PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Existential distress in patients with advanced cancer and their caregivers: study protocol of a longitudinal cohort study
AUTHORS	Philipp, Rebecca; Kalender, Anna; Härter, Martin; Bokemeyer, C; Oechsle, Karin; Koch, Uwe; Vehling, Sigrun

VERSION 1 – REVIEW

REVIEWER	Laurie McLouth, PhD University of Kentucky, USA
REVIEW RETURNED	14-Dec-2020

GENERAL COMMENTS	In “Existential distress in patients with advanced cancer and their caregivers: Study protocol of a longitudinal cohort study,” Philipp et al describe an assessment battery for a longitudinal cohort study designed to characterize existential distress and its correlates among advanced stage cancer patients and their informal caregivers. Study strengths include an important research question, a well-written manuscript, and well-designed assessment battery for a longitudinal design. Study limitations include omission of some psychometric data and measurement details and lack of specificity on how each self-report measure will be used in the analysis. These are addressable concerns. These and additional recommendations are described below. Abstract: 1. Recommend revising “Over a period of 12 months…” sentence to move the self-report questionnaire domains after “self-report questionnaires” and adding the planned 5 points of assessment (baseline, 3 months, etc). Strengths and limitations of this study: 1. Point 4: Recommend revising “highly distressed sample” to “potentially highly distressed sample” and or “understudied” – you do not know the distress rates you will observe in this sample Introduction: 1. Paragraph 1, line 10 “In about one third of patients…” – Recommend revising the sentence. Multiple sources of distress lead to increased levels of depression and anxiety…and physical symptom burden? Is physical symptom burden meant to be a source of distress leading to increased levels of depression and anxiety? 2. Paragraph 1, line 17: recommend omitting “existential” after “bio-psycho-social existential” 3. Paragraph 4, line 19: “They may also suffer from the loss of the patient’s identity…” – unless you are focusing specifically on brain tumors, recommend omitting “which is a frequent consequence of brain tumors” 4. Paragraph 6, line 42 – “Especially because a lack of perceived relatedness…” appears to be sentence fragment

	Methods and analysis: 1. Participants and recruitment. Allowing caregivers and patients to enroll in the cohort study at different timepoints is good for the reasons mentioned. However, recommend either citing other cohort studies that have allowed a non-uniform enrollment period (e.g., allowed pts to enroll at diagnosis or towards the end of treatment) or describing in analysis how will address the fact that those who enroll later into their cancer treatment are likely to have fewer assessment points compared to those who enroll at diagnosis. 2. Procedures. “At baseline and after 6 months, we will conduct structured…” recommend clarifying that you are doing structured interviews with both patients and caregivers 3. Procedures. Later in the manuscript you mention that patients can enroll without their caregivers. Recommend stating early on that you will enroll patients or patient-caregiver dyads. 4. Measures a. Table 1 is a great start. However, recommend adding which self-report measure is primary outcome for which objective and how others will be used in analysis (e.g., covariate, dependent, focal, etc) for each objective. This is especially important because of the extensive assessment battery being administered. b. Existential distress – multiple measures are listed, which is great for getting at this broader construct. However, for objective 1, it appears logistic regression is being used and it is unclear which self-report measure is the primary measure of existential distress for this purpose. Authors later mention SEM. Curious as to whether investigators are considering using SEM for objective 1 as well to have all of these measures of existential distress be indicators of the construct of existential distress. If not, need to specify which one is going to be the primary measure of existential distress and why. c. Demoralization – Provide citation supporting its validity in caregivers (if available) d. Across measures – if they have subscales, please indicate how many items comprise each subscale. Also, please provide citations for the internal consistency estimates listed (see MM-CGI-SF last sentence for an example of a sentence that doesn’t have the citation behind Cronbach’s alphas listed) and any evidence of their validity in caregivers.

REVIEWER	Annika von Heymann Department of Oncology, Center for Cancer and Organ Diseases, Rigshospitalet, Denmark
REVIEW RETURNED	31-Jan-2021

GENERAL COMMENTS	The authors have submitted a well written, clear, and comprehensive protocol paper for an important study addressing the prevalence, trajectory and impact on end-of-life outcomes of existential distress. It is particularly commendable that the authors include caregivers in this study. I believe the study will offer important new knowledge and is well described in the protocol. I do have a few suggestions that might increase the clarity and completeness of the paper, as outlined below for each section of the paper. Abstract Please include the expected numbers of patients and caregivers to be recruited.

Introduction

In the introduction to the concept of existential distress, the authors mention their taxonomy and provide a figure, while referring to ”earlier reviews and conceptual literature”. As readers cannot be expected to be familiar with this whole literature, it would be very helpful, if the authors could provide a brief explanation of how to understand the figure of the taxonomy. Further, the authors make no mention of how the taxonomy guides or will be employed in the present study. Please include this. Otherwise, the figure and mention of the taxonomy might well be omitted.

