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Interprofessional evidence-based counselling programme for Complementary and Integrative Health Care in cancer patients–study protocol for the controlled implementation study CCC - Integrativ

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Abstract

Introduction

According to international literature, cancer patients wish to have information on complementary and integrative health care (CIH). Medical guidelines recommend actively approaching cancer patients discussing potential benefits and risks of individual CIH methods. While some CIH methods e.g. acupuncture and yoga can be recommended based on high quality studies, some other CIH methods e.g. herbal drugs bear the risk of interactions with chemotherapeutics. Therefore, an evidence-based interprofessional counselling programme on CIH will be implemented at four Comprehensive Cancer Centres (CCC) in the federal state of Baden-Wuerttemberg, Germany.

Methods and analysis

A complex intervention with elements on patient, provider, and system level will be developed and evaluated within a multilayer evaluation design with confirmatory evaluation on patient level. Patients with a cancer diagnosis within the last 6 months will receive 3 individual counselling sessions on CIH within 3 months (=intervention on patient level). The counselling will be provided by an interprofessional team of medical and nursing staff. For this purpose, an intensive online training programme was developed for the project (=intervention on provider level). Moreover, training events on basics of CIH are offered in outpatient setting (=intervention on system level). Primary outcome of the evaluation at patient level is patient activation measured with the PAM-13 after 3 months. Secondary outcomes e.g. quality of life, self-efficacy and clinical parameters will be assessed at baseline, after 3 months and at 6 months follow-up. The intervention group (n=1000) will be compared with a control group (n=500, no CIH counselling) with the same follow up times but not concurrent calendarial dates. Moreover, use of health services will be compared with a reference group (n= 2000) based on health insurance data. A qualitative-quantitative process evaluation as well as a health economic evaluation will identify relevant barriers and enabling factors for a later roll-out.

Ethics and dissemination.

The study has been approved by the appropriate Institutional Ethical Committee of the University of Tuebingen, No. 658/2019BO1. The results of these studies will be disseminated to academic audiences and in the community.

Registration

German Clinical Trials Register (DRKS), DRKS00021779 registered on 12th June 2020

Keywords

Oncology, comprehensive cancer centre, complementary medicine and integrative health care, Interprofessional, integrative medicine, supportive therapy, counselling intervention, patient activation, controlled study

Strengths and limitations of this study

- For the first time a transsectoral, interprofessional, evidence-based counselling programme for Complementary and Integrative Health Care will be implemented at Comprehensive Cancer Centres Baden-Wuerttemberg, Germany.
- The complex evaluation will be conducted at the patient, provider, and system levels within a controlled design.
- The guiding (confirmatory) hypothesis is at patient level measured by patient activation (PAM-13).
- Randomization at patient level is not possible due to the naturalistic study design.
- On provider level a training programme for the counselling team is designed and evaluated as blended-learning programme with online (asynchronous) and onsite (synchronous) formats.

Introduction

According to previous studies there is a high use of naturopathic/complementary approaches (CIH= complementary and integrative health care) among cancer patients. A meta-analysis shows that about 40% of all oncology patients use CIH [1], for patients with breast cancer up to 80% can be assumed [2]. For some CIH methods, positive effects in cancer patients have been shown in RCTs and meta-analyses e.g. meditation, particularly mindfulness-based stress reduction for mood disturbance and depression, Yoga and Tai Ji for improving quality of life and fatigue, acupuncture and acupressure to reduce nausea and pain, individual phytotherapeutics and herbal medicines such as ginger for nausea [3-5]. In addition, many of these CIHs have the goal to empower and activate patients as well as to improve self-efficacy. [6] The promotion of patient activation [7], self-management strategies [8], and health literacy [9] have been shown to empower patients with cancer [10] and contribute to reduce the use of health services [11].

However, CIH also entails clinical risks; e.g. phytotherapeutics and micronutrients especially in high doses (vitamins, selenium) can interact with chemotherapy [12 13]. A further risk arises from the fact that patients often look for help outside conventional health care structures (e.g. alternative practitioners) with unforeseeable health consequences such as delayed diagnosis and failure to provide indicated treatments [14 15]. In addition, there are the risks for economic harm as the majority of costs for CIH procedures are not covered by public insurance.[16]. In 20% up to 77% of cases cancer patients do not inform their treating physicians when making use of CIH [17-19]. This lack of communication may endanger the doctor-patient relationship and contribute to discontinuation of conventional therapy [14 20 21].

Patient-centred care for cancer includes supportive measures that enable patients to cope as well as possible with their diagnosis and therapy, including its side effects [22-24]. These supportive measures may also include CIH methods. Therefore, according to current German S3 guidelines on breast cancer, cervical cancer, ovarian cancer as well as the guidelines on complementary medicine in the treatment of oncology patients [3], palliative medicine and psycho-oncology, there is a consensus recommendation that all patients should be asked about their need for information on their use of CIH procedures [3 25]. However, this recommendation contrasts starkly with a lack of human resources in oncologic clinics and insufficient CIH knowledge among medical and nursing staff. Therefore, this recommendation could hardly be implemented so far in everyday care and the topic of CIH is often not at all or not sufficiently addressed in patient communication. The aim of the CCC-Integrativ study is to develop and evaluate a complex intervention with elements on patient, provider and system level to improve CIH for cancer patients. In detail, we aim to evaluate whether interprofessional counselling about CIH improves patient activation and patients' confidence in contributing to their health.

Methods and analysis

Theoretical framework and objectives

The project pursues a health services research approach and therefore objectives and interventions will be differentiated in relation to the micro-, meso- and macro-level.

On the **micro (patient)-level** the project aims to activate patients and promote their self-efficacy (see Fig. 1). It is expected that by enhanced empowerment the patient´s quality of life and clinical outcomes will be improved, which can in turn lead to a reduced use of health services in the further course [26].

Please insert Fig 1 here

Objectives at the **meso (provider) level** are an improvement of the knowledge and communication skills regarding CIH as well as improved job satisfaction and interprofessional collaboration between doctors and nurses within the care setting.

At the **macro (system)-level** the objectives include costs and a transsectoral increase in knowledge of CIH (see Fig.2).

Please insert Fig 2 here

Setting and Study design

Within the CCC-Integrativ study an evidence-based interprofessional counselling programme on CIH for oncology patients will be implemented and evaluated at the four Comprehensive Cancer Centres (CCC) (Freiburg, Heidelberg, Tuebingen-Stuttgart, Ulm) in Baden-Wuerttemberg. Comprehensive Cancer Centres are implemented at most university hospitals in Germany to ensure a high standard of medical care for oncology patients and are considered centres of excellence in oncology.

As described above CCC-Integrativ will be evaluated at patient, provider and system level, whereby the confirmatory testing will be on patient level. The accompanying process evaluation, which also analyses aspects of the micro-, meso- and macro- level is presented in detail in a separate protocol.

The total study duration is 36 months. For the individual study participant, the study including the follow-up survey lasts 6 months (intervention group and control group). The preparation period runs from month 1-6, the primary data collection in the control group from month 7 to 18 (recruitment month 7-9). Data collection in the intervention group from month 13-30 (recruitment month 13-24).

The intervention group is compared with a control group and a reference group. The control group is recruited 6 months before the start of the intervention phase. Identical outcome parameters are

collected. The reference group results from claims data of the statutory health insurance of the Allgemeine Ortskrankenkasse Baden-Wuerttemberg (AOK BW) without additional primary data collection. The reference group allows us to examine representativity of the study population compared to the target population (members of AOK-BW). If differences between the control group and the reference group are detected, i.e. a study effects are present, these will be accounted for in the comparison of the reference group with the intervention group in order to disentangle study effects and intervention effects.

A classical parallel group design with randomization at patient level did not seem feasible, as previous studies have shown that patients with a high use or need for counselling on CIH cannot be randomized [23]. Also, cluster randomization had to be rejected due to possible contamination problems. Thus, we decided to choose different time intervals within the study period for controls and intervention patients.

Intervention on patient level

The intervention consists of an interprofessional, evidence-based counselling service for patients with counselling needs in the field of CIH. The CIH counselling service is provided by interprofessional teams consisting of specially trained physicians and nurses at each of the four participating CCCs and integrated into the existing structures at the four participating CCCs in Freiburg, Heidelberg, Tübingen-Stuttgart und Ulm. Our concept for counselling follows an evidence-based approach, integrating patient preferences and individual medical and nursing expertise.

