

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Towards an open and effective dialogue on complementary medicine in oncology. Protocol of patient participatory study 'COMMON'.
<b>AUTHORS</b>	Mentink, Marit; Noordman, Janneke; Busch, Martine; Van Vliet, Liesbeth; Timmer-Bonte, Johanna (Anja); van Dulmen, Sandra

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Patel, Priya Hospital for Sick Children
<b>REVIEW RETURNED</b>	05-Jul-2021

<b>GENERAL COMMENTS</b>	<p>The aims of this study protocol aim to fill a knowledge gap and improve patient care with respect to complementary medicines. I congratulate the investigators for undertaking this large task.</p> <p>A few thoughts:</p> <p>1) While I understand that the approach to developing the toolbox has many steps, including to recruit co-investigators who will help develop interview questions, I feel like the ultimate outcomes for the study could be more clearly stated.</p> <p>2) For the systematic review/meta-analysis piece: Is there a reason why PubMed vs Medline is being used? Why not Embase? As well, the steps of the systematic review (title and abstract screening, data extraction elements, risk of bias) and criteria for conducting a meta-analysis should be laid out. What outcomes will be put into meta-analysis?</p> <p>3) Can more details about the Nivel organization be provided (type of institution, services provided)?</p>
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<b>REVIEWER</b>	Nelson, Mary University of Southern California, Medical Education/Pediatrics
<b>REVIEW RETURNED</b>	05-Jul-2021

<b>GENERAL COMMENTS</b>	<p><b>Review of BMJopen-2021-053005: "Towards an open and effective dialogue on complementary medicine in oncology. Protocol of patient participatory study COMMON"</b></p> <p>This is a protocol paper detailing a Dutch research study on the use of complementary medicine in patients with breast cancer, toward an ultimate goal of developing a national toolbox for use in patients with cancer.</p> <p>The introduction provides only vague and general information on what are considered to be complementary therapies. It would be</p>
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	<p>helpful to have a more specific definition of what the authors consider to be complementary treatments; these are most often thought to include herbal supplements, chiropractic, acupuncture, etc, but may in fact include massage, reiki therapy, hypnosis, yoga and other exercise, to name a few. This is particularly relevant to the information that will be offered in the toolbox.</p> <p>In the methods section (page 7, line 52), the authors state that hospitals committed to recruiting for the study differ in how they implement or communicate about complementary medicine. How was this defined or measured?</p> <p>Recognizing that changes cannot be made to the protocol at this point, it seems worth noting that the plan to have researchers observe a “test-result/incurable cancer diagnosis consultation” (page 9, line 20) to note any information provided about complementary therapies could be problematic. In my experience attending many of these consultations, giving this type of news can be devastating to the patient and family, and options for alternative treatments are rarely discussed at this time, but more likely to be addressed at the next follow-up visit. This may be different in the Netherlands.</p> <p>Overall the study methods are appropriate and the inclusion of patients as co-researchers is a strength.</p>
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<b>REVIEWER</b>	Steinsbekk, Aslak Norwegian University of Science and Technology, Department of Public Health and General Practice
<b>REVIEW RETURNED</b>	02-Aug-2021

<b>GENERAL COMMENTS</b>	<p>This is a well-presented protocol for a comprehensive project. I can see no need for any changes in the presentation given that this is what is planned, and the description of this is clear. The only thing the authors could consider is some more information on what they expect to be in the toolbox, e.g. by adding a table; the toolbox can be very large depending on the cut of for when a CAM modality should be included.</p> <p>I can recommend <a href="https://cam-cancer.org/en">https://cam-cancer.org/en</a> as an additional place for quality summaries.</p>
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### VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

**Comments**

The aims of this study protocol aim to fill a knowledge gap and improve patient care with respect to complementary medicines. I congratulate the investigators for undertaking this large task.

A few thoughts:

1) While I understand that the approach to developing the toolbox has many steps, including to recruit co-investigators who will help develop interview questions, I feel like the ultimate outcomes for the study could be more clearly stated.

*The authors thank the reviewer for the compliments and feedback. In the last sentence of the article summary (page 12), the ultimate outcomes are laid out as follows:*

*“The use of the toolbox should result in a more common discussion of complementary medicine in oncology, thus minimizing the risks and maximizing the benefits of evidence-based complementary medicine for patients with cancer”.*

*As we understand that this is not sufficiently clearly phrased, we rephrased this sentence. It now reads:*

***“The toolbox aims to provide 1) tips and tricks on how to conduct an open and effective discussion about the use of complementary medicine in oncology, and 2) evidence-based complementary medicine interventions which patients with cancer can use safely alongside their conventional cancer treatment. Thereby, we want to minimize the risks and maximize the benefits of evidence-based complementary medicine for patients with cancer”.***

2) For the systematic review/meta-analysis piece: Is there a reason why PubMed vs Medline is being used? Why not Embase?

