Please add relevant references to the first statement of the

second paragraph, concerning parents and siblings.
Response: We added references of relevant systematic reviews. Thank you.
Changes in the manuscript: p. 4: Likewise, parents and siblings of the patient are confronted with major changes and burden in their lives when a child is diagnosed with cancer.[7, 8]

Comment: Third paragraph (page 4): Clarify that the overall survival rate of about 80% pertains to high-income countries.
Response: Thank you for this comment. As we investigate the reintegration of families in Germany, we refer to a German study. We clarified that in the respective sentence.
Changes in the manuscript: p. 4: Due to improved treatment methods the five-year survival rate in Germany has increased to approximately 80% for childhood cancer patients under the age of 15 years.[16]

Comment: First paragraph (page 5): The focus of reference number 17 could be specified. Reintegration into what is impeded by familial conflicts or high emotional burden.
Response: Thank you for this important note. We specified the focus of this reference.
Changes in the manuscript: p. 5: Still, familial conflicts can impede scholastic reintegration.[21]

Comment: Third paragraph (page 5): Among several factors, the importance of the study relates to the lack of longitudinal studies that focus mainly on aspects like quality of life in the context of family-oriented rehabilitation programmes. I would suggest that the authors rephrase the sentence, omitting the word ‘mainly’.
Response: What we wanted to say is that there are no longitudinal studies with an adequate reference group and in most of the previous studies the primary outcome was quality of life, whereas other important outcomes remained uninvestigated. This hasn´t been clearly formulated, so we rephrased the sentence. Thank you.
Changes in the manuscript: pp. 5-6: However, until now there are no longitudinal studies with an adequate reference group and previous studies focused primarily on aspects like quality of life.[24, 26, 28] Thereby, parental fear of progression or family functioning have not been investigated in the context of family-oriented rehabilitation programmes.

Comment: Research questions (page 6): Omit the word ‘do’ in research question 1 and 2. Research question 4 could be clarified; is “during the rehabilitation measure” the correct wording?
Response: We omitted the word "do" in the first two research questions. Thank you for this comment. In research question 4 "During the rehabilitation measure" is the correct wording. With "received treatments" we mean exactly the treatments received during the rehabilitation measure (see p. 14: Received treatments during the rehabilitation measure and recommendations for aftercare are extracted from the medical discharge records in study arm 2.).
Changes in the manuscript: p. 6:
1) Reintegration: which factors impede or facilitate reintegration?
2) Use of rehabilitation measures: which factors impede or facilitate use of rehabilitation measures?

Comment: METHODS AND ANALYSIS Following the SPIRIT recommendations, the manuscript would benefit from a schematic diagram of study enrolment. As written now, the selection of participants is somewhat difficult to follow.
Response: Thank you very much for the comment.
This study protocol followed no reporting guidelines due to the lack of appropriate checklists to report study protocols of prospective observational studies. However, we followed the STROEBE Statement for observational studies where possible.
We added a flow diagram on page 8 and described the measurement time points, the assessment of inclusion and exclusion criteria and the recruitment and procedure section more detailed.
Changes in the manuscript: pp. 8-10: Changes in the sections Measurement time points, Inclusion

and exclusion criteria, Recruitment and procedure
p. 8: An overview of the recruitment and procedure in the study arms 1 and 2 is displayed in figure 1.

Comment: If correctly understood, only one rehabilitation clinic offering family-oriented rehabilitation is involved. The study would be strengthened by a nationwide approach throughout, now only applied in study arm 1. Why are not additional cooperation partners/rehabilitation clinics engaged in the study?
Response: We agree, that it would have been better to include additional rehabilitation clinics, but due to economic limitations, we could only include one clinic. However, it is likely that some participants from study arm 1 will use rehabilitation measures in other clinics during the collection of data.
Changes in the manuscript: None.

Comment: When and how are the exclusion criteria physical and/or mental burden, cognitive limitations and insufficient language skills assessed?
Response: Thank you very much, we added further information.
Changes in the manuscript: pp. 8-9: In study arm 1 inclusion and exclusion criteria will be assessed by the study registries (age, diagnosis) and the healthcare providers in the clinics. The rehabilitation physicians will assess inclusion and exclusion criteria at the beginning of the rehabilitation measure in study arm 2.