Intervention and control group

Intervention group

Patients of the intervention group will be offered interprofessional individual counselling. Eligible patients will receive at least three counselling sessions on evidence-based nursing and/or medical interventions within three months. The first counselling session will be face-to-face and interprofessional and is planned for a duration of 60 minutes. The subsequent two counselling session may be mono-professional and performed by telephone or as a video counselling with a duration of approximately 30 minutes.

The counselling concept takes into account the resources of the patient, integrates conventional health care (as provided by the CCCs in routine care) and provides information on CIH and care services with CIH. The central point of the counselling is the specific CIH counselling needs of the patient (see Fig. 3). In addition to the specific patient needs, the topics of nutrition, exercise and stress management are addressed as resources. If there is a need for further counselling on these three topics, referrals

are made to the specific counselling services for nutrition, exercise and psychooncology offered in all participating CCCs.

Please insert Fig 3 here

If required within a counselling session, easy to understand information leaflets developed in the preparation phase for the most relevant symptoms and CIH methods and/or prescriptions for phytotherapeutics are handed out to patients to promote patient activation. In case of recommendation of external applications, these can also be shown to the patient on site. Furthermore, counselling on where to find serious information about CIH on the internet as well as how to evaluate CIH providers and CIH products will be provided.

To standardize the counselling process a structured guideline for the consulting teams is developed before intervention starts and will be practiced in the training programme.

Control Group and reference group

The control group and the reference group receive conventional health care as usual provided by the CCCs (treatment as usual).

Participants

Eligible participants consist of outpatient oncology patients at the four Comprehensive Cancer Centres. (Tübingen-Stuttgart, Ulm, Freiburg and Heidelberg) of the Federal State of Baden-Wuerttemberg, Germany).

In- and exclusion criteria

The following inclusion criteria apply to the intervention group and the control group:

- Diagnosis of cancer incl. progression or recurrence within the last 6 months (all cancer entities can be included).
- Patient must be able to attend a counselling on site.
- Treatment at one of the participating CCCs or consultation for a second opinion
- Age ≥18 years
- Need for CIH counselling (attested by actively contacting the local counselling centre by email, phone or in person).
- Present signed declaration of consent to the study and to data protection (Informed consent).

Exclusion criteria:

- For intervention group: participation in control group

- Language or cognitive impairments preventing patients from completing questionnaires independently

Recruitment

Recruitment procedure in the intervention group:

Information materials on the project (as flyers, brochures, and a website) are displayed in outpatient clinics, day clinics and the other counselling centres at the four CCCs. In addition, the project will be presented at other counselling services, support groups and established formats (senior physician conferences, nursing service meetings, etc.) in each CCC. In the preparatory phase, information events will also be held at each CCC to report on the project. Patients are to become aware of the counselling via flyer, newspaper reports, word-of-mouth information, via the treating physicians and via actively approach by the study staff.

Recruitment procedure in the control group:

Patients in the control group are actively approached by study staff (doctors, nurses, study assistants) during waiting times in the rooms of the CCC as in day clinic. The patients are informed about the study and asked whether they would enter the control group. The time points of data collection as well as the instruments used to collect the primary and secondary outcomes correspond to those in the intervention group (T1, T2, T3). Since the counselling service is not yet established, inclusion in the intervention group is not yet possible. As compensation for their time, the patients are offered the CIH counselling service after the end of the observation period of 6 months (outside the study setting).

Recruitment procedure in the reference group:

As there is no primary data collection in the reference group, no recruitment is needed. Instead, secondary data from the AOK-BW will be used in pseudonymized form.

Intervention on provider level

Blended-learning training programmes for counselling teams

The training programme is designed as blended-learning with online (asynchronous) and onsite (synchronous) formats such as webinar or face-to-face format. The contents of the training program were developed during the preparatory phase of the project on the basis of existing guidelines and expertise from two previous studies: the CONGO-study and the project KOKON. Data from KOKON (www.kompetenznetz-kokon.de) show the specific information that doctors need for good counselling [27] and how this can be implemented successfully [28], whereas CONGO focused. on nursing applications in the context of supportive cancer care [29 30]. The online content of CCC-Integrativ is presented through

an online learning management system (ILIAS-software). Training consists of evidence-based text material, live lectures and asynchronous lectures on individual CIH methods and of communication training. For the latter, training with simulation patients was integrated into the synchronous online formats. Structure and overall contents of the blended-learning training programme will be presented in detail a separate publication (in preparation).

Tool box for counselling teams

In order to achieve standardized and evidence-based counselling on CIH, specific symptom-driven guidelines for the most relevant symptoms (e.g. on chemotherapy induced nausea and vomiting) are developed on the basis of a structured literature research and expert consensus process. Altogether, 20 symptom-driven guidelines will be developed to provide a basic counselling source of information for the counselling teams.

Knowledge database on CIH

Within the KOKON Projekt (KOKONbase) a knowledge database on clinical efficacy and safety of complementary medicine in oncology was implemented. The contents of the database are linked to the international information portal of the CAM Cancer Project [31] and including free access via Onkopedia (https://www.onkopedia.com/de), the guideline portal of the German Society for Haematology and Medical Oncology. During the CCC-Integrativ Study the database will be constantly updated and supplemented with content on complementary nursing.

Interprofessional team building

Interprofessional counselling requires interprofessional team building of the counselling teams (nurse and physician). Therefore, workshops to promote interprofessional collaboration using the TEAM^c approach[32 33] are performed for each counselling team either onsite or online (synchronous) and complement the blended-learning programme.

Intervention on system level

As part of the system-level intervention, basic training on CIH is provided to healthcare professionals on a cross-sectoral level, ranging from university hospitals to primary care. The target groups are e.g. health workers in the CCCs, general practitioners and ambulatory care services. The aim of this training is to achieve a common understanding on the term CIH, discuss possible indications for the application as well as potential risks of CIH based on scientific literature and to address reliable sources of information on CIH. The number of training sessions and the exact target persons are not fixed in

advance, but will be determined by the demand of the different groups of actors during the intervention phase.

Primary and secondary outcomes on patient level

Primary outcome

The primary outcome parameter with regard to assessing the intervention effect is patient activation, operationalized by the Patient Activation Measure questionnaire of the German version (PAM-13-D) after 3 months (T2) [7 34]. The PAM-13 is widely used internationally, also within the oncology setting, and has been validated in German. It has shown to be a valid and reliable predictor of patient activation [34 35]. The PAM-13 measures the extent to which a patient actively participates in his or her treatment. Furthermore, it measures the patient´s active role in managing his/her own health and the extent to which he/she feels competent to fulfil that role. This construct includes aspects of health and patient knowledge, skill, and confidence for self-management and therefore allows us to omit other concept-specific questionnaires, reducing the patient´s overall burden of filling out questionnaires. A correlation between a higher level of patient activation (measured by the PAM-13) and better health outcomes, improved treatment adherence and a reduction in healthcare costs has been shown [36]. The PAM-13-D is completed by the patients themselves. In the control and the intervention group PAM-13-D will be measured at baseline (T1), after 3 months (T2) and 6 months follow-up (T3) according to table 1.

Secondary outcomes

One part of the secondary outcomes at patient level is collected via primary data collection, another part is based on routine data.

Secondary outcomes via primary data collection include quality of life, self-efficacy, depression, fatigue, symptom management, health literacy and health care utilization. All outcomes will be measured with validated instruments and assessed at baseline (T1), after 3 months (T2) and 6 months follow-up (T3) as described in table 1.

patients

outcomes	instrument	items	T1 Baseline	T2 3 months	T3 6 months follow up
primary outcome					
patient activation	PAM-13	13	x	x	x
secondary outcomes					
health status	EQ 5D	5	x	x	x
self-efficacy	SES6G	6	x	x	x
unmet needs	NEQ	27	x		
quality of life	EORTC-QLQ-C30 (only question 29 +30)	2	x	x	x
depression, agitation	PHQ-9	9	x	x	x
fatique	EORTC FA 12	12	x	x	x
measure yourself concerns and wellbeing	MYCaW	7	x	x	x
symptoms, therapy-assisted	MIDOS2	11	x	x	x
single item literacy screener	SILS	1	x		
health care utilization questionaire	HCU-Q (adapted)	11	x	x	x
sociodemographic data		26	x		
medical data		10	x	x	x

Tab. 1 Primary and secondary outcomes at patient level in the intervention and control group

The following clinical parameters, not shown in Tab. 1, are also collected at patient level (survey dates are given in brackets): diagnosis including TNM classification (T1), date of primary diagnosis of cancer (T1), if applicable, diagnosis of recurrence/progression (T1, T2, T3), ongoing or planned oncological therapies (chemotherapy, surgery etc.) (T1, T2, T3).

