PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Interprofessional evidence-based counselling programme for Complementary and Integrative Health Care in cancer patients – study protocol for the controlled implementation study CCC - Integrativ
AUTHORS	Valentini, Jan; Fröhlich, Daniela; Stolz, Regina; Mahler, Cornelia; Martus, Peter; Klafke, Nadja; Horneber, Markus; Frasch, Jona; Kramer, Klaus; Bertz, Hartmut; Grün, Barbara; Tomaschko-Ubeländer, Katrin; Joos, Stefani

VERSION 1 – REVIEW

REVIEWER	Carey, Matthew Churchill Hospital, Palliative Medicine
REVIEW RETURNED	12-Sep-2021

GENERAL COMMENTS	Many thanks for submitting your protocol for publication, I think it is great to see how you are undertaking this research project in an area which requires more solid evidence. I am very much looking forward to seeing the whole study published with analysis. I think on the whole this is a well-constructed Protocol article but requires some minor revisions for improvement to readability and to convey what and how you are trying to achieve most accurately. - Grammar and structure: there are many within the article, too numerous to offer simple corrections for by my review. Please reach out if you need someone to assist as it won't take long to do and will mean the article will have good reach and readability. - Please review the abstract, it requires more precision to ensure it's clear what you're trying to achieve. - When discussing Micro, Meso and Macro – I would probably introduce this a Patient, Provider and System first and then explain the link to micro/meso/macro as these specific terms in health economics and public health descriptions are less well known. This will help the reader to contextualise this better and understand why you're looking at things across healthcare economies and boundaries. - I would introduce a clear aim that you are trying to achieve with this intervention, something along the lines (I am assuming) the global improvement in quality of life and reduction in any specific harms as identified by 1) complications of CIH and underutilisation/appropriate utilisation of healthcare resources. - Are you measuring the patients' health literacy as related to CIH at all? If so I would include this in your outcomes discussion. - If this is considered as patient activation – I would expand on this meaning. I say this as patient activation, whilst used in some circles, is not a concept which is widely known in healthcare. For your protocol to be fully understood or even adopted, discussion

	about what patient activation as a concept in a complex intervention is important. - I would also define early on what you mean by counselling. It is widely accepted as a generic term for offering psychological or emotional support. In this protocol counselling seems to offer some of this but much more education, teaching and clinical review. - Who is blended online learning for?

REVIEWER	Kiley-Morgan, Judith Addenbrooke's Hospital, Psychological Medicine for Children, Young People and Families
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	This is a well-written paper on a topic that has the potential to be an extremely important contribution to the literature, and inform cancer care on an international level. The authors have set up a comprehensive study on integrating counselling on complementary and integrative health care (CIH) into Oncological health care provision, in line with patient-centred cancer care guidelines. This has the potential to both mitigate against the risks associated with some CIH methods due to lack of patient information, and also increase the potential positive effects of supportive CIH care. I offer here some minor suggestions for clarification and revision: Introduction - A central construct of this study is “patient activation”. This concept is explained in detail under ‘Primary Outcome’ in the Methods section. It would be helpful to a have brief definition included in the Introduction for the sake of clarity – e.g. patient activation as a measure of patient knowledge, skill and confidence for self-management. Include a reference for the definition. - The project is described as a “complex intervention” but no explanation is given as to what makes the intervention complex? Is this in reference to the multi-level approach of micro (patient), meso (provider) and macro (system) levels of intervention? Please clarify in the introduction what is meant by “complex intervention”. Methods and Analysis Setting and study design - More justification for why cluster randomization would to lead to possible contamination problems would be helpful. No explanation has been given for why this is the case, and if the readers are to trust why no form of randomization was possible, more explanation is needed. Intervention on patient level - It would be helpful to include clarification of your concept of counselling in this section. It needs to be clear that this is not therapeutic counselling for psychological support, but rather is information giving and guidance for health needs, for the purpose of increasing patient activation and self-efficacy. Is it more akin to health coaching? The term “counselling” is used very broadly within health care, so it is important to be clear on exactly what kind of counselling your intervention is offering. Additionally, it