The first paragraphs of the introduction relevantly describe the occurrence of existential distress and related concerns in patients and caregivers. Please clarify for the next-to-last paragraph (”Cross-sectional studies do not…”), whether findings here are solely from patients or both from patients and caregivers.

The last paragraph of the introduction seems devoted to the argument that increased knowledge about the mechanisms that link existential distress to end-of-life outcomes, could increase effects of interventions. However, it does not link meaning or existential distress to end-of-life outcomes, which seem to be the central outcomes in the analysis. The authors might consider elaborating on the hypothesized association or effect of existential distress/meaning with/on end of life outcomes. As this study includes both patients and caregivers, it might be relevant to elaborate also whether this effect/association is assumed to be the same across patients and caregivers. Please explain why/why not.

Participants and recruitments

Please provide further details about the settings in which patients are included., e.g. what characterizes “affiliated clinics”? The methods section mentions “a cross-section of treatment setting” – please specify further what range this includes. E.g. are in- and/or out-patients included from both oncological/surgical and palliative care units? Please provide further details on recruitment: When and how are patients and caregivers approached?

Please provide further details on the operationalization of “caregivers”, in light of the possible range of relations to the patient (spouse, partner, family member or friend). How is “care” defined? If no further criteria are applied, please discuss reasons for/implications of this choice. E.g. can different types of caregivers be expected to experience existential distress as the same levels and can their existential distress be expected to relate both to patients’ distress and their end-of-life outcomes in the same way?

Please comment on the applicability of scales previously used and validated in patients with the included caregivers. Were any changes needed? Please also ensure that it is clear which populations scales were validated or piloted in, when they will be used in both patients and caregivers. E.g. somatic/cancer patients, caregivers (only partners?), others? Further, please provide references for e.g. piloted scales, or describe the work as unpublished. Almost all scales are described in great detail, please also provide scoring information for the Structured Interview for Psychological Adjustment and Demoralization.

Please provide more detail on the palliative care outcomes. At present they seem to only be referred to as “involvement of specialized palliative care services or hospice services”.

Please provide information on the implications of beginning this study during the COVID-19 pandemic. Has this affected e.g. the planned mode of recruitment?

	Power /statistical analyses Please specify whether 500 patients or 500 dyads will be included at baseline. Please explain how dependency between patient- and caregiver-dyads is taken into account in the power calculation and how it will be handled in the models, or whether models will be run separately for caregivers and patients. Please elaborate the “potential bias in caregiver estimates” mentioned.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

In “Existential distress in patients with advanced cancer and their caregivers: Study protocol of a longitudinal cohort study,” Philipp et al describe an assessment battery for a longitudinal cohort study designed to characterize existential distress and its correlates among advanced stage cancer patients and their informal caregivers. Study strengths include an important research question, a well-written manuscript, and well-designed assessment battery for a longitudinal design. Study limitations include omission of some psychometric data and measurement details and lack of specificity on how each self-report measure will be used in the analysis. These are addressable concerns. These and additional recommendations are described below.

1. **Abstract: Recommend revising “Over a period of 12 months…” sentence to move the self-report questionnaire domains after “self-report questionnaires” and adding the planned 5 points of assessment (baseline, 3 months, etc).**

Comment

Thank you for this note. We revised the sentence according to the reviewer's suggestion.

Changed text passage

This longitudinal cohort study will consecutively recruit 500 patients with advanced cancer and 500 caregivers from oncological outpatient and inpatient clinics. Participants will complete self-report questionnaires (sociodemographic and disease-related characteristics, existential distress, end-of-life outcomes, resources, and support needs) at five points of assessment (at baseline and after 3, 6, 9, and 12 months).

2. **Strengths and limitations of this study: Point 4: Recommend revising “highly distressed sample” to “potentially highly distressed sample” and or “understudied” – you do not know the distress rates you will observe in this sample.**

Comment

We added both suggestions to bullet point 4.

Changed text passage

- *assessment of an extensive battery of instruments in a potentially highly distressed and understudied sample*

3. Introduction:

3.1. Paragraph 1, line 10 “In about one third of patients…” – Recommend revising the sentence. Multiple sources of distress lead to increased levels of depression and anxiety…and physical symptom burden? Is physical symptom burden meant to be a source of distress leading to increased levels of depression and anxiety?

Comment

Thank you for addressing this lack of clarity. We revised the sentence focusing on depression and anxiety, according to our research question.

Changed text passage

In about one third of the patients, multiple sources of distress are associated with increased levels of depression and anxiety [1, 2].

3.2. Paragraph 1, line 17: recommend omitting “existential” after “bio-psycho-social existential”

Comment

We deleted the word "existential".

Changed text passage

Although the existential domain of suffering has long been incorporated into a bio-psycho-social perspective in advanced cancer and palliative care [3–5], existential distress has received little attention in systematic quantitative or prospective research in these populations.