Comment: Outcomes and measurements section (pages 10-13): The outcomes are separated for ‘Children¨’ and ‘Adults’. Are the outcome measures for ‘Adults’ referring to outcomes reported by parents and/or also adult survivors. Please clarify.
Response: Thank you for this important comment. "Adult" is an inappropriate term in this study protocol. We replaced it with "parents".
Changes in the manuscript: We replaced "adults" with "parents" on pp. 11-13.

Comment: As described in the paper on page 8, the age range for inclusion (11 years or older) apply only to siblings, but in Table 1 the age range seem to apply to children overall. This needs to be clarified.
Response: Thank you for your important comment. We survey patients and siblings of 11 years of age and above. But we also include families with children under the age of 11 (see p. 9: inclusion criteria). In these families we only survey the parents. These parents fill in proxy-questionnaires for their children.
Changes in the manuscript: p. 8: In study arms 1 and 2 children and adolescents (≥ 11 years) and their siblings (≥ 11 years) as well as their parents are surveyed.

Comment: To clarify the clinical relevance of outcome measures it would be helpful if the presentation of these included a description of available age-adapted versions of the measurements, and which version(s) that will be used in the study .This is done for some measures but not all. Information about the psychometric properties would also clarify the relevance of the outcome measures.
Response: Thank you for this important note.
We added information on age-adapted versions (KINDL-R and KIDCOPE) and the versions we used in this section.
We also added information about the psychometric properties of the questionnaires.
Changes in the manuscript: p. 11: Children: Children’s health-related quality of life is assessed by the KINDL-R.[30] There are three self-assessment versions (4-6 years, 7-13 years, 14-17 years) and two proxy versions for parents (3-6 years, 7-17 years).[31] In this study we use the self-assessment version for 14- to 17-year olds and the proxy version for parents of 7- to 17-year olds. In an unpublished feasibility study the version for 14- to 17-year olds has also been used for children from 11 to 17 years of age without any difficulties.
p. 13: There are two versions of the KIDCOPE: a 15-item version for children (7-12.9 years) and a 11-item version for adolescents (13-18.9 years).[45] In this study we use the version for adolescents.

p. 11: The self-assessment version and the proxy version both have proved to be reliable and valid.[33]
p. 11: The ULQIE has satisfactory psychometric properties.[34]
p. 12: The self-report version and the version for parents both have adequate psychometric properties.[35, 36]
p. 12: The PHQ-9 has proved to be a valid and reliable questionnaire.[39, 40]
p. 12: The Generalized Anxiety Disorder Screener (GAD-7) is a valid and reliable seven-item self-report instrument designed to identify probable cases of generalized anxiety disorder.[41, 42]
p. 13: The FoP-Q-SF/PR has adequate psychometric properties.[43]
p. 13: The KIDCOPE has a sufficient reliability and validity.[45, 46]
p. 14: The reliability and validity of the CHIP have been proved.[48]
p. 14: The FAD-GF has proved to be reliable and valid.[50]

Comment: Have the self-developed items been evaluated?
Response: Yes, they have been evaluated in a feasibility study. Thank you for mentioning that. We added this information to the manuscript.
Changes in the manuscript: p. 14: The self-developed items have been evaluated in an unpublished feasibility study.

Comment: DISCUSSION First sentence. Those studies that do exist could preferably be cited here so it becomes clear what ‘few studies” refer to.
Response: Thank you for the comment. We added citations to the sentence.
Changes in the manuscript: p. 19: To the best of our knowledge, only few prospective, longitudinal studies have examined the situation of families with a child with cancer after the end of cancer treatment.[19, 26, 53, 54]

Comment: REFERENCES There seem to be formatting errors for reference numbers 19 and 20.
Response: Thank you! We revised reference number 19 (now number 22). The reference number 20 referred to a guideline that is no longer accessible online. Therefore, we replaced it by a recent guideline (reference number 23).
Changes in the manuscript: See p. 24 reference numbers 22 and 23.