*We thank the Reviewer for noticing this missing database. We take PubMed/MEDLINE as starting point and adapt it to other databases. We have added Embase to our list of databases in the Method section (page 11):*

***“The search on review studies is initially developed in PubMed/MEDLINE and adapted to other databases such as Cochrane Library, PsycINFO, CINAHL and Embase.”***

As well, the steps of the systematic review (title and abstract screening, data extraction elements, risk of bias) and criteria for conducting a meta-analysis should be laid out.

*We thank the Reviewer for these relevant suggestions. We would like to point out that we are planning to conduct a review of reviews, not a meta-analysis. We are sorry that this was not clear in the original manuscript, as the terms meta-analysis and review of reviews are used interchangeably. We have replaced the term meta-analysis throughout the paper with review of reviews. In addition, we have described the review of reviews in more detail:*

***“For this search, we make use of medical subject heading terms and/or keywords frequently used in literature on complementary medicine. The search is limited to systematic reviews and meta-analyses published after 2000, written in English. Two researchers will independently screen titles and abstracts. Subsequently, a full-text screening is conducted by two researchers. In case of inconsistencies between the two researchers, consensus will be reached by discussion. If necessary, a third researcher can be involved. For inclusion in the reviews of reviews, articles should meet the criteria of having a methods section that describes a search strategy and an a priori approach to synthesizing the data. Then, methodological quality is assessed by means of quality criteria adapted from the Quality of Reporting of Meta-analyses (QUOROM) [48] and the Assessment of Multiple Systematic Reviews (AMSTAR) [49]. A comprehensive, detailed protocol of the review of reviews will be registered in PROSPERO.”***

*A detailed, comprehensive protocol for the review of reviews is not established yet and would be beyond the scope of this protocol paper in our opinion.*

What outcomes will be put into meta-analysis?

*The intended outcomes of the review of reviews are stated in the Method section (page 10):*

*“A review of systematic reviews is conducted on the evidence on patient-reported outcomes (e.g. quality of life, coping skills, general well-being, perceived psychological and physical symptoms) of complementary medicine that is frequently used by patients with cancer”.*

3) Can more details about the Nivel organization be provided (type of institution, services provided)?

*We added a link to the website of Nivel (in English) to the contact details of the corresponding author.*

*Corresponding author*

*Marit Mentink*

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*<https://www.nivel.nl/en>*

**Reviewer: 2**

**Comments**

This is a very interesting and relevant study. Please see the comments attached for minor revisions.

This is a protocol paper detailing a Dutch research study on the use of complementary medicine in patients with breast cancer, toward an ultimate goal of developing a national toolbox for use in patients with cancer.

*First, we would like to thank the reviewer for their valuable time and considerate feedback.*

The introduction provides only vague and general information on what are considered to be complementary therapies. It would be helpful to have a more specific definition of what the authors consider to be complementary treatments; these are most often thought to include herbal supplements, chiropractic, acupuncture, etc, but may in fact include massage, reiki therapy, hypnosis, yoga and other exercise, to name a few. This is particularly relevant to the information that will be offered in the toolbox.

*The reviewer is right to point out that there is a widespread variation in available complementary therapies. Yet, there is no consensus in defining complementary medicine and some approaches are in the gray area between conventional supportive care and complementary medicine, as stated in the Introduction section (page 3):*

*“The current study focuses solely on complementary medicine and adopts a broad definition, encompassing all approaches that complement biomedical treatment of the oncological disease and that aim to contribute to the physical, mental or social well-being of the patient. The definition includes approaches that were previously considered complementary, but are now regularly incorporated in conventional supportive care (e.g. exercise and psychological therapies).”*

*Since we wanted to make sure we gain an overview of all approaches that patients with cancer use alongside conventional treatment, we deliberately chose to adopt a broad definition of complementary medicine. The toolbox will eventually incorporate information about complementary therapies frequently used by patients with cancer, as is now stated in the Method section (page 10):*

*“The co-researchers are involved in designing the structure and lay-out of the toolbox, which content will be mainly based on the information gathered in steps 1 to 3. **The toolbox will at least consist of a communication guideline to support patients and healthcare providers in discussing complementary medicine**, supplemented with a list of available evidence-based complementary medicine **frequently used by cancer patients in the Netherlands.**”*

We also would like to point out that the three complementary medicine approaches most frequently used among patients with cancer in Western countries are already stated in the Introduction section (page 3). We have added the fourth most used complementary therapy by patients with cancer according to the referenced systematic review:

*“Complementary medicine approaches frequently used by patients with cancer in Western countries are mind-body therapies, massage, nutrition counselling **and acupuncture** (1).”*

In the methods section (page 7, line 52), the authors state that hospitals committed to recruiting for the study differ in how they implement or communicate about complementary medicine. How was this defined or measured?