	would helpful to know what psychological support is available to participants if the CIH counselling sessions were to bring up psychological distress for any patients? Primary outcome - Is the only measure of effect the PAM-13? If so, is patient activation the only effect measured? At the end of the Introduction the stated aim is evaluation of whether CIH counselling improves patient activation and patients' confidence. How is patient confidence going to be evaluated? Is this through the process evaluation? This needs to be clarified. Secondary outcomes - It would be helpful to have more explanation of the purpose of the collection of the secondary outcome data? Is the purpose of the secondary data simply comparative to check for selective bias and study effects? Or is the aim also to explore the effect of CIH counselling on quality of life, self-efficacy, depression, fatigue, etc? This needs to be clarified. Miscellaneous - There are a few grammatical errors throughout the manuscript. For example p.4 lines 20, 31, 50; p.7 line 49; p.8 line 21-22; p.9 line 10; p.13 line 31. Please read through carefully to check for grammar and typos. - p.10 line 3 – what is meant by "actors"? Stake-holders perhaps?

REVIEWER	Christie, Vita The University of Sydney, Poche Centre for Indigenous Health
REVIEW RETURNED	15-Sep-2021

GENERAL COMMENTS	Thanks for inviting me to review this protocol. I commend you on the hard work and well thought out work you have done thus far.

REVIEWER	Falandry, Claire Hospices Civils de Lyon, Geriatrics unit
REVIEW RETURNED	26-Sep-2021

GENERAL COMMENTS	I acknowledge the authors for performing a study on the difficult topic of CIH, and for proposing the protocol for external expertise. However, I have some concerns about the methodology: 1) Since the intervention is about counselling, the primary endpoint could have been according to my point of view the quality of the counselling ie the content of patients' knowledge on CIH. The rationale explaining how counselling on CIH would lead to patient activation is not demonstrated and could lead to disappointing results. 2) The way that the control group was chosen is also questionable, according to 3 main points: a. When considering that inclusion criteria include: "Need for CIH counselling (attested by actively contacting the local counselling center by email, phone or in person)." One could consider that patients in the control arm may have expectations towards such needs, that will be disappointed, artificially leading to a decrease in patient activation. A way to avoid that could be a proposal for written counselling according to current evidence.

	b. One may imagine that the time spent in a face-to-face counselling in the intervention arm only may increase patient activation whatever the subject discussed during the interview. A control arm would have better maintained the same face-to-face time with a different content (other than CIH). c. Likewise, the imbalance between the control arm and the intervention arm can lead to the Hawthorne effect (observer) since the intervention arm is much more closely monitored (the initial face-to-face interview then the two 60-minute calls). This effect could be avoided if the follow up of both control and intervention arms are exactly the same. 3) The authors should add the SPIRIT checklist as supplementary data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Matthew Carey, Churchill Hospital

Reviewer comment	Authors' answer
Many thanks for submitting your protocol for publication, I think it is great to see how you are undertaking this research project in an area which requires more solid evidence. I am very much looking forward to seeing the whole study published with analysis. I think on the whole this is a well-constructed Protocol article but requires some minor revisions for improvement to readability and to convey what and how you are trying to achieve most accurately	Thank you very much for your positive feedback.
- Grammar and structure: there are many within the article, too numerous to offer simple corrections for by my review. Please reach out if you need someone to assist as it won't take long to do and will mean the article will have good reach and readability.	We had the manuscript revision thoroughly proofread by a native English speaker and paid particular attention to grammar and structure.
- Please review the abstract, it requires more precision to ensure it's clear what you're trying to achieve	Thank you for this remark. We have checked the abstract again after revision and have tried to be as concise as possible.
- When discussing Micro, Meso and Macro – I would probably introduce this a Patient, Provider and System first and then explain the link to micro/meso/macro as these specific terms in health economics and public health descriptions are less well known. This will help the reader to contextualise this better and understand why you're looking at things across healthcare economies and boundaries.	Thank you for this remark. We introduced the patient, provider and system in our Methods and analysis-section first, according to your suggestion.
- I would introduce a clear aim that you are trying to achieve with this intervention, something along the lines (I am assuming) the global improvement in quality of life and reduction in any specific harms as identified by	Thank you for this remark. Our main goal with our intervention is to improve patient activation, measured by PAM-13, as defined as our primary outcome.