Reviewer 2: David Bara

Comment: 1. Title - The title is confusing
Response: Thank you for pointing this out. We reworded the title to make it more concise and less confusing.
Changes in the manuscript: p. 1: The role of rehabilitation measures in reintegration of children with brain tumour or leukaemia and their families after completion of cancer treatment - A study protocol

Comment: 2. Treatment – the treatment, effects and late effects for leukaemia and Brain Tumours are very different as such
Response: Yes, they are definitively different. We focus on these two diagnoses, because they are the most frequent peadiatric cancer diagnoses in Germany. This is now clarified in our manuscript. Thank you very much for your comment.
Changes in the manuscript: p. 4: The most frequent cancer diagnoses in children under the age of 18 years in Germany are leukaemia and brain tumours.[16]

Comment: a. Reintegration and rehabilitation is very different
Response: Yes it is, we totally agree with you. With "rehabilitation" we mean rehabilitation measures (e.g. the family-oriented paediatric oncological rehabilitation programme). With "reintegration" we

mean the reintegration into daily life (e.g. school or working life; see p. 4: Depending on diagnosis and treatment, children and adolescents are torn out of their daily life such as family and social life as well as school for months or even for years.). To be more precise we replaced "rehabilitation" by "rehabilitation measure" or "rehabilitation programme" in the manuscript.
Changes in the manuscript: We replaced "rehabilitation" by "rehabilitation measure" or "rehabilitation programme" in the manuscript.

Comment: b. In the introduction the word ‘ill’ is used, once a child completes treatment by they are cancer free as such the child and family are dealing with the effects/late of treatment not the cancer itself
Response: Thank you for the comment. We used the word "ill" in three sections of the study protocol:
1. Introduction section of the abstract: In this section, we actually mean the ill child, from diagnosis to the end of cancer treatment. We think in this section "ill" is the appropriate term.
2. Outcomes and measurements: In this section, we only used the words "ill" or "illness" in the descriptions of the questionnaires or in connection with illness related burden.
3. Qualitative analyses: We wrote "ill children and healthy siblings". Which is, as you described correctly, an inaccurate formulation. We rewrote this part. Thank you.
Changes in the manuscript: p. 17: Using univariate analyses (t-test, ANOVA) or comparable non-parametric tests, differences between subgroups (e.g. mothers and fathers, cancer patients and siblings, users and non-users of rehabilitation measures, leukaemia and brain tumour patients) will be explored.

Comment: 3. Language - Language is emotional for example they use the word ‘burden’ and on p4 ‘cancer suffer physical changes’ is that what was reported if so by who OR are the person going through physical changes as a result of Lukimea and Brain Tumours and the treatment
Response: Thank you for this note. "Burden" is a commonly used word in the articles we cited. That is why we also used it in our manuscript.
On p. 4 was written: Children and adolescents with cancer suffer from physical changes and display impaired quality of life and well-being compared to their healthy peers.[2, 3]
The references refer to the impaired quality of life and well-being. We added another reference referring to the physical changes. Thank you.
Changes in the manuscript: p. 4: Children and adolescents with cancer suffer from physical changes and display impaired quality of life and well-being compared to their healthy peers.[1-3]

Comment: I recommend the research be split into articles two one for the brain tumours and one for the leukaemia,…
Response: Thank you for your recommendation. As you said, leukaemia and brain tumour patients deal with very different treatments and late effects. But these patients use rehabilitation measures in the same clinics and they attend the same group sessions (e.g. psychological group sessions) in these clinics. Therefore, the results of the evaluation of the rehabilitation measure will be published in one article.
Additionally, it is also interesting to analyse differences between leukaemia and brain tumour patients and their family members.
But there will be possibly secondary analyses and maybe it will be appropriate for these articles. Thank you.
Changes in the manuscript: p. 17: Using univariate analyses (t-test, ANOVA) or comparable non-parametric tests, differences between subgroups (e.g. mothers and fathers, cancer patients and siblings, users and non-users of rehabilitation measures, leukaemia and brain tumour patients) will be explored.

Comment: …the language be change to be more objective.
Response: See above.