3.3. Paragraph 4, line 19: “They may also suffer from the loss of the patient’s identity…” – unless you are focusing specifically on brain tumors, recommend omitting “which is a frequent consequence of brain tumors”

Comment

We deleted the phrase "which is a frequent consequence of brain tumors".

Changed text passage

They may also suffer from the patient’s perceived loss of identity.[6]

3.4. Paragraph 6, line 42 – “Especially because a lack of perceived relatedness…” appears to be sentence fragment

Comment

Thank you for this comment. We rephrased this text passage for more clarity.

Changed text passage

Whereas some couples manage to renegotiate roles and find ways to communicate about these issues, patients also tend to feel alienated by their caregivers' denial and avoidance of conflict.[7] This lack of perceived relatedness in close relationships is a common source of existential distress for patients and caregivers.[8] Moreover, difficulties in coping with existential concerns have been associated with complicated grief.[9, 10] Yet, there is a clear need for research on how caregivers may be affected by their own existential fears and hopelessness.[11]

4. Methods and analysis:

4.1. Participants and recruitment. Allowing caregivers and patients to enroll in the cohort study at different timepoints is good for the reasons mentioned. However, recommend either citing other cohort studies that have allowed a non-uniform enrollment period (e.g., allowed pts to enroll at diagnosis or towards the end of treatment) or describing in analysis how will address the fact that those who enroll later into their cancer treatment are likely to have fewer assessment points compared to those who enroll at diagnosis.

Comment

We have added a description in the analysis section on how the expected longitudinal drop-out will be handled.

Changed text passage

We will analyse the longitudinal trajectory of existential distress across the 12-month study period using growth mixture models. These models estimate distinct groups of existential distress trajectories based on a structural equation-modelling framework. The expected longitudinal dropout of patients with a prognosis of less than 12 months will be handled by full information maximum likelihood estimation.[12]

4.2. Procedures. "At baseline and after 6 months, we will conduct structured…" recommend clarifying that you are doing structured interviews with both patients and caregivers

Comment

For more clarity, we added "for patients and caregivers" to the sentence.

Changed text passage

At baseline (T1) and after 6 months (T3), we will conduct structured diagnostic interviews with patients and caregivers face-to-face or via telephone to assess mental disorders.

4.3. Procedures. Later in the manuscript you mention that patients can enroll without their caregivers. Recommend stating early on that you will enroll patients or patient-caregiver dyads.

Comment

Thank you for this suggestion. We added an according sentence to the section "Participants and recruitment".

Changed text passage

We will consecutively recruit 500 patients and 500 informal caregivers from outpatient and inpatient clinics including oncological and palliative care units at the University Cancer Center Hamburg (UCCH, University Medical Center Hamburg and affiliated hospitals located in the Hamburg metropolitan region). Eligible patients are at least 18 years old and are diagnosed with advanced cancer as defined by Union for International Cancer Control (UICC) stage IV solid tumor. Eligible caregivers (spouse or partner, family member or close friend) are at least 18 years old. Assessment will include patients with advanced cancer and caregivers across all phases of advanced disease from diagnosis to terminal stages to reflect a cross-section of treatment settings, tumor entities, and time since diagnosis. Recruitment is not limited to patient-caregiver dyads; patients and caregivers can participate individually. Exclusion criteria for patients and caregivers are severe cognitive or physical impairment and insufficient ability to speak German to give informed consent and to complete the self-report questionnaires.

4.4. Measures

4.4.1. Table 1 is a great start. However, recommend adding which self-report measure is primary outcome for which objective and how others will be used in analysis (e.g., covariate, dependent, focal, etc.) for each objective. This is especially important because of the extensive assessment battery being administered.

Comment

We have added this information to the table in order to clarify the status of each variable as predictor, covariate or outcome, respectively. In line with comment 2.2 of reviewer 2, we have also revised Figure 1 to more clearly depict existential distress variables and end-of-life outcome variables, respectively. All names in the Figure align with the names in the table. We have also added detail to the description of the research objectives. The objectives now clearly refer to each group pf variables.