The analyses of the routine data are based on claims data collected for billing purposes from the medical insurance company - the Allgemeine Ortskrankenkasse Baden-Wuerttemberg (AOK BW). The AOK BW is the fifth largest health insurance fund in Germany and the largest in Baden-Wuerttemberg with approximal 4.5 million insured persons. These data come from all AOK BW-insured persons who had received an ICD-10 cancer diagnosis in the relevant time periods. Claims data cover the inpatient and outpatient care, prescription drugs, therapeutics remedies and medical aids.

Sample size

The number of cases for the intervention group and control group was initially determined on the basis of pragmatic considerations (existing staff and structures, feasibility, statistical power) regarding the implementation character of the study. Thus, the sample size of the intervention group was set at 250 patients per CCC (total n=1000), while 500 patients (n=125 per site) were calculated for the control

group. For the reference group, a total of 2000 patients are to be analysed (n=500 patients per CCC) (see Fig.4).

Consistent data on distribution of the primary endpoint PAM-13 is found in the literature. In a paper by Rademakers [37], sample size and standard errors are each given for a Danish, a Dutch, a German and a Norwegian sample with a total of approx. 3500 patients. Back-calculation to the standard deviation yields values between 14.49 and 14.61. In a study by Bates [38], standard deviations between 14.3 and 14.8 were found. We therefore conservatively assume a standard deviation of 15 in our planning. In the first study mentioned, a difference of 6.5 points was seen under intervention (68.5 vs. 75.0). With a study effect in the control group (e.g. caused by using the instrument twice) of 30% (= 1.95 points) we could expect a difference of 4.55 points. Conservatively assuming a difference of 3 points and the already justified standard deviation of 15 points in the main outcome parameter PAM-13 between intervention and control group, a sample size of 1185 patients is calculated (type 2 error of 0.10 and ratio of 2:1 between intervention n=790, and control group, n=395). Assuming a drop-out of 20%, 988 patients must be included in the intervention group and 494 must be included in the control group. Thus, we aim to recruit 1000 patients in the intervention group and 500 patients in the control group.

With the sample size of 1500 patients (1000+500) minus 20% drop outs, a group difference of 3 points on the PAM-13 would have a power of 90%. By adjusting the baseline in a covariance analysis, a degree of freedom is lost, but it can be assumed that due to the reduction in dispersion after adjustment, the power should be even higher.

Please insert Fig 4 here

Data analysis

Electronic data collection from the patients´ questionnaires is recorded using REDCap (Research Electronic Data Capture) a browser-based software for clinical and translational research [39]. All quantitative data will be transformed and imported into SPSS for further statistical analysis.

Analysis of primary data: The primary outcome parameter for the comparison of the intervention group with the control group is patient activation, which is measured by the Patient Activation Measure PAM-13 after 3 months. For the primary outcome analysis of covariance with baseline adjustment and adjustment for study centre as a categorical variable will be applied. Secondary analyses of the primary endpoint include an additional analysis of covariance adjusted for age (quantitative), sex, diagnosis, and disease stage as well as a mixed model for T1, T2 and T3 to analyse the temporal trend and test for maintenance effects at T3. Quantitative secondary endpoints will be

analysed analogously to PAM, categorical data will be analysed using identically adjusted logistic regression models. For analyses of the secondary outcomes, p-values are reported but are not to be interpreted confirmatorily. The primary analysis population will be the intent to treat population which includes all subjects with baseline assessment. Multiple imputation methods are used to replace missing values. Imputation will be based on baseline values. Confirmatory interim analyses are not planned. The level of significance will be 0.05 (two-sided).

Analysis of secondary data: Secondary data as described above will be compared between the intervention, the control and the reference group. In a first step, the control group will be compared to the reference group to assess possible selection bias and study effects. In a second step, the intervention group is compared to the reference group with adjustments derived from the first step comparison.

Process evaluation

In addition to the analyses mentioned above, a detailed qualitative-quantitative process evaluation will be conducted. This process evaluation is based on the Consolidated Framework for Implementation Research (CFIR), a recognized framework in implementation research [40]. In addition to evaluating the the perspectives of patients and providers on the counselling sessions, the process evaluation aims to identify significant barriers and facilitating factors for a successful implementation as well as for a later transferability of the intervention into standard care. All details regarding the concept and planned analyses can be found in a separate publication (in preparation).

Health economic evaluation

To evaluate the intervention´s efficiency, a cost effectiveness and cost utility analysis will be performed. To that end, the intervention and control group will be compared on both the absolute and incremental costs and effects of care. The main analysis is conducted from the perspective of the insurees of the statutory health insurances, meaning that costs and effects incurred by the statutory health insurance as well as by the patients themselves are counted. A societal perspective will be considered in a sensitivity analysis. On the cost side, the intervention specific costs, the costs of inpatient and outpatient care, the costs of prescription drugs, therapeutic remedies, aids, informal care, productivity losses and CIH are considered. Data is collected using an adapted version of the healthcare utilization questionnaire (HCU-Q) [41] and supplemented for part of the intervention and control group with information from the AOK BW routine data (billing data). Using an incremental cost-effectiveness ratio, the efficiency of the intervention is quantified. This enables statements to be made about the programme´s incremental costs per increment in quality of life and patient activation. Data from the reference group serves to supplement and validated the data and analyses used and helps

with contextualizing the results. The time horizon of the analysis is 6 months. Both costs and effects are discounted at 3% p.a.. In a deterministic sensitivity analysis, discounting rates of both 0% and 5% will be applied. Uncertainty will be accounted for in sensitivity as well as subgroup analyses.

Trial Status

Recruitment of the control group (n=502) was successfully completed in January 2021. The counselling for the intervention group started in January 2021. Last-Patient out is expected for March 2022. Analyses will be completed in December 2022.

Patient and public involvement

Patients from different oncological support groups were involved during the preparation of the study. The questionnaires used in the study as well as patient informational materials on CIH were developed in cooperation with support groups. Given the nature of our naturalistically controlled trial, the public and media were addressed actively with information on the project, lectures on CIH were held on patient days etc. in order to achieve our recruitment goal.

Ethical considerations, data protection aspects and dissemination

The study has been approved by the appropriate Institutional Ethical Committee of the participating medical faculties (Freiburg, Heidelberg, Tuebingen, Ulm), No. 658/2019BO1.

Before study entry all study participants are comprehensively informed about the project and a written declaration of consent for participation is obtained. Access to the new form of care is open to all patients, regardless of their particular statutory health insurance company. There are no additional costs or disadvantages for the participating patients. Patients' participation is voluntary. Participants will be informed in writing and verbally about the nature and scope of the planned procedure before the start of the study. Given informed consent, including the processing of patients´ data, documented by signing the consent form, can be withdrawn at any time and without giving reasons. Disclosure takes place in pseudonymized form for the purpose of analysis. The names of the participating patients and all other confidential information are subject to medical confidentiality and the provisions of the EU Data Protection Regulation of 25th May 2018.

A comprehensive data protection concept with a data set prescription of the routine data was developed for the handling, transfer, and analysis of all data within the project. Contracts of data protection and for order processing were concluded with the partners. The partners are guided by the

applicable standard for research projects and by the applicable data protection regulations. An approval according to §75 SGB 5 for the transfer of social data for research was obtained from the AOK Baden-Wuerttemberg.

The results of the study will be presented to academic audiences through publication in peer-reviewed journals and presentations at national and international conferences. The results will also be disseminated in the community. The study is being conducted in collaboration with a health insurance company. The process evaluation will also include the identification of significant barriers and facilitating factors for implementation. If the evaluation of the project is successful, a transfer into standard care is planned.

Authors' contributions

SJ, CM, JV and RS conceptualized the design of the trial and interventions. All authors except PM, JF, KT are involved in the final elaboration of the intervention components. PM conducted the sample size calculation and contributed to the section on statistical methods. JV, DF and SJ wrote the first draft of this article. RS, CM, PM, NK, MH, JF, KK, HB, BG and KT critically revised it. JF contributed to the section on the health economic evaluation. All authors read and approved the final version of the manuscript.