Changes in the manuscript:

Reviewer 3: Katie Devine

Comment: 1. For readers unfamiliar with the German rehabilitation system, please clarify the timing of entry into the rehabilitation program. Does it overlap with acute cancer treatment since it is an inpatient program? Are there other rehabilitation programs besides the one cooperating in the study (and will this be accounted for in study arm 1)?
Response: Patients and families enter into the family-oriented rehabilitation programme after the inpatient cancer treatment (see p. 5).
They can attend the family-oriented rehabilitation measure in five specialised rehabilitation clinics in Germany. In addition, there is a rehabilitation programme in small groups for adolescent cancer patients (p. 5).
Thank you for you notes. We added further information.
Changes in the manuscript: p. 5: In the German rehabilitation system two rehabilitation concepts are established to support childhood cancer patients and their families after the inpatient cancer treatment.[22, 23]
p. 5: For adolescent cancer patients (>15 years) a rehabilitation programme in small groups was developed to adapt to the specific developmental needs of adolescents (e.g. support with development of autonomy).[22] In this rehabilitation programme adolescents are not accompanied by their family members.

Comment: 2. Please clarify why the timing of assessments was chosen and why the timing does not match between study arm 1 and 2? (My understanding was that the rehabilitation program is 4 weeks, so the difference pre/post will be 4 weeks in arm 2 but the difference in arm 1 will be 4-6 months).
Response: Thank you for your comment.
Families enter into the family-oriented rehabilitation measure after the end of inpatient cancer treatment (see p. 5). From clinical experience we know that the beginning of the rehabilitation measure varies between families, but most of the families attend the rehabilitation clinic and start the programme within about three months after the end of inpatient cancer treatment. We therefore assume that the rehabilitation measure will be finished after four to six months after the end of cancer treatment. Therefore, T2 in study arm 1 is temporally delayed in comparison to T2 in study arm 2. We want to give the families the chance to use a rehabilitation measure between T1 and T2 in order to receive matching times of measurements for T2 and T3 in both study arms and because reintegration into daily life after the rehabilitation measure is the focus of our study.
However, as the timing of the entry into a rehabilitation measure depends on the family, it is very difficult to survey families from study arm 1 and 2 at matching measurement time points.
We will definitely discuss that in the resulting publications. We added further information and a flow chart.
Changes in the manuscript: p. 8: The different measurement time points in study arm 1 and 2 have been chosen for two reasons. First, the timing of the entry into a rehabilitation measure depends on the families and their specific situation. Consequently, we cannot survey families after the end of cancer treatment in study arm 2. Second, the follow-up measurement in study arm 1 is temporally delayed in comparison to the post measurement in study arm 2 because we want to give the families the chance to use a rehabilitation measure between the first two measurement time points in order to receive matching times of measurements for the last two measurements in both study arms.
p. 8: An overview of the recruitment and procedure in the study arms 1 and 2 is displayed in figure 1.

Comment: 3. For recruitment, how many siblings will be enrolled per family? Also, how do the registries know that a patient is at the end of acute treatment (and how quickly are the registries updated to allow for your recruitment window)?

Response: In principle, we want to enroll as many siblings (from the age of 11 years and above) as the patient has. However, parents can only assess two siblings in their questionnaires. As we have chosen a paper-pencil survey, we had to restrict the length of the questionnaires due to economic and ecological reasons. We have added this information to the manuscript. Thank you for this important comment.

Study registries receive information on the time of diagnosis and the treatment protocol of the children. With the help of this information, they can estimate the end of cancer treatment. They inform the clinic and healthcare providers at the clinics ask the patients and their families to participate when treatment is completed. Hence, the end of treatment is double-checked by the registries and clinics. This was also an important note. We explained it more precisely in the manuscript. Thank you.

Changes in the manuscript: p. 15: About children (patient and max. two siblings)

p. 9: The study registries estimate the end of cancer treatment of their registered patients based on the information available (i.a. time of diagnosis, treatment protocol). They inform the clinic where the patient receives treatment about the study. Healthcare providers at the clinics inform the patients and their families about the study after the end of cancer treatment, ask them to participate and pass a data set containing an invitation and information letter as well as a consent form to contact the family.