1) complications of CIH and underutilisation/appropriate utilisation of healthcare resources.	An improvement in quality of life and reduction in any specific harms will be analysed as secondary outcomes.
- Are you measuring the patients' health literacy as related to CIH at all? If so I would include this in your outcomes discussion.	Thank you for this important question. We are considering health literacy as one element of patient activation, assessed by the PAM-13. In addition, we use the single item literacy screener (SILS), as described in Tab. 1.
- If this is considered as patient activation – I would expand on this meaning. I say this as patient activation, whilst used in some circles, is not a concept which is widely known in healthcare. For your protocol to be fully understood or even adopted, discussion about what patient activation as a concept in a complex intervention is important.	From our point of view, the concept of patient activation is a concept which is widely known in healthcare, as a robust body of international literature is showing (e.g., the term "patient activation" leads to 101.101 results or the term "PAM 13" to 1,176 results on PubMed (access on 04.Oct. 2021)). See also reviewer 2. We described it in the "Primary and secondary outcomes on patient level"-section.
- I would also define early on what you mean by counselling. It is widely accepted as a generic term for offering psychological or emotional support. In this protocol counselling seems to offer some of this but much more education, teaching and clinical review.	Thank you for this important remark. Upon your suggestion, we decided to move the paragraph describing what we mean by counselling closer to the beginning of the manuscript.
- Who is blended online learning for?	As mentioned in the section "Strengths and limitations of this study" and a subheading of the "Intervention on provider level", the Blended-learning training program was designed for the counselling teams. Thanks to your comment, we also added this point for clarification in the main text.

Reviewer: 2

Ms. Judith Kiley-Morgan, Addenbrooke's Hospital

Reviewer comment	**Authors' answer**
This is a well-written paper on a topic that has the potential to be an extremely important contribution to the literature, and inform cancer care on an international level. The authors have set up a comprehensive study on integrating counselling on complementary and integrative health care (CIH) into Oncological health care provision, in line with patient-centred cancer care guidelines. This has the potential to both mitigate against the risks associated with some CIH methods due to lack of patient information, and also increase the potential positive effects of supportive CIH care.	Thank you very much for your positive remark.

I offer here some minor suggestions for clarification and revision:	
Introduction	
- A central construct of this study is “patient activation”. This concept is explained in detail under ‘Primary Outcome’ in the Methods section. It would be helpful to a have brief definition included in the Introduction for the sake of clarity – e.g. patient activation as a measure of patient knowledge, skill and confidence for self-management. Include a reference for the definition.	Thank you for this comment. We included a brief explanation in the Introduction along with the used reference as suggested.
- The project is described as a “complex intervention” but no explanation is given as to what makes the intervention complex? Is this in reference to the multi-level approach of micro (patient), meso (provider) and macro (system) levels of intervention? Please clarify in the introduction what is meant by “complex intervention”.	We clarified the use of the term “complex intervention” in the introduction.
Methods and Analysis	
Setting and study design - More justification for why cluster randomization would to lead to possible contamination problems would be helpful. No explanation has been given for why this is the case, and if the readers are to trust why no form of randomization was possible, more explanation is needed.	Thank you for this important remark. We provided further explanations in the “Setting and Study design” section for why cluster randomization could lead to possible contamination.
Intervention on patient level - It would be helpful to include clarification of your concept of counselling in this section. It needs to be clear that this is not therapeutic counselling for psychological support, but rather is information giving and guidance for health needs, for the purpose of increasing patient activation and self-efficacy. Is it more akin to health coaching? The term “counselling” is used very broadly within health care, so it is important to be clear on exactly what kind of counselling your intervention is offering. Additionally, it would helpful to know what psychological support is available to participants if the CIH counselling sessions were to bring up psychological distress for any patients?	Thank you for this important remark. Upon your suggestion and that of reviewer 1, we decided to move the paragraph on what we mean by counselling closer to the beginning of our manuscript. Furthermore, based on your helpful comment, we have expanded the explanation of our consulting concept. We added that referrals are made to specific counselling services, e.g. psycho-oncology in case the CIH counselling sessions bring up psychological distress for any patients.
Primary outcome - Is the only measure of effect the PAM-13? If so, is patient activation the only effect measured? At the end of the Introduction the stated aim is evaluation of whether CIH counselling improves patient activation and patients’ confidence. How is patient confidence	Thank you for this question. Our primary outcome (in the sense of a confirmatory trial design) is patient activation measured by the PAM-13. We don’t have any specific outcome instrument to measure patients’ confidence. We understand patients’ confidence as one of the elements of patient activation (“*This*