Changed text passages

Table 1. *Self-report questionnaires and observer-rated instruments*

	Construct measured	***Patients***	***Caregivers***
Existential distress (predictor)			
Death Anxiety and Distress Scale (DADDS)	*Death anxiety*	●	●
Depressive Experiences Questionnaire (DEQ) Subscales: Dependence, Relatedness	*Perceived relatedness*	●	●
Revised Loss Orientation and Life Engagement in Advanced Cancer Scale (LOLES)	*End-of-life preparation and adaptation*	●	●
Dignity-Item (SDI)	*Dignity-related distress*	●	
Patient Dignity Inventory (PDI)	*Dignity-related distress*	●	
Demoralization Scale-II (DS-II)	*Demoralization*	●	●
Structured Interview for Psychological Adjustment and Demoralisation[c]	*Demoralization, suicidal ideation*	●	●
Marwit-Meuser Caregiver Grief Inventory (MM-CGI-SF)[a]	*Anticipatory grief*		●
Caregiver Guilt Questionnaire (CGQ)[a]	*Caregiver guilt*		●
End-of-life outcomes and prevalence of mental disorders (outcome)			
Disease- and medical care-related characteristics[b]	*Aggressiveness of care*	●	
Structured Clinical Interview for DSM-5 (SCID-5)[c]	*Affective disorders* *Anxiety disorders* *Posttraumatic stress disorder* *Adjustment disorder*	●	●
Adjustment Disorder-CIDI – New Module (AjD-CIDI)[c]	*ICD-11 adjustment disorder*	●	●
Schedule of Attitudes Toward Hastened Death – Short Form (SAHD-A)	*Desire for hastened death*	●	
Beck Scale for Suicide Ideation (BSS)	*Suicidal ideation*	●	●
Inventory of Complicated Grief (ICG)[d]	*Complicated grief*		●

Quality of Dying and Death Questionnaire (QODD)[d]	*Quality of dying and death*		●
Symptom burden and resources (covariate)			
Memorial Symptom Assessment Scale – Short Form (MSAS-SF)	*Physical symptom burden*	●	
Patient Health Questionnaire-9 (PHQ-9)	*Symptoms of depression*	●	●
Generalized Anxiety Disorder Questionnaire-7 (GAD-7)	*Symptoms of anxiety*	●	●
Sources of Meaning and Meaning in Life Questionnaire (LeBe)	*Meaningfulness in life, crisis of meaning*	●	●
Support needs			
Structured questionnaire of psychosocial support needs for existential distress	*Need for and utilization of psychosocial support for existential distress*	●	●

[a]Not assessed after the patient's death

[b]Assessed via medical chart review

[c]Observer-rated interview

[d]Assessed after the patients' death only

This study will systematically assess existential distress and investigate its impact on patient- and caregiver-relevant outcomes at the end of life. Therefore, we aim

1) to investigate the frequency and longitudinal trajectory of existential distress in patients with advanced cancer and their caregivers,

2) to examine the predictive impact of existential distress on patient- and caregiver-relevant end-of-life outcomes,

3) to determine patients' and caregivers' specific need for and utilization of psychosocial support with respect to existential concerns, and

4) to explore typical profiles of existential distress in patients and caregivers.

Reviewer #2

1. Abstract: Please include the expected numbers of patients and caregivers to be recruited.

<u>Comment</u>

We have added these numbers to the abstract.

<u>Changed text passage</u>

This longitudinal cohort study will consecutively recruit 500 patients with advanced cancer and 500 caregivers from oncological outpatient and inpatient clinics.

2. Introduction

2.1. In the introduction to the concept of existential distress, the authors mention their taxonomy and provide a figure, while referring to "earlier reviews and conceptual literature". As readers cannot be expected to be familiar with this whole literature, it would

be very helpful, if the authors could provide a brief explanation of how to understand the figure of the taxonomy.

2.2. **Further, the authors make no mention of how the taxonomy guides or will be employed in the present study. Please include this. Otherwise, the figure and mention of the taxonomy might well be omitted.**