Comment: 4. For arm 3, how will parents be selected for interview (e.g., the first consecutive 20-25 that agree or a purposeful sampling of particular characteristics?). Please clarify whether multiple members of the same family will be interviewed.

Response: Thank you for your valuable comment. We will conduct a consecutive sampling of the first 20-25 families that agree to participate in the interview study. We will also include multiple members, if both parents agree to participate. However, single parents or families with only one interested parent will be included as well. We added this information to the manuscript.

Changes in the manuscript: p. 10: We conduct a consecutive sampling of the first 20-25 families that agree to participate in the interview study. We include multiple family members if both parents agree to participate. However, single parents or families with only one interested parent will also be included.

Comment: 5. There are multiple outcomes per reporter. Please clarify if any are considered primary outcomes vs. secondary outcomes, or if all will be analyzed.

Response: Yes, we decided to capture many outcomes. The main aim of our study is to further the understanding of the process of reintegration and the role of rehabilitation measures in this process. This has not been systematically examined yet. Therefore, we wanted to cover many important outcomes in this exploratory examination and we will not distinguish between primary and secondary outcomes.

Changes in the manuscript: None.

Comment: 6. The proposed data analyses do not account for non-independence of the data (i.e., there will be multiple reports from the same family and these data may not be independent). How will this be accounted for in the analyses?

Response: Thank you for this important comment. We are aware of the potential non-independence. As a first step, we will prove the non-independence of our data. Further analyses depend on the sample size. Multilevel analyses may be possible. It is also planned to conduct a dyadic data analysis of the parental data as a secondary analysis.

Changes in the manuscript: p. 17: Correlations will be calculated to explore associations between outcome variables and to measure potential non-independence of data in families.

The longitudinal nature of this study allows multivariate analysis strategies such as regression analysis, multilevel modeling and repeated measure analysis of variance to investigate the role of other factors and to examine changes over time.

Comment: 7. In the sample size/power calculation section: please clarify if the sample in arm 2 will

come from the same pool as the sample in arm 1? Also, please clarify if 142 total or per group is needed.
Response: Participants from study arm 1 will not come from the same pool as the participants in study arm 2. They will come from the study registries CoALL, I-HIT-MED and SIOP-LGG, whereas participants in study arm 2 will be recruited in the rehabilitation clinic Bad Oexen. But there might be overlaps between the two study arms. It is possible, that families from study arm 1 will attend the family-oriented rehabilitation measure in the cooperating rehabilitation clinic and will drop out of study arm 1 and then will be surveyed in study arm 2 (see p. 8 and figure 1). These families would somehow come from the same pool.
142 is the total sample size. Thank you for that important note.
Changes in the manuscript: p. 17: Sample size calculation indicates that a total sample size of 142 patients is sufficient to detect medium group differences (f=0.25) with a power of 95% at a significance level of p<.05.

VERSION 2 – REVIEW

REVIEWER	Emma Hovén Karolinska Institutet, Sweden
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	I believe that the manuscript has improved considerably by having taken into account the comments by the reviewers. Good work!

REVIEWER	David Bara University of East London, United Kingdom
REVIEW RETURNED	24-Apr-2017

GENERAL COMMENTS	-Title - the Methods and Analysis (after the intro) needs to have a clearer link to the title - The introduction - are the children ill, if so are they still going through treatment or are they post treatment and the rehab is dealing with the effects/late effects? As this is confusing as does not link clearly with the methods and analysis which follows- these sections need to be tighten up - Design - what is meant by 'unselected sample of patients '? - General question about what is meant by rehabilitation- when does this start as for some treatments rehabilitation starts the moment treatment starts i,e for surgery and the treatment continues- so when does rehab start in Germany ? Does it start in/on a ward or in a clinic? - I feel the research is trying to do to much and needs to deign is to broad and needs to focus on 1 possibly 2 study arms but not 3 as while this will provide triangulation it is confusing for this paper It is very interesting and worth while what they are doing but needs to be split down into another papers or research projects as it is confusing

REVIEWER	Katie Devine Rutgers Cancer Institute of New Jersey, USA
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	The authors have thoughtfully responded to the initial reviews.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2: David Bara