going to be evaluated? Is this through the process evaluation? This needs to be clarified.	*construct includes aspects of health and patient knowledge, skill, and confidence for self-management […]*").
Secondary outcomes - It would be helpful to have more explanation of the purpose of the collection of the secondary outcome data? Is the purpose of the secondary data simply comparative to check for selective bias and study effects? Or is the aim also to explore the effect of CIH counselling on quality of life, self-efficacy, depression, fatigue, etc? This needs to be clarified.	Thank you for this important remark. Indeed, the collection of the secondary outcome data is needed to explore the effect of CIH counselling on further endpoints. We added this information in the revised manuscript.
Miscellaneous - There are a few grammatical errors throughout the manuscript. For example p.4 lines 20, 31, 50; p.7 line 49; p.8 line 21-22; p.9 line 10; p.13 line 31. Please read through carefully to check for grammar and typos.	Thank you for this comment. We apologize for the typos and corrected the mentioned grammatical errors. We had the manuscript revision thoroughly proofread by a native English speaker and paid particular attention to grammar and structure.
- p.10 line 3 – what is meant by "actors"? Stake-holders perhaps?	By actors, we meant healthcare professionals and revised this accordingly in the manuscript.

Reviewer: 3

Ms. Vita Christie, The University of Sydney

Reviewer comment	**Authors' answer**
Thanks for inviting me to review this protocol. I commend you on the hard work and well thought out work you have done thus far.	Thank you very much for your positive feedback.
Overall comments I think when you talk about the statistics of uptake of CIH (Introduction) you are referring to Germany- perhaps you could add that detail?	Thank you for your comment. The numbers we showed are from a meta-analysis (reference Nr. 1) referring to different countries (e.g. Australia, Canada, Europe, New Zealand and the United States). We added "international studies" in the manuscript in order to clarify this point.
I would be interested in what constitutes CIH and what doesn't, but I am not sure if this is beyond the scope of your protocol?	Thank you for this important remark. There is an ongoing international discussion on what exactly constitutes the term CIH. As it was not our primary scope of this study protocol and to be as concise as possible in the manuscript, we decided not to dive into the discussion of this term. Nevertheless, we tried to describe what we mean by CIH in the first two chapters of the introduction.
I am also interested in how the reliability of the CIH has been measured thought this too might be beyond the scope of the protocol.	Thank you for this important remark. Please see our answer above. We tried to cite some exemplary international literature on the positive effects of some CIH methods that have been shown in RCTs (reference 3-5)
Minor amendments	Thank you for this comment. We apologize for the typos and corrected the mentioned

Abstract Line 21: 'level' should be levels (plural)	grammatical error. We had the manuscript revision thoroughly proofread by a native English speaker and paid particular attention to grammar and structure.
Introduction Lines 6-8: Do the references refer to Germany specifically and if so, perhaps that should be included?	Thank you for your comment. As stated in the answer above, the numbers we showed are from a meta-analysis (reference Nr. 1) referring to different countries (e.g. Australia, Canada, Europe, New Zealand and the United States). We added "international studies" in the manuscript in order to clarify this point.
Line 31: The statement "In 20%....." needs clarification; do you mean "Between 20 and 77% of cases….." or "From 20% to 77% of cases…."?	Thank you for this remark. We mean between 20 and 77% of cases and corrected this accordingly in the manuscript.
Line 45: should the word "their" be "the"?	Thank you for this remark. We meant "their" as it is referring to their personal need.
Lines 49-51: Consider replacing "Therefore, this recommendation could hardly be implemented so far" with "Therefore, this recommendation can not be implemented properly"	Thank you for your remark. We changed this according to your suggestion.
Line 54: "level" should be plural- levels	Thank you for this comment. We apologize for the typo and corrected the mentioned grammatical error.
Methods and analysis Page 7 Line 26: When you refer to "costs" do you mean, cost reduction? Needs clarifying of how it will affect costs	Thank you for your remark. We changed this according to your suggestion.
Line 46: "As describe above" needs a comma before "CCC Integrativ" and the word "level" needs to be plural- levels	Thank you for your remark. We changed this according to your suggestion.
Lines 55-57: the word "month" needs to be plural in all cases (months)	Thank you for your remark. We changed this according to your suggestion.
Page 8 Line 49: "session" needs to be plural (sessions)	Thank you for your remark. We changed this according to your suggestion.

Page 9 Line 18: “serious” might be changed to “trustworthy” or something similar?	Thank you for your remark. We changed this according to your suggestion.
Line 45: consider replacing “entities” with “types”	Thank you for your remark. We changed this according to your suggestion.
Line 59: full stop after “focused” needs to be removed	Thank you for this comment. We apologize for the typo and corrected the mentioned grammatical error.

