PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Implementation of the Symptom Navi© Program for cancer patients in the Swiss outpatient setting: A study protocol for a cluster randomised pilot study (Symptom Navi© Pilot Study)
AUTHORS	Bana, Marika; Ribi, Karin; Kropf-Staub, Susanne; Zürcher-Florin, Sabin; Näf, Ernst; Manser, Tanja; Bütikofer, Lukas; Rintelen, Felix; Peters, Solange; Eicher, Manuela

VERSION 1 - REVIEW

REVIEWER	Christine Miaskowski Professor University of California San Francisco, CA
REVIEW RETURNED	03-Jan-2019

GENERAL COMMENTS	This paper presents an interesting protocol for a symptom management intervention study. Some added information would strengthen the paper. 1. It is not clear if patients with metastatic disease will be eligible for enrollment. 2. Additional information is needed on when the patients will be approached for enrollment into the study. It is not clear when the first consultation will occur. What will trigger this consultation. It is not clear in the intervention group if the patients will receive two consultations after the first one or a total of two consultations. 3. It would be interesting for the authors to state the rationale for their primary outcome. 4. Information is needed on when the structured interviews with the nursing staff will be done. In addition, clarification is needed on the purpose of the interview with the medical oncologist.

REVIEWER	Deirdre Connolly Trinity College, Dublin, Ireland
REVIEW RETURNED	21-Feb-2019

GENERAL COMMENTS	Overall the protocol for this study is clearly described however some important details regarding the intervention are missing – see comments below Pg. 6: Strength and limitations Pg. 6 Line 5 states that the SN©P been standardised? Not clear from the article how it was standardised

	Introduction section was well written literature review supporting the rationale for the study. Methods and analysis p.11, line 20: authors state that that the delivery and consultation process is guided by a standardisation process and give a reference number 44 to support this. However, in the reference list (Pg.28, line5) this reference is stated as being “in press in 2012”. In addition, as this reference is in German, it would be useful to know what level of publication is it – a thesis, journal article, conference presentation? Intervention Symptom Navi© flyers Pg. 11: lines 34-53 As this is the main intervention for this study, this section needs considerably more clarity on the intervention. This section needs to be explicit about the intervention so that others will know what exact symptoms are being addressed through this intervention. A clearer explanation is needed on the flyers and clarity on which patients will get the flyers and when will they get them. Are there 16 separate leaflets or will it be a single leaflet that covers all 16 symptoms. What are the 16 symptoms that are covered in the leaflet/s? What exact information is supplied in the leaflet/s? If they are separate leaflets for each symptom how will it be decided which leaflet/s a patient receives or do all patients receive all 16 leaflet/s? Have these leaflets been tested for health literacy? Have they been assessed by service users/patients for their acceptability, readability, accessibility? The reference supporting the content validity of the leaflets is a conference presentation (reference 46). This would generally not be considered a high level of publication to support the validity of the primary intervention in this trial. p. 11, lines 56 to page 12, line 33: Semi-structured nurse-led consultations Clarity is needed on when these consultations will be delivered – will patients have these consultations before and after they receive the leaflets? Do all patients recruited into the study receive the consultations or will it be only patients who need assistance with symptom management? How is this decided? P.12: line 5: step 2 of the consultation process: how will a patient’s willingness and motivation for consultation be evaluated? As the reference given for the six key elements of the nurse led consultations is not in English, greater clarity is needed on development of the six steps. Line 21 states that nurses may provide additional written information if needed. This will therefore result in some patients in the intervention receiving different levels and types of interventions to manage their symptoms. How will this be manged in the trial – for example how will it be recorded and how will it impact on data analysis? Line 23: nurses will use motivational interviewing; will the nurses be trained to do this and if so, who will provide the training? Training for nurses: Pg. 12 Line 41: states that the training manual has been validated by nursing experts. Who are these nursing experts and how did they ‘validate’ the training manual? Line 49 states nurses will receive ‘pocket cards’ what are these and how will they be used during the study? Page 14, Effectiveness