Collaborators

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Competing interests statement.

The authors JV, DF, RS, CM, PM, NK, MH, JF, KK, HB, BG and KT and SF declare that they do not have any competing interests.

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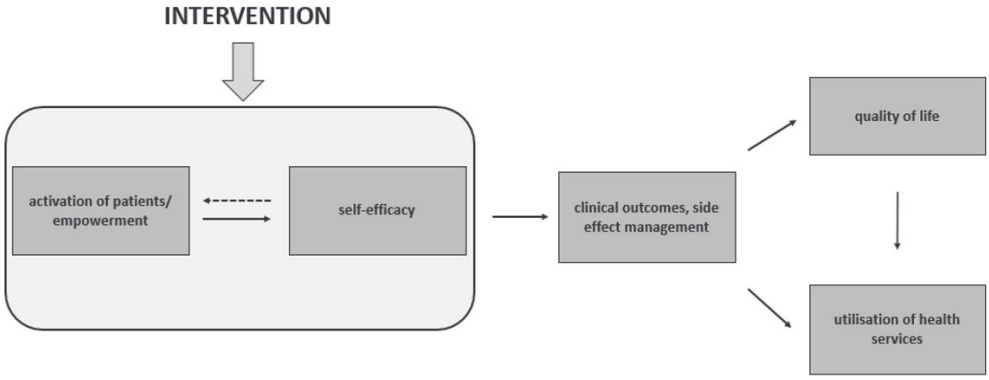

Fig. 1 Theoretical model for outcomes on patient level

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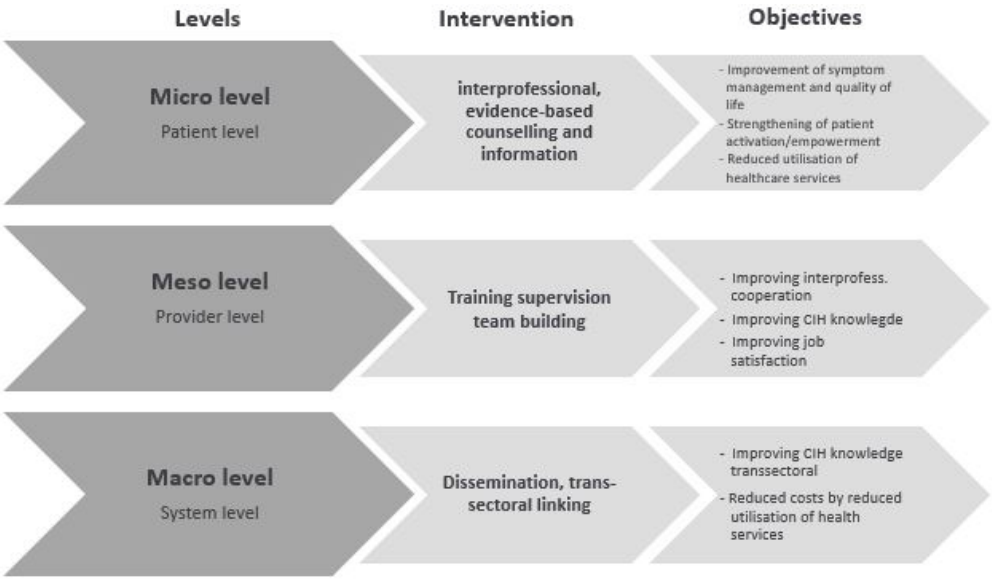

Fig. 2 Outcomes framework for CCC-Integrativ

165x97mm (96 x 96 DPI)

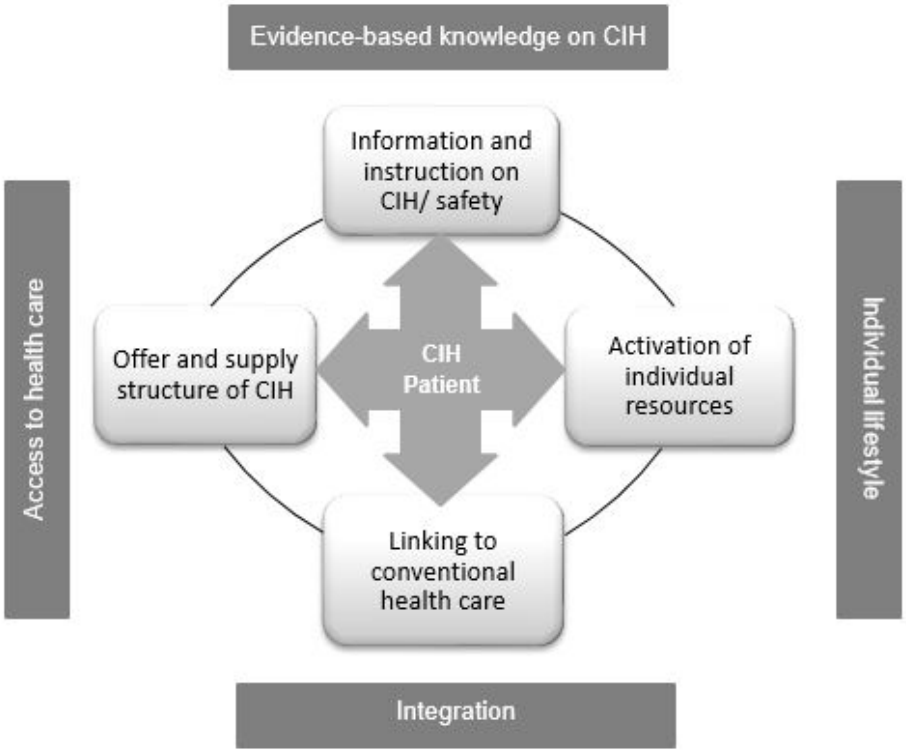

Fig. 3 CCC-integrative counselling model of the intervention

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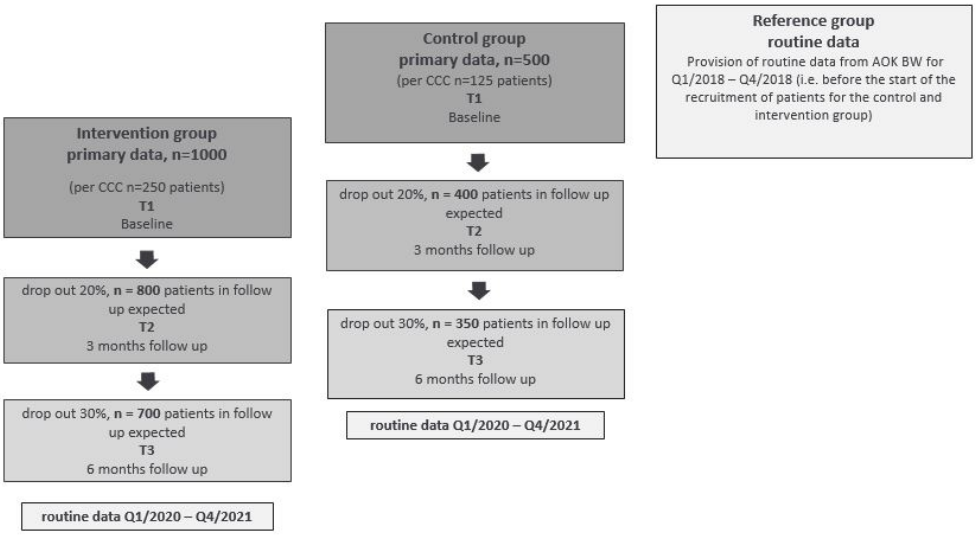

Fig. 4 Flowchart data collection (T1-T3)/ routine data

223x121mm (96 x 96 DPI)

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Interprofessional evidence-based counselling programme for Complementary and Integrative Health Care in cancer patients–study protocol for the controlled implementation study CCC - Integrativ

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Abstract

Introduction

According to international literature, cancer patients wish to have information on complementary and integrative health care (CIH). Medical guidelines recommend actively approaching cancer patients discussing potential benefits and risks of individual CIH methods. While some CIH methods, e.g. acupuncture and yoga, have been proven effective in high-quality studies, other CIH methods lack studies or bear the risk of interactions with chemotherapeutics, e.g. herbal drugs. Therefore, an evidence-based interprofessional counselling programme on CIH will be implemented at four Comprehensive Cancer Centres (CCC) in the federal state of Baden-Wuerttemberg, Germany.