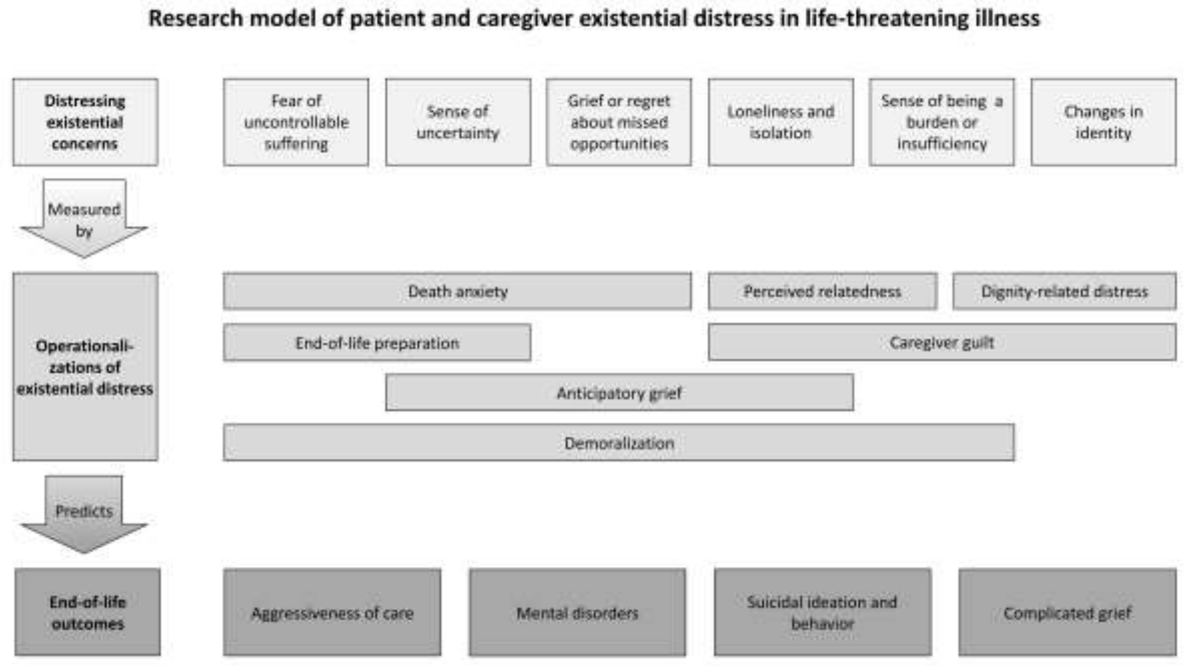
<u>Comment</u>

We now provide further elaboration of the contribution and use of this taxonomy ad depicted in Figure 1. It may guide readers through the sometimes confusing variety of concerns and concepts used to describe existential distress in the context of advanced cancer in qualitative and quantitative studies. We have clarified that Figure 1 serves as a research model illustrating for the reader predictors and outcomes as conceptualized in the present study.

To improve Figure 1 in this regard, we have revised it to better represent the conceptual relationship of existential concerns, existential distress concepts, and end-of-life outcomes.

<u>Changed text passage</u>

Based on earlier reviews and conceptual literature,[13–19] we propose a taxonomy that integrates different existential concerns among patients and caregivers and links them to operationalizations of existential distress (Figure 1, first and middle part). According to this taxonomy, frequently described existential concerns including fear of what will happen at death, uncertainty, unpreparedness, a sense of being a burden to others, or a sense of profound loneliness, can be systematically measured by clearly defined concepts. Operationalizations of existential distress concepts [20] in cancer patients include for example among other, death anxiety,[21, 22], demoralization,[23] and dignity-related concerns[24] (Figure 1, middle part). Figure 1 (middle and lower part) further illustrates the research model of the examined association between these concepts and end-of-life outcomes.



2.3. **The first paragraphs of the introduction relevantly describe the occurrence of existential distress and related concerns in patients and caregivers. Please clarify for the next-to-last**

paragraph ("Cross-sectional studies do not…"), whether findings here are solely from patients or both from patients and caregivers.

Comment

We now clearly specify for this part of the manuscript that the findings refer to patients only.

Changed text passages

Among patients with advanced cancer, cross-sectional studies do not only suggest a positive association between demoralization and an increased risk for adjustment, depressive and anxiety disorders, they also found positive associations between existential distress and suicidal ideation or the desire for hastened death.[25–27]

2.4. The last paragraph of the introduction seems devoted to the argument that increased knowledge about the mechanisms that link existential distress to end-of-life outcomes, could increase effects of interventions. However, it does not link meaning or existential distress to end-of-life outcomes, which seem to be the central outcomes in the analysis. The authors might consider elaborating on the hypothesized association or effect of existential distress/meaning with/on end of life outcomes.

Comment

This paragraph was confusing and unclear. We intended to describe the potential association of approach- and acceptance oriented coping mechanisms with positive end-of-life outcomes as suggested by secondary analyses of the early palliative care intervention trials by Temel, Greer, Nipp et al. We have now added these references and included this point within the paragraph discussing the rationale for examining the association between existential distress and end-of-life outcomes to clarify the focus of the present study on the association between existential distress and end-of-life outcomes.

Changed text passage

Among patients with advanced cancer, cross-sectional studies do not only suggest a positive association between demoralization and an increased risk for adjustment, depressive and anxiety disorders, they also found positive associations between existential distress and suicidal ideation or the desire for hastened death.[25–27] Also, in the context of legalizing physician-assisted suicide in Canada, Li et al.[28] observed existential distress to be an important motive for these requests. A rare longitudinal study found an increase of existential distress over time.[29] Moreover, existential issues may contribute to receiving aggressive treatments in the last weeks of life.[30, 31] Studies also indicate a positive association of religious coping with aggressive treatment at the end of life.[32, 33] It is possible that existential distress is linked to a form of coping that interferes with prognostic awareness and timely end-of-life discussions. There is growing evidence that the ability to maintain a sense of meaning, acceptance and use of approach-oriented coping may contribute to better end-of-life outcomes.[34, 35] However, the role of death anxiety, lack of preparedness, a strong hope for cure, and incongruence of patient and caregiver acceptance for end-of-life care outcomes is currently unclear.[36] Although the impact of caregiver existential distress on patient end-of-life outcomes may be partially mediated by patient existential distress, a relevant impact may be expected.[37]

2.5. As this study includes both patients and caregivers, it might be relevant to elaborate also whether this effect/association is assumed to be the same across patients and caregivers. Please explain why/why not.