	Lines 35 to 47 move section describing the time lines for data collection to after the section on the study measures Page 14, Line 46 states that the final assessment will be carried out 16 weeks after BL assessment – what happens if the patient's treatments get delayed. Should this be based on time of final treatment? Measures – all measure need information on their psychometric properties with specific reference to their suitability for individuals with cancer. Pg. 15: Depressive mood will be tested on a single item VAS – this is a very limited measure of mood. What exactly will patients be asked to rate on the VAS – please state the exact question As this is a pilot study to inform a larger study, qualitative interviews would be recommended with patients on their experiences of the intervention and the acceptability of this approach to self-management of their symptoms as per the MRC framework. Pg.16, line 4 – reference figure 1 to show when the second focus group with nurses will occur. Pg.16, Line 51 refers to a section on the questionnaires for nursing to give their opinions of patients' goals that they set for self-management – when were the goals set and will these be recorded and analysed as data for the trial given the role of gaol-setting in self-management interventions. Sample size and randomisation; Pg. 20, line 5: please clarify what is the difference between a cluster and a 'group'.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewers' comments:

Reviewer 1 comment 1

It is not clear if patients with metastatic disease will be eligible for enrollment.

Response:

We acknowledge that we did not clearly point out that patients with metastatic disease will be eligible for enrolment. We therefore specified this in table 1, eligibility criteria, second bullet point: Newly diagnosed with any early or advanced/metastatic cancer disease within 15 weeks of providing informed consent.

Reviewer 1 comment 2

Additional information is needed on when the patients will be approached for enrollment into the study. It is not clear when the first consultation will occur. What will trigger this consultation. It is not clear in the intervention group if the patients will receive two consultations after the first one or a total of two consultations.

Response:

We thank the reviewer for this comment. We amended figure 1 "study flow chart" and added information clarifying the time points of patient enrolment and consultations in table 2.

Reviewer 1 comment 3

It would be interesting for the authors to state the rationale for their primary outcome.

Response

We agree with the reviewer that the rationale for the outcome of main interest is important. In the paragraph Outcomes, Effectiveness (second sentence) of the submitted manuscript we stated that the choice for the primary outcome is based on a previous study using the TSSM reporting that patients' functional performance increased after nurse-led interventions on symptom self-management support. We made this clearer in the text: The rationale for the primary outcome is based on a previous study using the TSSM reporting that patients' functional performance increased after nurse-led interventions on symptom self-management support. Complementary statements are included in our response to reviewer 2, comment 11.

Reviewer 1 comment 4

Information is needed on when the structured interviews with the nursing staff will be done. In addition, clarification is needed on the purpose of the interview with the medical oncologist.

Response

We acknowledge the need for more information on the time points of the focus group interviews with nurses. We 've amended the manuscript by making this more explicit: We will conduct a first focus group interview with nurses before they will be trained for the SN©P to learn about the current symptom self-management support and handling of written information at each intervention centre. A second focus group interview (after last patient is out of study at the centre) will be conducted with those nurses who provided the intervention to assess perceived barriers and facilitators (e.g. work-related factors, available resources) for adopting the SN©P within daily routines.

As we are not only interested in the view of the nurses, but also in the view of the oncologists on the acceptance and feasibility of the SN©P within daily routines (Implementation, point 2) and on their assessment of patients safety (Implementation point 4). We therefore added a sentence to the paragraph Implementation 2): Interviews with oncologists have been included to represent the institutions voice regarding acceptance and feasibility of the SN©P within daily routines.

Reviewer 2 comment 1

Pg. 6: Strength and limitations

Pg. 6 Line 5 states that the SN©P been standardised? Not clear from the article how it was standardised

Introduction section was well written literature review supporting the rationale for the study.