Methods and analysis

A complex intervention consisting of elements on patient, provider and system levels will be developed and evaluated within a multilayer evaluation design with confirmatory evaluation on patient level. Patients with a cancer diagnosis within the last 6 months will receive 3 individual counselling sessions on CIH within 3 months (=intervention on patient level). The counselling will be provided by an interprofessional team of medical and nursing staff. For this purpose, an intensive online training programme, a CIH knowledge database and an interprofessional team-building process were developed and implemented (=intervention on provider level). Moreover, training events on the basics of CIH are offered in the outpatient setting (=intervention on system level). Primary outcome of the evaluation at the patient level is patient activation measured with the PAM-13 after 3 months. Secondary outcomes, e.g. quality of life, self-efficacy and clinical parameters, will be assessed at baseline, after 3 months and at 6 months follow-up. The intervention group (n=1000) will be compared with a control group (n=500, treatment as usual, no CIH counselling. The outcomes and follow-up times in the control group are the same as in the intervention group. Moreover, the use of health services will be analysed in both groups using routine data. A qualitative-quantitative process evaluation as well as a health economic evaluation will identify relevant barriers and enabling factors for later roll-out.

Ethics and dissemination.

The study has been approved by the appropriate Institutional Ethical Committee of the University of Tuebingen, No. 658/2019BO1. The results of these studies will be disseminated to academic audiences and in the community.

Registration

German Clinical Trials Register (DRKS), DRKS00021779 registered on 12th June 2020

Keywords

Oncology, comprehensive cancer centre, complementary medicine and integrative health care, Interprofessional, integrative medicine, supportive therapy, counselling intervention, patient activation, controlled study

Strengths and limitations of this study

- For the first time, a transsectoral, interprofessional, evidence-based counselling programme for Complementary and Integrative Health Care will be implemented at Comprehensive Cancer Centres Baden-Wuerttemberg, Germany.
- The complex evaluation will be conducted at the patient, provider, and system levels within a controlled design.
- The guiding (confirmatory) hypothesis is at the patient level measured by patient activation (PAM-13).
- Randomization at the patient level is not possible due to the naturalistic study design.
- On the provider level, a training programme for the counselling team is designed and evaluated as blended-learning programme with online (asynchronous) and onsite (synchronous) formats.

Introduction

According to previous international studies, there is a high use of naturopathic/complementary approaches (CIH= complementary and integrative health care) among cancer patients. A meta-analysis shows that about 40% of all oncology patients use CIH [1]; for patients with breast cancer, up to 80% can be assumed [2]. For some CIH methods, positive effects in cancer patients have been shown in RCTs and meta-analyses, e.g. meditation, particularly mindfulness-based stress reduction for mood disturbance and depression, Yoga and Tai Ji for improving quality of life and fatigue, acupuncture and acupressure to reduce nausea and pain, individual phytotherapeutics and herbal medicines such as ginger for nausea [3-5]. In addition, many of these CIHs have the potential to empower and activate patients as well as improve self-efficacy [6]. The promotion of patient activation [7], self-management strategies [8], and health literacy [9] have been shown to empower patients with cancer [10] and contribute to reducing the use of health services [11]. Thereby, patient activation is considered as an overarching concept including knowledge, skill and confidence for self-management in chronic diseases [12].

However, CIH also entails clinical risks; e.g. phytotherapeutics and micronutrients, especially in high doses (vitamins, selenium), can interact with chemotherapy [13 14]. A further risk arises as patients often seek help outside conventional health care structures (e.g. alternative practitioners) with unforeseeable health consequences such as delayed diagnosis and failure to provide indicated treatments [15 16]. In addition, there are risks for economic harm as the majority of costs for CIH procedures are not covered by public insurance [17]. Between 20 and 77% of cancer patients do not inform their treating physicians when using CIH [18-20]. This lack of communication may endanger the doctor-patient relationship and contribute to the discontinuation of conventional therapy [15 21 22].

Patient-centred care for cancer includes supportive measures that enable patients to cope as well as possible with their diagnosis and therapy, including its side effects [23-25]. These supportive measures may also include CIH methods. Therefore, according to current German S3 guidelines on breast cancer, cervical cancer, ovarian cancer, as well as the guidelines on complementary medicine in the treatment of oncology patients [3], palliative medicine and psycho-oncology, there is a consensus recommendation that all patients should be asked about their need for information on their use of CIH procedures [3 26]. However, this recommendation contrasts with a lack of human resources in oncologic clinics and insufficient CIH knowledge among medical and nursing staff. Therefore, this recommendation cannot be implemented properly in everyday care, and the topic of CIH is often not sufficiently or not at all addressed in patient communication. The aim of the CCC-Integrativ study is to develop and evaluate a complex intervention as defined by elements on patient, provider and system levels to improve CIH for cancer patients. In detail, we aim to evaluate whether interprofessional counselling about CIH improves patient activation and patients' confidence in contributing to their health.

Methods and analysis

Theoretical framework and objectives

The project pursues a health services research approach, and therefore, objectives and interventions will be differentiated in relation to the patient-, provider- and system-level or -seen from a health services research perspective- in relation to micro-, meso- and macro-level.

On the **patient (micro)-level,** the project aims to activate patients and promote their self-efficacy (see Fig.1). It is expected that by enhanced empowerment, the patient´s quality of life and clinical outcomes will be improved, which can, in turn, lead to reduced use of health services in the further course [27].

Please insert Fig 1 here

Objectives at the **provider (meso)-level** are an improvement of knowledge and communication skills regarding CIH as well as improved job satisfaction and interprofessional collaboration between doctors and nurses within the care setting.

At the system (**macro)-level,** the objectives include cost reduction and a transsectoral increase in knowledge of CIH (see Fig.2).

Please insert Fig 2 here

Setting and Study design

Within the CCC-Integrativ study, an evidence-based interprofessional counselling programme on CIH for oncology patients will be implemented and evaluated at the four Comprehensive Cancer Centres (CCC) (Freiburg, Heidelberg, Tuebingen-Stuttgart, Ulm) in Baden-Wuerttemberg. Comprehensive Cancer Centres are implemented at most university hospitals in Germany to ensure a high standard of medical care for oncology patients and are considered centres of excellence in oncology.

As described above, CCC-Integrativ will be evaluated at patient, provider and system levels, whereby the confirmatory testing will be on patient level. The accompanying process evaluation, which also analyses aspects of the micro-, meso- and macro- level, is presented in detail in a separate protocol.

The total study duration is 36 months. For the individual study participant, the study lasts 6 months, including the follow-up survey (intervention group and control group). The preparation period runs from months 1-6, the primary data collection in the control group from months 7 to 18 (recruitment months 7-9). Data collection in the intervention group from months 13-30 (recruitment months 13-24).

The intervention group is compared with a control group and a reference group. The control group is recruited 6 months before the start of the intervention phase. Identical outcome parameters are collected. The reference group results from claims data of the statutory health insurance of the Allgemeine Ortskrankenkasse Baden-Wuerttemberg (AOK BW) without additional primary data collection. The reference group allows us to examine the representativity of the study population compared to the target population (members of AOK-BW). If differences between the control group and the reference group are detected, i.e. study effects are present, these will be accounted for in the comparison of the reference group with the intervention group to disentangle study effects and intervention effects.

A classical parallel-group design with randomization at the patient level did not seem feasible, as previous studies have shown that patients with high use of or need for counselling on CIH cannot be randomized [24]. Also, cluster randomization had to be rejected due to possible contamination problems. Given that all four participating CCCs are located in the same federal state (Baden-Wuerttemberg, Germany) and thus within a few hours' drive, we could not exclude that patients treated in one CCC would seek counselling in another participating CCC. Thus, we decided to choose different time intervals within the study period for control and intervention patients.

Intervention on patient level

The intervention consists of an interprofessional, evidence-based counselling service for patients with counselling needs in the field of CIH. Key points of the counselling are information giving and guidance for health needs in the context of CIH to increase patient activation and self-efficacy.

The counselling concept takes into account the patient's resources, integrates conventional health care (as provided by the CCCs in routine care) and provides information on CIH and care services with CIH. The central point of the counselling is the specific CIH counselling needs of the patient (see Fig. 3). In addition to the specific patient needs, nutrition, exercise and stress management are addressed as resources. If there is a need for further counselling on these three topics or CIH counselling sessions were to bring up psychological distress for any patients, referrals are made to the specific counselling services for nutrition, exercise and psycho-oncology offered in all participating CCCs.