Comment: -Title - the Methods and Analysis (after the intro) needs to have a clearer link to the title
Response: Thank you for your comment. Although we think that title and methods and analysis part correspond adequately to each other, we amended the introduction of the methods and analysis section according to your comment in order to emphasise the connection of title and methods and analysis section once more.
Changes in the manuscript: pp. 6-7: In order to address the research questions with regard to the role of rehabilitation measures in the reintegration of children and their families after completion of cancer treatment mentioned above, we conduct a prospective observational study with a longitudinal design including a baseline measurement and two follow-up measurements. The study focusses on the most frequent childhood cancers in Germany [16] and thus includes children with brain tumour or leukaemia and their families.

Comment: - The introduction - are the children ill, if so are they still going through treatment or are they post treatment and the rehab is dealing with the effects/late effects? As this is confusing as does not link clearly with the methods and analysis which follows- these sections need to be tighten up
Response: Usually the patients have already completed inpatient cancer treatment (see p. 5). However, the timing of the entry into the rehabilitation measure depends on the families (see p. 8). It is possible that some patients still receive remission maintenance therapy during the rehabilitation measure. The primary aim of the family-oriented rehabilitation measure is to achieve the patients' rehabilitation goals, to ensure the treatment success and to help patients and families to reintegrate into their normal lives. That includes dealing with physical late effects of the illness and the treatment, but also with psychological and social burden, the families possibly experienced and are still experiencing after the primary treatment. We added this information. Thank you for your comment.
Changes in the manuscript: p. 5: The primary aim of the four-week inpatient rehabilitation programme is to achieve the patients' rehabilitation goals and to ensure the treatment success.[22] Therefore, multiprofessional therapeutic teams of physicians, clinical psychologists, social education workers and other professionals offer group or individual therapies and activities as required for all family members during the rehabilitation programme.[22]

Comment: - Design - what is meant by 'unselected sample of patients '?
Response: Thank you for your comment. “Unselected sample” indeed seems to be an unfortunate choice of words. It should be replaced with “consecutive sample”: In study arm 2, we survey families using the family-oriented rehabilitation measure in our cooperating rehabilitation clinic. These families are recruited consecutively. In study arm 1, we survey families from the cooperating study registries, irrespective of whether they will use a rehabilitation measure or not. These families are also recruited consecutively. However, of course, all participants have to fulfill the inclusion and exclusion criteria and are therefore not “unselected”. As “consecutive sample” is much more appropriate, we changed the manuscript accordingly. Thank you very much!
Changes in the manuscript: p. 7: Therefore, this study aims to include a consecutive sample of patients and families at the end of cancer treatment in order to include both subsequent users and non-users of rehabilitation measures.

Comment: - General question about what is meant by rehabilitation- when does this start as for some treatments rehabilitation starts the moment treatment starts i,e for surgery and the treatment

continues- so when does rehab start in Germany ? Does it start in/on a ward or in a clinic?
Response: In the German rehabilitation system, patients and families enter into the four-week inpatient family-oriented rehabilitation measure after the primary inpatient cancer treatment (see p. 5). However, the timing of the entry into the rehabilitation measure depends on the families and their specific situation (see p. 8). The family-oriented rehabilitation programme takes place in specialised rehabilitation clinics that are separate from acute care clinics.
Changes in the manuscript: None.

Comment: - I feel the research is trying to do to much and needs to deign is to broad and needs to focus on 1 possibly 2 study arms but not 3 as while this will provide triangulation it is confusing for this paper
It is very interesting and worth while what they are doing but needs to be split down into another papers or research projects as it is confusing
Response: Thank you for your comment. We agree, the study design is rather complex. However, the investigation of the role of rehabilitation measures in reintegration after the end of cancer treatment requires the inclusion of both subsequent users and non-users of rehabilitation measures. This will be achieved with study arm 1 and 2 (see p. 7). Study arm 3 is also an important part of our study, as it will focus on a deeper understanding of the reintegration processes (see pp. 7, 16). Therefore, we cannot abandon any of our study arms and we also think, that it is important to describe all study arms in one study protocol because they are part of one study.
Changes in the manuscript: None.