Response

We acknowledge that the standardisation of the program is not well described. By also taking into account the comments of the editors, we completely revised the section strengths and limitations, not referring to the standardization of the SN©P anymore.

Reviewer 2 comment 2

Methods and analysis

p.11, line 20: authors state that that the delivery and consultation process is guided by a standardisation process and give a reference number 44 to support this. However, in the reference list (Pg.28, line5) this reference is stated as being "in press in 2012". In addition, as this reference is in

German, it would be useful to know what level of publication is it – a thesis, journal article, conference presentation?

Response

We thank the reviewer for this comment. We deleted this reference. A detailed description of the development and content of the SN©P would exceed the scope of this article. Therefore, a separate article is in preparation that we plan to submit by end of March 2019. We amended the last sentence of the corresponding paragraph: The development, content, and evaluation of the SN©P is detailed in a separate manuscript (Bana et al, in preparation).

Reviewer 2 comment 3

Pg. 11: lines 34-53

As this is the main intervention for this study, this section needs considerably more clarity on the intervention. This section needs to be explicit about the intervention so that others will know what exact symptoms are being addressed through this intervention. A clearer explanation is needed on the flyers and clarity on which patients will get the flyers and when will they get them. Are there 16 separate leaflets or will it be a single leaflet that covers all 16 symptoms. What are the 16 symptoms that are covered in the leaflet/s? What exact information is supplied in the leaflet/s? If they are separate leaflets for each symptom how will it be decided which leaflet/s a patient receives or do all patients receive all 16 leaflet/s? Have these leaflets been tested for health literacy? Have they been assessed by service users/patients for their acceptability, readability, accessibility? The reference supporting the content validity of the leaflets is a conference presentation (reference 46). This would generally not be considered a high level of publication to support the validity of the primary intervention in this trial.

Response

We see the reviewers need for more information about content of flyers. We address this by including a new table (table 2) that provides an overview of all available SN©Flyers and the timing of semi-structured nurse-led consultations.

We agree that the intervention is not comprehensively described in this study protocol. As mentioned earlier, detailed description of the development, content and evaluation of the SN©P would exceed the scope of this article. This will be described in detail in a separate article that will be submitted by end of March 2019 (see response to comment reviewer 2 comment 2).

Reviewer 2 comment 4

p. 11, lines 56 to page 12, line 33: Semi-structured nurse-led consultations

Clarity is needed on when these consultations will be delivered – will patients have these consultations before and after they receive the leaflets? Do all patients recruited into the study receive the consultations or will it be only patients who need assistance with symptom management? How is this decided?

Response

We acknowledge that this information was not sufficiently described in the manuscript. We therefore revised the first sentence of the above mentioned paragraph: Nurses will provide two semi-structured consultations with all patients starting a first-line systemic anti-cancer treatment, tailored to the patient's treatment protocol and expected side effects. Further, we included information that the

leaflets will be delivered during semi-structured consultation in the table 2 (see response to reviewer 2 comment 3).

Reviewer 2 comment 5

P.12: line 5: step 2 of the consultation process: how will a patient's willingness and motivation for consultation be evaluated? As the reference given for the six key elements of the nurse led consultations is not in English, greater clarity is needed on development of the six steps.

Response

More information on the intervention and provision of semi-structured consultations is added in the revised version of the manuscript by following two sentences. Patient's willingness will be assessed by asking his consent for the consultation. The interpretation of patient's motivation will be based on the active participation and being attentive during the conversation.

Reviewer 2 comment 6

Line 21 states that nurses may provide additional written information if needed. This will therefore result in some patients in the intervention receiving different levels and types of interventions to manage their symptoms. How will this be manged in the trial – for example how will it be recorded and how will it impact on data analysis?