Reviewer: 4

Dr. Claire Falandry, Hospices Civils de Lyon, University of Lyon

Reviewer comment	**Authors’ answer**
I acknowledge the authors for performing a study on the difficult topic of CIH, and for proposing the protocol for external expertise.	Thank you very much for your positive feedback.
However, I have some concerns about the methodology:	
1) Since the intervention is about counselling, the primary endpoint could have been according to my point of view the quality of the counselling ie the content of patients' knowledge on CIH. The rationale explaining how counselling on CIH would lead to patient activation is not demonstrated and could lead to disappointing results.	Thank you for your remark. As commented by reviewer 2, we moved our paragraph on what we mean by counselling to the beginning of our “Intervention on patient level” section in the revised manuscript. The goal with our counselling on CIH was not only to increase patients’ ‘knowledge of CIH’ but also to empower patients to make their own decisions about CIH. Furthermore, we provide patients with specific information on self-care to be able to cope as well as possible with symptoms of their oncological disease or with the side effects of its treatment. There is evidence showing that counselling interventions can lead to a higher patient activation as measured by the PAM-13, supporting our hypothesis (e.g. https://www.insigniahealth.

	com/research/archive/results?q=counselling&submit=Working...)
2) The way that the control group was chosen is also questionable, according to 3 main points: a. When considering that inclusion criteria include: “Need for CIH counselling (attested by actively contacting the local counselling center by email, phone or in person).” One could consider that patients in the control arm may have expectations towards such needs, that will be disappointed, artificially leading to a decrease in patient activation. A way to avoid that could be a proposal for written counselling according to current evidence.	Thank you for this important remark. The choice for a suitable control group was not an easy one. We know already from international literature (see introduction) that the need for CIH counselling is high in cancer patients. When starting with the recruitment of the control group, no counselling intervention on CIH had started in our study yet. Patients were fully informed about this. In addition, we offered counselling (outside the study setting) to patients in the control group after completion of the follow-up phase.
2b. One may imagine that the time spent in a face-to-face counselling in the intervention arm only may increase patient activation whatever the subject discussed during the interview. A control arm would have better maintained the same face-to-face time with a different content (other than CIH).	Thank you for this important remark. As our study aims to follow a naturalistic study design, any other face-to-face time with a different counselling content (other than CIH) would not have been feasible, in our opinion. This is mainly for two reasons: a) as described in the “Methods and analysis section*”, a classical parallel group design with randomization at patient level did not seem feasible, as previous studies have shown that patients with high use or need for counselling on CIH cannot be randomized* (Ref. 23) b) Furthermore, the range of topics in our counselling on CIH is rather broad, ranging from topics of nutrition, exercise and stress management to specific CIH topics and individual issues (e.g. dealing with death in a palliative situation). We could not think of another topic that is neither offered in “conventional cancer care” nor touched upon by our counselling and which would still be reasonable and ethically acceptable to include for cancer patients.
2c. Likewise, the imbalance between the control arm and the intervention arm can lead to the Hawthorne effect (observer) since the intervention arm is much more closely monitored (the initial face-to-face interview then the two 60-minute calls). This effect could be avoided if the follow up of both control and intervention arms are exactly the same.	Thank you for this important comment. The follow up of both control and intervention arms in our study are in fact exactly the same, with assessment of the primary and secondary outcomes at baseline, after 3 and after 6 months, as shown in Tab. 1.
3) The authors should add the SPIRIT checklist as supplementary data.	Thank you for this important suggestion. As requested by the editor, we included a copy of the SPIRIT checklist indicating the page/line numbers of our manuscript in the supplementary file section.

VERSION 2 – REVIEW

REVIEWER	Kiley-Morgan, Judith Addenbrooke's Hospital, Psychological Medicine for Children, Young People and Families
REVIEW RETURNED	03-Dec-2021

GENERAL COMMENTS	Thank you to the authors for paying such careful attention to all the reviewer comments and suggestions in their revision of this manuscript. The result is a much improved article. The grammar and language revisions have resulted in a much better written article as well. The authors have made all the changes and revisions I asked for. I only have one minor comment, which I will leave with the editors to decide whether this is needed: the definition of the counselling intervention is now much clearer, and it is clear that the purpose of the intervention is information giving and health guidance. However, I would still include a phrase making clear that the counselling is not therapeutic - it is not an intervention that is offering emotional or psychological support for patients. I think this is needed for clarity - I would include this in the abstract as well as in the main text.