The CIH counselling service is provided by interprofessional teams consisting of specially trained physicians and nurses at each of the four participating CCCs and is integrated into the existing structures at the four participating CCCs in Freiburg, Heidelberg, Tuebingen-Stuttgart und Ulm. Our concept for counselling follows an evidence-based approach, integrating patient preferences and individual medical and nursing expertise.

Intervention and control group

Intervention group

Patients of the intervention group will be offered interprofessional individual counselling. Eligible patients will receive at least three counselling sessions on evidence-based nursing and/or medical interventions within three months. The first counselling session will be face-to-face and interprofessional and is planned for a duration of 60 minutes. The subsequent two counselling sessions may be mono-professional and performed by telephone or as video counselling with a duration of approximately 30 minutes.

Please insert Fig 3 here

If required within a counselling session, easy to understand information leaflets developed in the preparation phase for the most relevant symptoms and CIH methods and/or prescriptions for phytotherapeutics are handed out to patients to promote patient activation. In case of recommendation of external applications, these can also be shown to the patient on-site. Furthermore, counselling on where to find trustworthy information about CIH on the internet as well as how to evaluate CIH providers and CIH products will be provided.

To standardize the counselling process, a structured guideline for the consulting teams is developed before the intervention starts and will be practised in the training programme.

Control Group and reference group

The control group and the reference group receive conventional health care as usual provided by the CCCs (treatment as usual).

Participants

Eligible participants consist of outpatient oncology patients at the four Comprehensive Cancer Centres (Tuebingen-Stuttgart, Ulm, Freiburg and Heidelberg) of the Federal State of Baden-Wuerttemberg, Germany).

In- and exclusion criteria

The following inclusion criteria apply to the intervention group and the control group:

- Diagnosis of cancer incl. progression or recurrence within the last 6 months (all cancer types can be included).
- The patient must be able to attend counselling on site.

- Treatment at one of the participating CCCs or consultation for a second opinion
- Age ≥18 years
- Need for CIH counselling (attested by actively contacting the local counselling centre by email, phone or in-person).
- A present signed declaration of consent to the study and to data protection (Informed consent).

Exclusion criteria:

- For intervention group: participation in the control group
- Language or cognitive impairments preventing patients from completing questionnaires independently

Recruitment

Recruitment procedure in the intervention group:

Information materials on the project (as flyers, brochures, and a website) are displayed in outpatient clinics, day clinics and the other counselling centres at the four CCCs. In addition, the project will be presented at other counselling services, support groups and established formats (senior physician conferences, nursing service meetings, etc.) in each CCC. In the preparatory phase, information events will also be held at each CCC to report on the project. Patients are to become aware of the counselling via flyers, newspaper reports, word-of-mouth information, via the treating physicians and via being actively approached by the study staff.

Recruitment procedure in the control group:

Patients in the control group are actively approached by study staff (doctors, nurses, study assistants) during waiting times in the rooms of the CCC of the day clinic. The patients are informed about the study and asked whether they would enter the control group. The time points of data collection as well as the instruments used to collect the primary and secondary outcomes correspond to those in the intervention group (T1, T2, T3). Since the counselling service is not yet established, inclusion in the intervention group is not yet possible. As compensation for their time, the patients are offered the CIH counselling service after the end of the observation period of 6 months (outside the study setting).

Recruitment procedure in the reference group:

As there is no primary data collection in the reference group, no recruitment is needed. Instead, secondary data from the AOK-BW will be used in pseudonymized form.

Intervention on provider level

Blended-learning training programmes for counselling teams

The training programme for counselling teams is designed as blended-learning with online (asynchronous) and onsite (synchronous) formats such as webinars or face-to-face format. The contents of the training program were developed during the preparatory phase of the project based on existing guidelines and expertise from two previous studies: the CONGO study and the project KOKON. Data from KOKON (www.kompetenznetz-kokon.de) show the specific information that doctors need for good counselling [28] and how this can be implemented successfully [29], whereas CONGO focused on nursing applications in the context of supportive cancer care [30 31]. The online content of CCC-Integrativ is presented through an online learning management system (ILIAS-software). Training consists of evidence-based text material, live lectures and asynchronous lectures on individual CIH methods and of communication training. For the latter, training with simulation patients was integrated into the synchronous online formats. The structure and overall contents of the blended-learning training programme will be presented in detail in a separate publication (in preparation).

Tool box for counselling teams

In order to achieve standardized and evidence-based counselling on CIH, specific symptom-driven guidelines for the most relevant symptoms (e.g. on chemotherapy-induced nausea and vomiting) are developed on the basis of structured literature research and expert consensus process. Altogether, 20 symptom-driven guidelines will be developed to provide a basic counselling source of information for the counselling teams.

Knowledge database on CIH

Within the KOKON Project (KOKONbase), a knowledge database on clinical efficacy and safety of complementary medicine in oncology was implemented. The contents of the database are linked to the international information portal of the CAM Cancer Project [32] and include free access via Onkopedia (https://www.onkopedia.com/de), the guideline portal of the German Society for Haematology and Medical Oncology. During the CCC-Integrativ Study, the database will be constantly updated and supplemented with content on complementary nursing.

Interprofessional team building

Interprofessional counselling requires interprofessional team building of the counselling teams (nurse and physician). Therefore, workshops to promote interprofessional collaboration using the TEAM^c approach[33 34] are performed for each counselling team, either onsite or online (synchronous) and complement the blended-learning programme.

Intervention on system level

As part of the system-level intervention, basic training on CIH is provided to healthcare professionals on a cross-sectoral level, ranging from university hospitals to primary care. The target groups are, e.g. health workers in the CCCs, general practitioners and ambulatory care services. The aim of this training is to achieve a common understanding of the term CIH, discuss possible indications for the application and potential risks of CIH based on scientific literature and to address reliable sources of information on CIH. The number of training sessions and the exact target persons are not fixed in advance but will be determined by the demand of the different groups of healthcare professionals during the intervention phase.

Primary and secondary outcomes on patient level

Primary outcome

The primary outcome parameter for assessing the intervention effect is patient activation, operationalized by the Patient Activation Measure questionnaire of the German version (PAM-13-D) after 3 months (T2) [7 35]. The PAM-13 is widely used internationally, also within the oncology setting, and has been validated in German. It has been shown to be a valid and reliable predictor of patient activation [35 36]. The PAM-13 measures the extent to which a patient actively participates in his or her treatment. Furthermore, it measures the patient´s active role in managing his/her own health and the extent to which he/she feels competent to fulfil that role. This construct includes aspects of health and patient knowledge, skill, and confidence for self-management and therefore allows us to omit other concept-specific questionnaires, reducing the patient´s overall burden of filling out questionnaires. A correlation between a higher level of patient activation (measured by the PAM-13) and better health outcomes, improved treatment adherence and a reduction in healthcare costs has been shown [37]. The PAM-13-D is completed by the patients themselves. In the control and the intervention groups, PAM-13-D will be measured at baseline (T1), after 3 months (T2) and 6 months follow-up (T3) according to table 1.

Secondary outcomes

One part of the secondary outcomes at patient level is collected via primary data collection; another part is based on routine data. Secondary outcomes via primary data collection include quality of life, self-efficacy, depression, fatigue, symptom management, health literacy and health care utilization. All outcomes will be measured with validated instruments and assessed at baseline (T1), after 3 months (T2) and 6 months follow-up (T3) as described in table 1.

patients					
outcomes	**instrument**	**items**	**T1 Baseline**	**T2 3 months**	**T3 6 months follow up**
primary outcome					
patient activation	PAM-13	13	x	x	x
secondary outcomes					
health status	EQ 5D	5	x	x	x
self-efficacy	SES6G	6	x	x	x
unmet needs	NEQ	27	x		
quality of life	EORTC-QLQ-C30 (only question 29 +30)	2	x	x	x
depression, agitation	PHQ-9	9	x	x	x
fatique	EORTC FA 12	12	x	x	x
measure yourself concerns and wellbeing	MYCaW	7	x	x	x
symptoms, therapy-assisted	MIDOS2	11	x	x	x
single item literacy screener	SILS	1	x		
health care utilization questionnaire	HCU-Q (adapted)	11	x	x	x
sociodemographic data		26	x		
medical data		10	x	x	x

Tab. 1 Primary and secondary outcomes at patient level in the intervention and control group

The following clinical parameters, not shown in Tab. 1, are also collected at patient level (survey dates are given in brackets): diagnosis including TNM classification (T1), date of primary diagnosis of cancer (T1), if applicable, diagnosis of recurrence/progression (T1, T2, T3), ongoing or planned oncological therapies (chemotherapy, surgery etc.) (T1, T2, T3).