Response

Thank you for this important comment. We only document whether additional information is available at a centre and not whether a specific patient was exposed to it, which would have been difficult to assess. We can therefore not adjust on the level of the patient and cannot exclude that this may lead to some additional heterogeneity. However, the availability of further information at the centre is documented and will be considered as a potential confounder. In a sensitivity analysis, we plan to add potential confounders to the linear mixed model. We added a sentence to the revised manuscript: In a sensitivity analysis, we will adjust the model for potential confounders, i.e. patient, nurse, or cluster characteristics that show imbalances at baseline.

Reviewer 2 comment 7

Line 23: nurses will use motivational interviewing; will the nurses be trained to do this and if so, who will provide the training?

Response

We thank the reviewers for this comment and acknowledge that this information was lacking in table 2. Therefore, we added in the table 2, which is table 3 in the revised version of the manuscript a bullet point for the initial training course: Motivational interviewing techniques. To clarify the professional and educational background of these nursing experts, we added a sentences: The two trainers are members of the research team that developed the training courses, hold a master degree in nursing science, and are senior lecturers.

Reviewer 2 comment 8

Training for nurses:

Pg. 12 Line 41: states that the training manual has been validated by nursing experts. Who are these nursing experts and how did they 'validate' the training manual?

Response

We thank the reviewer for pointing out that this information was not included in the manuscript. We amended the manuscript by completing the following sentence: Nurses will be trained with two standardised training courses (in total 6 hours of training) based on a training manual that has been face-validated by a steering committee including two clinical experts for oncology nursing, a nursing manager, and two study researchers.

Reviewer 2 comment 9

Line 49 states nurses will receive 'pocket cards' what are these and how will they be used during the study?

Response

We added a sentence to inform about what pocket cards are and how nurses will use them in the study. Pocket cards provide nurses with concrete examples how to guide the communication during the consultations based on motivational interviewing techniques.

Reviewer 2 comment 10

Page 14, Effectiveness

Lines 35 to 47 move section describing the time lines for data collection to after the section on the study measures

Response

Thank you for this comment. We moved this section as proposed by the reviewer to the paragraph data collection.

Reviewer 2 comment 11

Page 14, Line 46 states that the final assessment will be carried out 16 weeks after BL assessment – what happens if the patient's treatments get delayed. Should this be based on time of final treatment?

Measures – all measure need information on their psychometric properties with specific reference to their suitability for individuals with cancer.

Response

Thank you for this comment. 16 weeks after BL assessment was set as last measurement time because patients are usually still under treatment and supposed to express high symptom severity and interference scores. We further added: Number and type of experienced symptoms depend on cancer type and treatment. We therefore chose a period of 16 weeks assuming that most patients are still under treatment. We also assume that the SN©P might affect patient's estimation on symptom interference over this period, because patient's positive attitude for self-management has been shown to be associated with increased physical, emotional, and functional well-being over six months. An assessment based on time of final treatment was not planned.

We acknowledge that we did not include sufficient information on instruments' psychometric properties and their suitability for individuals with cancer. Therefore, we introduced a new table (Table 4: Instruments used for patient-reported outcomes). Introducing this table generated some redundant information in the main text of the manuscript. This redundancy has been deleted.

Reviewer 2 comment 12

Pg. 15: Depressive mood will be tested on a single item VAS – this is a very limited measure of mood. What exactly will patients be asked to rate on the VAS – please state the exact question

As this is a pilot study to inform a larger study, qualitative interviews would be recommended with patients on their experiences of the intervention and the acceptability of this approach to self-management of their symptoms as per the MRC framework.

Response

We added more details on the VAS to assess mood in the text and in table 4: To control for the emotional state of the patients, we added a one-item Visual Analogue Scale on mood asking 'how do you rate your mood during the last two weeks?'

Interviews with patients took place before we started the pilot study. We therefore know that patients felt safer with the SN©P and that they confirmed that they felt empowered to self-manage their symptoms. These results have been published only in German so far, but will be included in the above-mentioned article on the development, content and evaluation of the SN©P that we will submit by end of March 2019.