Comment

The effect of caregiver existential distress on patient end-of-life outcome may be expected to turn out lower compared to the respective association for patients, as these effects may be mediated through the patients' existential distress.

<u>Changed text passage</u>

However, the role of death anxiety, lack of preparedness, a strong hope for cure, and incongruence of patient and caregiver acceptance for end-of-life care outcomes is currently unclear.[36] Although the impact of caregiver existential distress on patient end-of-life outcomes may be partially mediated by patient existential distress, a relevant impact may be expected.[37]

3. Participants and recruitments

3.1. Please provide further details about the settings in which patients are included, e.g. what characterizes "affiliated clinics"? The methods section mentions "a cross-section of treatment setting" – please specify further what range this includes. E.g. are in- and/or out-patients included from both oncological/surgical and palliative care units? Please provide further details on recruitment: When and how are patients and caregivers approached?

<u>Comment</u>

We have specified that patients and caregivers will be recruited from outpatient and inpatient clinics including oncological and palliative care units at the University Medical Center Hamburg and hospitals in the Hamburg metropolitan region (all part of the University Cancer Center Hamburg UCCH).

<u>Changed text passage</u>

We will consecutively recruit 500 patients and 500 informal caregivers from outpatient and inpatient clinics including oncological and palliative care units at the University Cancer Center Hamburg (UCCH, University Medical Center Hamburg and affiliated hospitals located in the Hamburg metropolitan region). Eligible patients are at least 18 years old and are diagnosed with advanced cancer as defined by Union for International Cancer Control (UICC) stage IV solid tumor. Eligible caregivers (spouse or partner, family member or close friend) are at least 18 years old. Assessment will include patients with advanced cancer and caregivers across all phases of advanced disease from diagnosis to terminal stages to reflect a cross-section of treatment settings, tumor entities, and time since diagnosis. Recruitment is not limited to patient-caregiver dyads, patients and caregivers are able to participate individually. Exclusion criteria for patients and caregivers are severe cognitive or physical impairment and insufficient ability to speak German to give informed consent and to complete the self-report questionnaires.

3.2. Please provide further details on the operationalization of "caregivers", in light of the possible range of relations to the patient (spouse, partner, family member or friend). How is "care" defined? If no further criteria are applied, please discuss reasons for/implications of this choice. E.g. can different types of caregivers be expected to experience existential distress as the same levels and can their existential distress be expected to relate both to patients' distress and their end-of-life outcomes in the same way?

<u>Comment</u>

We have decided to include a white range of caregiver "types" due to the limited data on caregiver burden generally available. The recruitment strategy focuses on close others who accompany the patient to the clinic to support him/her through treatment and/or close others who the patient nominates as caregiver. From the clinical observation and qualitative studies, these individuals, although formally related to the patient different ways, carry a similar emotional burden. We expect potential bias may be lowered through the larger number of caregivers recruited, permitting to obtain a cross-section of caregiver types that is representative for those being most affected by the patients illness. We have added this limitation of the heterogeneous caregiver group to he discussion.

Changed text passage

This longitudinal study will provide unique systematic knowledge about patients' and caregivers' existential concerns. The empirical data will allow for conclusions concerning frequency and course of existential distress throughout one year. There is a need for quantitative studies focusing explicitly on existential concerns of caregivers, who are sometimes referred to as 'hidden patients' whose distress tends to be overlooked.[38] The recruitment strategy will allow enrollment of a large, heterogeneous sample of patients with advanced cancer from a range of clinics and treatment facilities. Limitations include potentially high dropout rates due to patients' physical decline or death within the study period. Heterogeneous patient and caregiver samples will limit subgroup-specific interpretations. Despite these limitations, the extensive assessment of psychological distress in a potentially highly distressed and understudied sample will contribute to the recognition of existential distress in patients and caregiver populations and to development of targeted interventions. Profiles of existential distress may be applied by clinicians from multiple professions and help to address existential concerns effectively.

3.3. Please comment on the applicability of scales previously used and validated in patients with the included caregivers. Were any changes needed? Please also ensure that it is clear which populations scales were validated or piloted in, when they will be used in both patients and caregivers. E.g. somatic/cancer patients, caregivers (only partners?), others? Further, please provide references for e.g. piloted scales, or describe the work as unpublished. Almost all scales are described in great detail, please also provide scoring information for the Structured Interview for Psychological Adjustment and Demoralization.

Comment

We have added these specifics to each instrument where the information was missing.

Changed text passages

Please see the complete Measures section with changes highlighted in yellow.

3.4. Please provide more detail on the palliative care outcomes. At present they seem to only be referred to as "involvement of specialized palliative care services or hospice services".

Comment

We have provided further detail on the assessed aspects of end-of-life outcomes and palliative care outcomes more specifically.