*That is an interesting query. We deliberately tried to ensure variety in the included hospitals for this study. Therefore, we gathered some general information about the level of implementation of initiatives regarding complementary medicine during the process of selecting hospitals for the study. For example, one of the eventually involved hospitals already offered an integrative medicine consultation to patients with cancer whilst another hospital showed interest in complementary medicine but did not undertake any concrete initiatives yet. To clarify the process of selection, we have rewritten the sentence in the Method section as follows:*

*“Three non-academic hospitals with an oncology department have committed to recruiting participants for the study. **We deliberately selected hospitals that differ in the extent to which they implemented initiatives regarding complementary medicine in standard oncology care.** This contributes to the diversity of the study participants and provides opportunities to learn from fellow hospitals’ experiences.”*

Recognizing that changes cannot be made to the protocol at this point, it seems worth noting that the plan to have researchers observe a “test-result/incurable cancer diagnosis consultation” (page 9, line 20) to note any information provided about complementary therapies could be problematic. In my experience attending many of these consultations, giving this type of news can be devastating to the patient and family, and options for alternative treatments are rarely discussed at this time, but more likely to be addressed at the next follow-up visit. This may be different in the Netherlands.

*We agree with the Reviewer that this aspect is very important to consider when interpreting the findings of the observational study. We would like to inform the Reviewer that all consultations from Study 1 are evaluative follow-up visits to discuss test-results (i.e. scan, blood) with advanced breast cancer patients. No initial consultations (i.e. first-time hearing that their disease is incurable) were included in Study 1 eventually, although the inclusion criteria allowed for recording these visits. To avoid confusion, we amended the description of this category of participants as follows:*

*“5: Patients with incurable breast cancer, female, >18 years of age, with sufficient command of Dutch language, **scheduled for a test-result consultation.**”*

Overall the study methods are appropriate and the inclusion of patients as co-researchers is a strength.

**Reviewer: 3**

### **Comments**

This is a well-presented protocol for a comprehensive project. I can see no need for any changes in the presentation given that this is what is planned, and the description of this is clear. The only thing the authors could consider is some more information on what they expect to be in the toolbox, e.g. by adding a table; the toolbox can be very large depending on the cut of for when a CAM modality should be included.

I can recommend <https://cam-cancer.org/en> as an additional place for quality summaries.

*We thank the author for the compliments and for the recommendation to incorporate the very useful website by the NAFKAM for quality summaries of complementary medicine modalities. Considering the suggestion to add a table on the contents of the toolbox, we would like to let the reviewer know that we prefer to not pin down the content of the toolbox too much at this point, since it mainly depends on information that is not gathered yet and on the input from the co-*

researchers. However, to clarify our expectations of the content of the toolbox and to specify that we only include complementary medicine modalities frequently used by patients with cancer in Western countries (1) in the toolbox, the Method section (page 10) was adjusted as follows:

*“The co-researchers are involved in designing the structure and lay-out of the toolbox, which content will be mainly based on the information gathered in steps 1 to 3. **The toolbox will at least consist of a communication guideline to support patients and healthcare providers in discussing complementary medicine**, supplemented with a list of available evidence-based complementary medicine **frequently used** by cancer patients in the Netherlands. This list will be based on a review of systematic reviews on the evidence of complementary medicine on patient-reported outcomes and an online survey amongst persons and organizations providing complementary medicine in the Netherlands.”*

### **Additional amendments**

In addition to the revisions described above, some minor adjustments have been made to the text (e.g. misspellings, updated information about participant numbers).

### **References**

1. Seely D, Weeks L, Young S. A systematic review of integrative oncology programs. *Current oncology*. 2012;19(6):e436.
2. Schofield PE, Juraskova I, Butow PN. How oncologists discuss complementary therapy use with their patients: an audio-tape audit. *Supportive Care in Cancer*. 2003;11(6):348-55.