Reviewer 2 comment 13

Pg.16, line 4 – reference figure 1 to show when the second focus group with nurses will occur.

Response

Thank you for this comment: we added the reference to figure 1.

Reviewer 2 comment 14

Pg.16, Line 51 refers to a section on the questionnaires for nursing to give their opinions of patients' goals that they set for self-management – when were the goals set and will these be recorded and analysed as data for the trial given the role of gaol-setting in self-management interventions.

Response

We agree that this information needs more clarity. In the paragraph "Data collection and management" we included following information on the recording of patient's goal setting in the revised version of the manuscript: After every semi-structured consultation with a patient, nurses will complete an electronic questionnaire assessing their fidelity to the training manual, and patient's complaints and goals for symptom self-management as discussed during the consultation.

Patient's goals for symptom self-management will be recorded for the pilot study and analysed by using thematic analyses. We made this clear in the paragraph analysis. .., as well as narrative information from the questionnaires on fidelity including patient's goals for symptom self-management)

Reviewer 2 comment 15

Sample size and randomisation; Pg. 20, line 5: please clarify what is the difference between a cluster and a 'group'

Response

We thank the review for pointing out the difference between group and cluster We amended this sentence to make the difference clear: We aim to include a total of 140 patients in 9 clusters—with

approximately 70 patients to be included in both the intervention and the control group, and about 10 to 20 patients in each cluster (at each centre).

VERSION 2 – REVIEW

REVIEWER	Deirdre Connolly Trinity College, Dublin, Ireland
REVIEW RETURNED	29-Mar-2019

GENERAL COMMENTS	The majority of the recommendations from the initial review have been addressed. The following elements still need to be clarified: Pg 3: strength and limitations, lines 12-14 The statement here states “the SN©P (which is the intervention in the study) is based on content evaluation of the Symptom Navi© Flyers (written information leaflets) and patients’ experience with the SN©P”. It is not clear how this applies to the strengths and/or limitations of this study – please clarify. Pg. 6, Secondary Objective number 2 Assessing the quality of nursing care is not an objective related to effectiveness it is related to implementation. This needs to be a separate objective. If the authors wish to maintain this as a study objective it must be stated as a separate implementation objective on page 6. This is referred to again in the methods section page 12, in effectiveness section. If keeping this as a study objective, a clear discussion of the methods to address this objective is needed under implementation. Pg. 8, line 49 – you need to give the full explanation for I-CVI before using an abbreviation. Pg. 10, line 15: as identified in my original review, providing nurses with the option to provide additional information to patients in the study will affect the fidelity of this intervention and will most likely impact on the findings. A clear explanation is needed on why this will be allowed within the study protocol and how will the data be handled/analysed from the study centres that provide additional information. Pg 14 and 15: Give references for the guidelines that will be used to guide the focus group interviews and telephone interviews. Methods: what procedures will be followed to collect data from the control cancer centres?

VERSION 2 – AUTHOR RESPONSE

The majority of the recommendations from the initial review have been addressed. The following elements still need to be clarified:

Pg 3: strength and limitations, lines 12-14

The statement here states “the SN©P (which is the intervention in the study) is based on content evaluation of the Symptom Navi© Flyers (written information leaflets) and patients’ experience with the SN©P”. It is not clear how this applies to the strengths and/or limitations of this study – please clarify.

Response:

Thank you for this comment. We agree that the strength or limitation of this statement is not clear. Therefore, we revised this statement and re-arranged the order of the bullet points to indicate that this pilot study is based on a rigorously developed intervention that is now ready for preliminary testing in clinical settings [1].

In the revised strengths and limitation statements, we start with:

One strength of the study protocol is its integration in a larger research and development program: After several steps of development and content validation of the SN©P, we now conduct a pilot implementation study including the evaluation of preliminary effectiveness of the SN□P.