Changed text passage

Information about aggressiveness of care will include receipt of chemotherapy in the last two weeks of life, emergency hospital admissions or intensive-care treatment during the last month of life[39] will be obtained from medical chart reviews for deceased patients. Further, we will document the uptake and duration of specialized palliative care or hospice services received and place of death. We will further assess documentation of end-of-life care discussions as well as medical orders for life sustaining treatment in the electronic health record.

3.5. Please provide information on the implications of beginning this study during the COVID-19 pandemic. Has this affected e.g. the planned mode of recruitment?

Comment

We were confronted with the problem that caregivers have limited access during the pandemic to most treatment facilities. We have added this and adapted recruitment procedures to the "procesdures" section.

Changed text passage

The COVID-19-pandemic has led to limited access of caregivers to oncological treatment facilities. We will adapt the recruitment strategy accordingly and approach caregivers via phone upon the patient's approval.

4. Power /statistical analyses

4.1. Please specify whether 500 patients or 500 dyads will be included at baseline. Please explain how dependency between patient- and caregiver-dyads is taken into account in the power calculation and how it will be handled in the models, or whether models will be run separately for caregivers and patients.

Comment

Patients and caregivers will be recruited and analyzed individually. There are now research questions concerning dyads.

Changed text passages

Participants:

Recruitment is not limited to patient-caregiver dyads, patients and caregivers are able to participate individually.

Statistical analyses:

Analyses will be conducted separately for patients and caregivers.

4.2. Please elaborate the "potential bias in caregiver estimates" mentioned.

Comment

We have clarified the sentence to describe the analyses planned.

Changed text passage

Existential distress may be higher among caregivers of patients who are physically too weak to participate and potentially close to death. We will account for this effect by including patient participation as a control variable in caregiver models.

REFERENCES

1 Mehnert A, Brähler E, Faller H, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. *J Clin Oncol* 2014;32(31):3540–46.

2 Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *Lancet Oncol* 2011;12(2):160–74.

3 Saunders CM. The Management of terminal malignant disease. London, UK: Edward Arnold 1984.

4 Cassel EJ. The Nature of suffering and the goals of medicine. *N Engl J Med* 1982;306(11):639–45.

5 Weisman AD, Worden JW. The existential plight in cancer: Significance of the first 100 days. *Int J Psychiatry Med* 1976;7(1):1–15.

6 Reblin M, Small B, Jim H, et al. Mediating burden and stress over time: Caregivers of patients with primary brain tumor. *Psycho-Oncology* 2018;27(2):607–12. doi:10.1002/pon.4527 [published Online First: 31 August 2017].

7 Manne S, Badr H. Intimacy and relationship processes in couples' psychosocial adaptation to cancer. *Cancer* 2008;112(11 Suppl):2541–55.

8 Philipp R, Mehnert A, Müller V, et al. Perceived relatedness, death acceptance, and demoralization in patients with cancer. *Support Care Cancer* 2020;28:2693–700 (accessed 28 Jan 2020).

9 Chiu Y-W, Huang C-T, Yin S-M, et al. Determinants of complicated grief in caregivers who cared for terminal cancer patients. *Support Care Cancer* 2010;18(10):1321–27.

10 Lobb EA, Kristjanson LJ, Aoun SM, et al. Predictors of complicated grief: A systematic review of empirical studies. *Death Stud* 2010;34(8):673–98.

11 Mystakidou K, Tsilika E, Parpa E, et al. Caregivers of advanced cancer patients: Feelings of hopelessness and depression. *Cancer Nurs* 2007;30(5):412–18.

12 Asendorpf JB, van de Schoot, R., Denissen, J. J. A., et al. Reducing bias due to systematic attrition in longitudinal studies: The benefits of multiple imputation. *International Journal of Behavioral Development* 2014;38(5):453–60 (accessed 8 Apr 2016).

13 Breitbart W. Spirituality and meaning in supportive care: spirituality- and meaning-centered group psychotherapy interventions in advanced cancer. *Support Care Cancer* 2002;10(4):272–80.

14 LeMay K, Wilson KG. Treatment of existential distress in life threatening illness: A review of manualized interventions. *Clin Psychol Rev* 2008;28(3):472–93.

15 Henoch I, Danielson E. Existential concerns among patients with cancer and interventions to meet them: An integrative literature review. *Psychooncology* 2009;18(3):225–36.

16 Best M, Aldridge L, Butow PN, et al. Conceptual analysis of suffering in cancer: a systematic review. *Psycho-Oncology* 2015;24(9):977–86. 25754062 (accessed 16 Mar 2015).

17 Boston PH, Bruce A, Schreiber R. Existential suffering in the palliative care setting: An integrated literature review. *J Pain Symptom Manage* 2011;41(3):604–18.

18 Cherny NI, Coyle N, Foley KM. Suffering in the advanced cancer patient: A definition and taxonomy. *J Palliat Care* 1994;10:57–70.