Secondary outcomes based on routine data are use of inpatient and outpatient health care services, prescription of drugs, days of incapacity to work.

Routine (=claims) data are collected for billing purposes from the medical insurance company - the Allgemeine Ortskrankenkasse Baden-Wuerttemberg (AOK BW). The AOK BW is the fifth largest health insurance fund in Germany and the largest in Baden-Wuerttemberg, with approximately 4.5 million insured persons. These data come from all AOK BW-insured persons who had received an ICD-10 cancer diagnosis in the relevant time periods.

Sample size

Consistent data on the distribution of the primary endpoint PAM-13 is found in the literature. In a paper by Rademakers [38], sample size and standard errors are each given for a Danish, a Dutch, a German and a Norwegian sample with a total of approx. 3500 patients. Back-calculation to the

standard deviation yields values between 14.49 and 14.61. In a study by Bates [39], standard deviations between 14.3 and 14.8 were found. We, therefore, conservatively assume a standard deviation of 15 in our planning. In the first study mentioned, a difference of 6.5 points was seen under intervention (68.5 vs 75.0). With a study effect in the control group (e.g. caused by using the instrument twice) of 30% (= 1.95 points), we could expect a difference of 4.55 points. Conservatively assuming a difference of 4 points and the already justified standard deviation of 15 points in the main outcome parameter PAM-13 between intervention and control group, a sample size of 669 patients is calculated (type 2 error of 0.10 and ratio of 2:1 between intervention n=446, and control group, n=223). Assuming a drop-out of 30%, 638 patients must be included in the intervention group, and 319 must be included in the control group. For pragmatic considerations regarding the implementation character of the study (existing staff, established structures), we aim to recruit 1000 patients in the intervention group and 500 patients in the control group (see Fig.4). With a sample size of 1500 patients (1000+500) minus 30% dropouts, a group difference of 3.2 points on the PAM-13 would have a power of 90%. By adjusting the baseline in a covariance analysis, a degree of freedom is lost, but it can be assumed that the power should be even higher due to the reduction in dispersion after adjustment.

For the reference group, health insurance data will be used

Please insert Fig 4 here

Data analysis

Electronic data collection from the patients´ questionnaires is recorded using REDCap (Research Electronic Data Capture), a browser-based software for clinical and translational research [40]. All quantitative data will be transformed and imported into SPSS for further statistical analysis.

Analysis of primary data outcomes: The primary outcome parameter for the comparison of the intervention group with the control group is patient activation, which is measured by the Patient Activation Measure PAM-13 after 3 months. For the primary outcome analysis of covariance will be applied with baseline adjustment and adjustment for study centre as a categorical variable. Secondary analyses of the primary endpoint include an additional analysis of covariance adjusted for age (quantitative), sex, diagnosis, and disease stage, as well as a mixed model for T1, T2 and T3 to analyse the temporal trend and test for maintenance effects at T3. Quantitative secondary endpoints will be analysed analogously to PAM, categorical data will be analysed using identically adjusted logistic regression models. For analyses of the secondary outcomes, p-values are reported but are not to be interpreted as confirmatory. The primary analysis population will be the intent to treat a population which includes all subjects with a baseline assessment. Multiple imputation methods are used to replace missing values. Imputation will be based on baseline values. Confirmatory interim analyses are not planned. The level of significance will be 0.05 (two-sided).

Analysis of routine data outcomes: Routine data outcomes as described above will be compared between the intervention, the control and the reference group. In a first step, routine data outcomes of the control group will be compared to the reference group to assess possible selection bias due to the fact that study patients are all treated at the CCCs.In a second step, routine data outcomes of the intervention group are compared to the control group with adjustments derived from the first step comparison.

Process evaluation

In addition to the analyses mentioned above, a detailed qualitative-quantitative process evaluation will be conducted. This process evaluation is based on the Consolidated Framework for Implementation Research (CFIR), a recognised framework in implementation research [41]. In addition to evaluating the perspectives of patients and providers on the counselling sessions, the process evaluation aims to identify significant barriers and facilitate factors for successful implementation and later transferability of the intervention into standard care. All details regarding the concept and planned analyses can be found in a separate publication (in preparation).

Health economic evaluation

To evaluate the intervention´s efficiency, a cost-effectiveness and cost-utility analysis will be performed. To that end, the intervention and control groups will be compared on both the absolute and incremental costs and effects of care. The main analysis is conducted from the perspective of the insurees of the statutory health insurances, meaning that costs and effects incurred by the statutory health insurance as well as by the patients themselves are counted. A societal perspective will be considered in a sensitivity analysis. On the cost side, the intervention specific costs, the costs of inpatient and outpatient care, the costs of prescription drugs, therapeutic remedies, aids, informal care, productivity losses and CIH are considered. Data is collected using an adapted version of the healthcare utilization questionnaire (HCU-Q) [42] and supplemented for part of the intervention and control group with information from the AOK BW routine data (billing data). Using an incremental cost-effectiveness ratio, the efficiency of the intervention is quantified. This enables statements to be made about the programme´s incremental costs per increment in quality of life and patient activation. Data from the reference group supplement and validate the data and analyses used and help contextualise the results. The time horizon of the analysis is 6 months. Both costs and effects are discounted at 3% p.a.. In a deterministic sensitivity analysis, discounting rates of both 0% and 5% will be applied. Uncertainty will be accounted for in the sensitivity as well as subgroup analyses.

Trial Status

Recruitment of the control group (n=502) was successfully completed in January 2021. The counselling for the intervention group started in January 2021. Last-Patient out is expected for March 2022. Analyses will be completed in December 2022.

Patient and public involvement

Patients from different oncological support groups were involved during the preparation of the study. The questionnaires and patient informational materials on CIH used in the study were developed in cooperation with support groups. Given the nature of our naturalistically controlled trial, the public and media were addressed actively with information on the project, and lectures on CIH were held on patient days etc., in order to achieve our recruitment goal.

Ethical considerations, data protection aspects and dissemination

The study has been approved by the appropriate Institutional Ethical Committee of the participating medical faculties (Freiburg, Heidelberg, Tuebingen, Ulm), No. 658/2019BO1.

Before study entry, all study participants are comprehensively informed about the project and a written declaration of consent for participation is obtained. Access to the new form of care is open to all patients, regardless of their particular statutory health insurance company. There are no additional costs or disadvantages for the participating patients. Patients' participation is voluntary. Participants will be informed verbally and in writing about the nature and scope of the planned procedure before the start of the study. Given informed consent, including the processing of patients´ data, documented by signing the consent form, can be withdrawn at any time and without giving reasons. Disclosure takes place in pseudonymised form for the analysis. The names of the participating patients and all other confidential information are subject to medical confidentiality and the provisions of the EU Data Protection Regulation of 25th May 2018.

A comprehensive data protection concept with a data set prescription of the routine data was developed for the handling, transfer, and analysis of all data within the project. Contracts of data protection and for order processing were concluded with the partners. The partners are guided by the applicable standard for research projects and by the applicable data protection regulations. Approval according to §75 SGB 5 for the transfer of social data for research was obtained from the AOK Baden-Wuerttemberg.

After completion of the analyses, the data will be made available upon reasonable request in anonymized form in accordance with the institutional regulations and the General Data Protection Regulation (exception is the health insurance data of the reference group).

The study results will be presented to academic audiences through publication in peer-reviewed journals and presentations at national and international conferences. The results will also be disseminated in the community. The study is being conducted in collaboration with a health insurance company. The process evaluation will also include the identification of significant barriers and facilitating factors for implementation. If the evaluation of the project is successful, a transfer into standard care is planned.