Pg. 6, Secondary Objective number 2

Assessing the quality of nursing care is not an objective related to effectiveness it is related to implementation. This needs to be a separate objective. If the authors wish to maintain this as a study objective it must be stated as a separate implementation objective on page 6. This is referred to again in the methods section page 12, in effectiveness section. If keeping this as a study objective, a clear discussion of the methods to address this objective is needed under implementation.

Response:

Thank you for this important comment. We agree that this outcome corresponds to implementation as described at the RE-AIM homepage: At the setting level, implementation refers to the intervention agents' fidelity to the various elements of an intervention's protocol. This includes consistency of delivery as intended and the time and cost of the intervention (http://www.re-aim.org/about/what-is-reaim/implementation/). Therefore, we added a fifth aim and revised this objective to : 5. Explore patients' evaluation on nurses support for symptom management (Implementation) on page 7.

This adaptation required other subsequent adaptations: We moved therefore this corresponding part in the method section to page 16. Further, we complemented: Quality of nursing care evaluated by patients will assess five concerns: do nurses ask patients about symptoms, provide useful information, and / or practical advice to manage symptoms, are they aware of patient's symptom severity, and whether patients feel confident to manage symptoms. Following this adaptation, we also revised the table 4 (p. 14) and table 5 (p. 17 - 18)

Pg. 8, line 49 – you need to give the full explanation for I-CVI before using an abbreviation.

Response:

We thank the reviewer for this comment and agree that we did not clearly explain the abbreviation ICVI. Therefore, we slightly adapted the sentence:

During the development phase of the SN©Flyers, the contents were evaluated by 48 health care professionals and patients using the Item Content Validity Index (I-CVI) achieving an excellent ICVI of 0.9 .

Pg. 10, line 15: as identified in my original review, providing nurses with the option to provide additional information to patients in the study will affect the fidelity of this intervention and will most likely impact on the findings. A clear explanation is needed on why this will be allowed within the study protocol and how will the data be handled/analysed from the study centres that provide additional information.

Response:

We acknowledge that this issue was not sufficiently adapted in our revised manuscript. We added information to explain that the SN©P is complementary to usual care and that we will assess and report descriptively additional information material provided by the centres (p. 10):

The SN©P is an intervention that aims to stimulate patient's self-management of symptoms and complements usual care, which mainly focuses on information provision. Differences between centres regarding information provision might be a bias. To reduce this bias, we will record all additional information material delivered at each centre and report them descriptively (brochures, leaflets).

Pg 14 and 15: Give references for the guidelines that will be used to guide the focus group interviews and telephone interviews.

Methods: what procedures will be followed to collect data from the control cancer centres?

Response:

Thank you for your comment. We completed the sentence at page 15 with our reference: Guidelines for semi-structured focus groups will be based on Morgan [2]

At page 15 we added the references for individual interviews and focus groups: Focus group and telephone interviews will be directed by semi-structured interview guidelines.[2, 3] Topics addressed in both interviews will focus on symptom self-management support based on the frameworks of Howell [4] and Schofield[5].

Both references are included in the manuscript.

We do not collect qualitative data at the control centres. This is shown in the study flow chart figure 1.

Reference:

1. Craig, P., et al., Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ, 2008. 337: p. a1655.

2. Morgan, D.L., Focus groups as qualitative research. Qualitative research methods series, Second edition. 1997, Thousand Oaks, California: Sage Publications.

3. Creswell, J.W., Data Collection, in Qualitative Inquiry & Research Design. 2013, Sage Publications: Thousand Oaks, California. p. 145 - 178.

4. Howell, D., et al., Self-management education interventions for patients with cancer: a systematic review. Supportive Care in Cancer, 2017. 25(4): p. 1323-1355.

5. Schofield, P. and S. Chambers, Effective, clinically feasible and sustainable: Key design features of psycho-educational and supportive care interventions to promote individualised self-management in cancer care. Acta Oncologica, 2015(54): p. 805-812.