19 Kissane DW. The relief of existential suffering. *Arch Intern Med* 2012;172(19):1501–05.

20 Lo C, Panday T, Zeppieri J, et al. Preliminary psychometrics of the Existential Distress Scale in patients with advanced cancer. *Eur J Cancer Care* 2017;26(6):e12597.

21 Krause S, Rydall A, Hales S, et al. Initial validation of the Death and Dying Distress Scale for the assessment of death anxiety in patients with advanced cancer. *J Pain Symptom Manag* 2015;49(1):126–34.

22 Lo C, Hales S, Zimmermann C, et al. Measuring death-related anxiety in advanced cancer: Preliminary psychometrics of the Death and Dying Distress Scale. *J Pediatr Hematol Oncol* 2011;33 Suppl 2:S140-5.

23 Kissane DW, Clarke DM, Street AF. Demoralization syndrome -A relevant psychiatric diagnosis for palliative care. *J Palliat Care* 2001;17(1):12–21.

24 Chochinov HM, Hack T, Hassard T, et al. Dignity in the terminally ill: A cross-sectional, cohort study. *The Lancet* 2002;360(9350):2026–30.

25 Fang C-K, Chang M-C, Chen P-J, et al. A correlational study of suicidal ideation with psychological distress, depression, and demoralization in patients with cancer. *Support Care Cancer* 2014;22(12):3165–74.

26 Robinson S, Kissane DW, Brooker J, et al. The relationship between poor quality of life and desire to hasten death: A multiple mediation model examining the contributions of depression, demoralization, loss of control, and low self-worth. *J Pain Symptom Manag* 2017;53(2):243–49 (accessed 24 Oct 2016).

27 Vehling S, Kissane DW, Lo C, et al. The association of demoralization with mental disorders and suicidal ideation in patients with cancer. *Cancer* 2017;123(17):3394–401 (accessed 14 Jun 2017).

28 Li M, Watt S, Escaf M, et al. Medical assistance in dying - Implementing a hospital-based program in Canada. *N Engl J Med* 2017;376(21):2082–88.

29 Lichtenthal WG, Nilsson M, Zhang B, et al. Do rates of mental disorders and existential distress among advanced stage cancer patients increase as death approaches? *Psycho-Oncology* 2009;18(1):50–61. doi:10.1002/pon.1371.

30 Dasch B, Kalies H, Feddersen B, et al. Care of cancer patients at the end of life in a German university hospital: A retrospective observational study from 2014. *PLoS One* 2017;12(4):e0175124 (accessed 7 Apr 2018).

31 Radbruch L, Andersohn F, Walker J. Palliative care: Oversupply curative – undersupply palliative? Analysis of selected treatments at the end of life 2015. Available at: https://www.bertelsmann-stiftung.de/fileadmin/files/BSt/Publikationen/GrauePublikationen/Studie_VV__FCG_Ueber-Unterversorgung-palliativ.pdf.

32 Steinhauser KE, Fitchett G, Handzo GF, et al. State of the Science of Spirituality and Palliative Care Research Part I: Definitions, Measurement, and Outcomes. *J Pain Symptom Manag* 2017;54(3):428–40 (accessed 26 Mar 2018).

33 Phelps, Andrea C., Maciejewski PK, et al. Religious coping and use of intensive life-prolonging care near death in patients with advanced cancer. *JAMA* 2009;301(11).

34 Greer JA, Jacobs JM, El-Jawahri A, et al. Role of Patient Coping Strategies in Understanding the Effects of Early Palliative Care on Quality of Life and Mood. *J Clin Oncol* 2017:JCO2017737221 (accessed 29 Nov 2017).

35 Nipp RD, Greer JA, El-Jawahri A, et al. Coping and Prognostic Awareness in Patients With Advanced Cancer. *J Clin Oncol* 2017;35(22):2551–57.

36 Applebaum AJ, Stein EM, Lord-Bessen J, et al. Optimism, social support, and mental health outcomes in patients with advanced cancer. *Psycho-Oncology* 2014;23(3):299–306. doi:10.1002/pon.3418 [published Online First: 7 October 2013].

37 Williams A-L, McCorkle R. Cancer family caregivers during the palliative, hospice, and bereavement phases: A review of the descriptive psychosocial literature. *Palliat Support Care* 2011;9(3):315–25.

38 Hoerger M, Cullen BD. Early integrated palliative care and reduced emotional distress in cancer caregivers: Reaching the "hidden patients". *Oncologist* 2017;22(12):1419–20.

39 Earle CC, Park ER, Lai B, et al. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. *J Clin Oncol* 2003;21(6):1133–38.

VERSION 2 – REVIEW

REVIEWER	Annika von Heymann Department of Oncology, Center for Cancer and Organ Diseases, Rigshospitalet, Denmark
REVIEW RETURNED	04-Mar-2021

GENERAL COMMENTS	The authors have addressed all concerns and included relevant changes to the paper. I wish them luck in completing this very interesting study and look forward to seeing their results.