Authors' contributions

SJ, CM, JV and RS conceptualised the design of the trial and interventions. All authors except PM, JF, KT were involved in the final elaboration of the intervention components. PM conducted the sample size calculation and contributed to the section on statistical methods. JV, DF and SJ wrote the first draft of this article. RS, CM, PM, NK, MH, JF, KK, HB, BG and KT critically revised it. JF contributed to the section on the health economic evaluation. All authors read and approved the final version of the manuscript.

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Competing interests statement.

The authors JV, DF, RS, CM, PM, NK, MH, JF, KK, HB, BG and KT and SF declare that they do not have any competing interests.

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Figure legends

Fig. 1: Theoretical model for outcomes on patient level

Fig. 2: Outcomes framework for CCC-Integrativ

Fig. 3: CCC-Integrativ counselling model of the intervention

Fig. 4: Flowchart data collection (T1-T3)/ routine data

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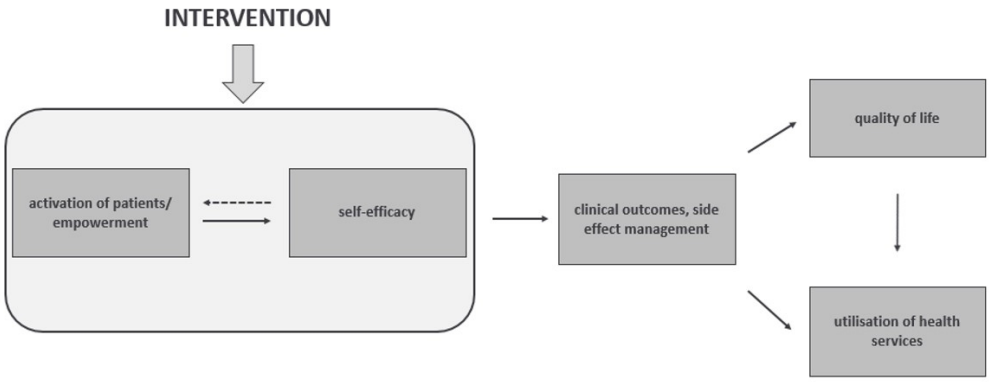

Fig. 1 Theoretical model for outcomes on patient level

308x122mm (95 x 95 DPI)

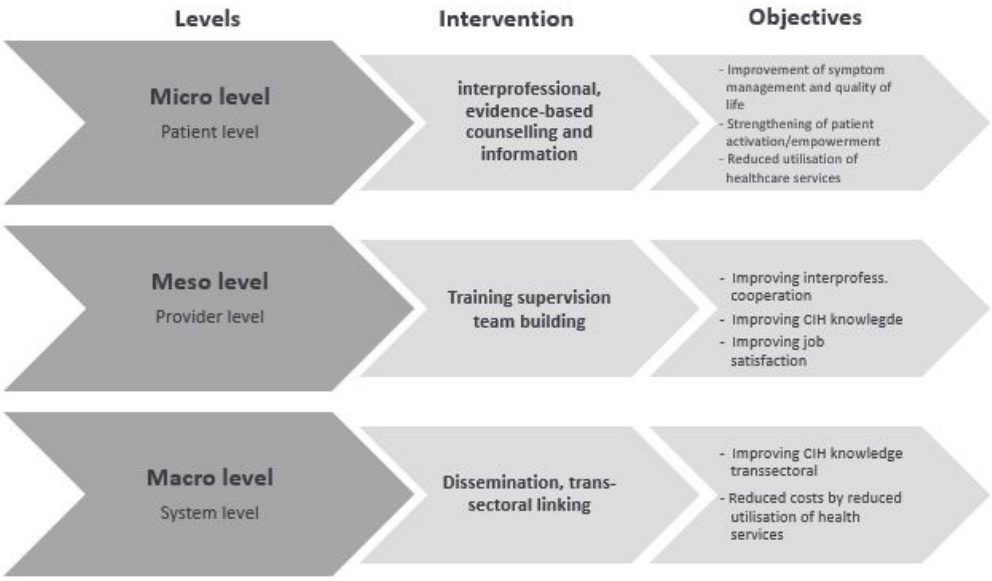

Fig. 2 Outcomes framework for CCC-Integrativ

165x97mm (96 x 96 DPI)

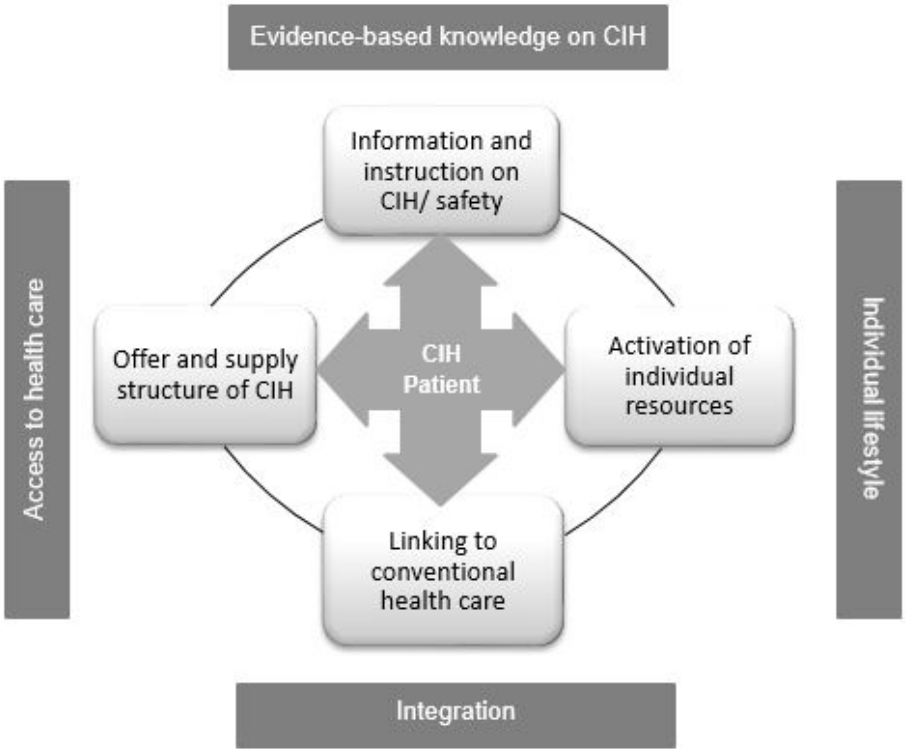

Fig. 3 CCC-Integrativ counselling model of the intervention

137x114mm (96 x 96 DPI)

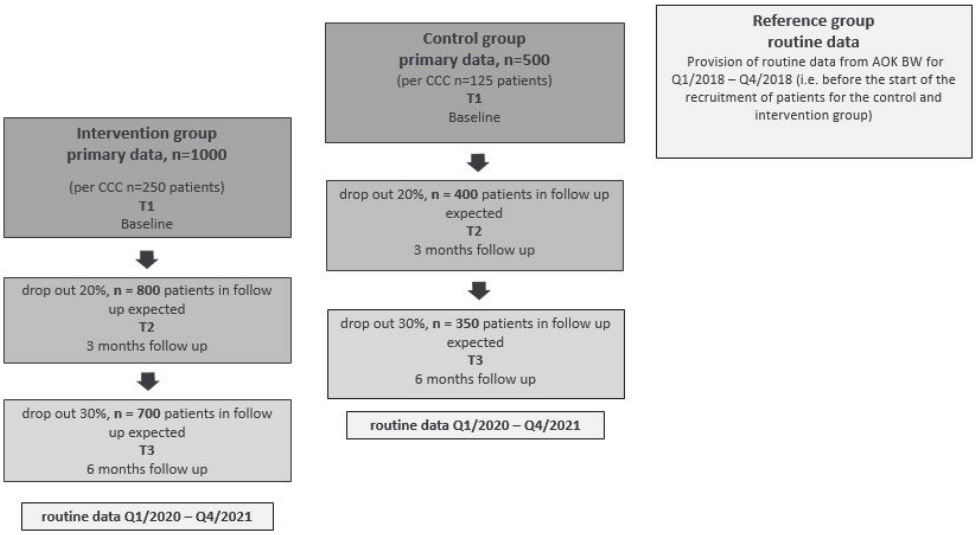

Fig. 4 Flowchart data collection (T1-T3)/ routine data

223x121mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5/6
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5/6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5/6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7/8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7/ 9/10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10/11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11/12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12/13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12/13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12/13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12/13

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12/13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14/15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14/15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14/15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14/15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14/15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14/15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.