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METHOD

Personalized Combined Nutrition & Exercise Intervention in Newly Diagnosed Cancer Patients - a Trial Protocol

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ABSTRACT

The prevalences of malnutrition and sarcopenia are high already at the time of cancer diagnosis and significantly impact on treatment outcomes. Here, we present the protocol of a multicenter, randomized controlled trial to evaluate the efficacy of personalized, combined nutrition and physical exercise interventions in parallel to first-line cancer treatment. A total of 472 patients will be included and randomized into one of the two study arms. In the intervention arm (A) patients will receive an individualized, needs-adapted preventive and supervised nutritional and exercise program over at least four and up to six months in parallel to cancer treatment. In the control arm (B), patients receive recommendations for physical activity, prescriptions and nutrition counseling in a non-supervised manner. The physical and nutritional status, as well as quality of life will be analyzed in all patients by a multi-dimensional

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assessment program, termed resource-oriented needs assessment (RONA), before and at distinct time points during and after the intervention period. The primary combined endpoint will be the reduction of needs for supportive care defined by the RONA score at the end of the first-line cancer treatment or after six months of study intervention whichever comes first.

ARTICLE HIGHLIGHTS

- Protocol for a large randomized controlled, multicenter trial including patients with all types of newly diagnosed cancer.
- The experimental arm provides personalized, needs-adapted combined nutrition and physical exercise interventions with start of and in parallel to the cancer treatment, whereas in the control arm, patients will be offered current standard of supportive care.
- Multidimensional assessments of the patients' nutrition status, physical fitness and quality of life will be performed by a battery of validated tools termed "resource-oriented needs assessment (RONA)" (German: Ressourcen-orientierte Bedarfsanalyse (RoBa))
- The main combined primary endpoint is a clinically meaningful reduction of the needs determined by the RONA at the end of the cancer treatment after a minimum of four to a maximum of six months after intervention start.
- The ultimate goal of this trial is to facilitate the implementation of early and combined personalized nutrition and exercise interventions in patients with newly diagnosed cancer into the clinical routine of cancer care in Germany.

PLAIN LANGUAGE SUMMARY

Many people with cancer already have malnutrition (not getting enough of the right nutrients) or sarcopenia (loss of muscle mass and strength) when they are first diagnosed. Both can make cancer treatment less effective and recovery more difficult. This study is testing whether a personalized and needs-adapted program of nutrition and exercise interventions, given alongside standard cancer treatment, can improve patients' health and quality of life. A total of 472 patients are planned to be included into the study and randomly assigned to one of the two study arms.

- Group A (intervention group): Patients will receive an individualized program tailored to their needs. This includes supervised nutrition and exercise support for at least four and up to six months while they undergo cancer treatment.
- Group B (control group): Patients will receive general advice and counseling on diet and exercise, but without ongoing supervision and adaptations.

Researchers will regularly measure nutrition, physical function, and quality of life using a structured assessment called *resource-oriented needs assessment* (RONA).

The main goal of the study is to see if the supervised program can reduce patients' needs for extra support after their camcer treatment by preventing or correcting nutrition and physical health problems during cancer treatment.

1. Background

Due to rising life expectancy, life styles and environmental factors, it is currently expected that one in two inhabitants in Germany will encounter cancer during lifetime [1]. Nevertheless, advancements in modern diagnostic and therapeutic modalities have steadily improved the outcomes of oncological treatments. However, the effectiveness and tolerability of most systemic cancer therapies depend on the patients' individual performance status including nutritional, muscular and psychological status as well as comorbidities [2,3]. In patients with a reduced performance status treatment per-plan is often limited by increased therapy-associated toxicities such as cytopenia, polyneuropathy, malnutrition, fatigue and increased infection rates [4–6]. Thus, treatment delays and consecutive dose reductions can limit the full potential of the intended treatment, and on the long term, also impair the patient's quality of life and rehabilitation capacity. On the other hand, a large body of clinical evidence has been generated which show the beneficial effects of nutritional support and physical exercise interventions in cancer patients [7]. However, due to structural processes and reimbursement issues these recommendations have so far not been implemented at every treatment site in Germany.

National and international clinical guidelines recommend early assessment of individual risks and immediate supportive care interventions by nutritional and physical exercise therapy [8–10]. These recommendations are based on numerous clinical trial data that have shown benefits for nutritional counseling and physical exercise interventions in cancer patients. While the majority of the published data have so far come from retrospective studies focusing on specific cancer entities and either investigated nutritional or physical exercise therapy separately, more recent trials have also addressed the combination of both interventions [11–13]. However,

most of the current data are separately available for patients with gynaecological, urological, and gastrointestinal carcinomas, revealing that both treatment types offer substantial benefits across various endpoints, including improvement in quality of life, reduction of treatment-related adverse events, lower malnutrition risk, and enhanced physical fitness [14–17]. Specifically, nutritional interventions have been successful applied to reduce malnutrition and therapy-related side effects while leading to improved quality of life in numerous studies [15,18,19]. For cancers with a high risk of cachexia, early and consistent nutritional therapy is particularly essential [8,20]. On the other hand, physical exercise therapy has been shown to significantly reduce the incidence of common chemotherapy-associated side effects such as fatigue, polyneuropathy, and cognitive dysfunction both during and after radio- and/or chemotherapy, ultimately improving quality of life [21,22]. A combined supportive intervention comprising of nutritional and physical exercise therapy may yield superior results compared to either intervention alone, as suggested by recent research with prostate or lung cancer patients [16,23,24]. However, the optimal timepoint and composition of the combined supportive treatment is currently unknown as well as if cancer patients in general would benefit from it.

Despite the increasing demand and mounting evidence for nutritional and physical exercise therapy mediated benefits in cancer patients, national cancer centers in Germany have currently implemented these supportive care options to various extends. This high regional variability is mainly based on a lack of standardized re-imbursement and facility structures. On the other hand, professional education programs especially for exercise therapy in oncology have in the recent years led to increased numbers of health-care professionals that could offer evidence-based and structured exercise treatments.

The randomized, controlled multicenter INTEGRATION trial aims to close these gaps by implementing a cross-sectoral, needs-adapted, integrated approach for nutrition and physical exercise therapy in newly diagnosed cancer patients – regardless of the entity, and as soon as the first-line systemic cancer treatment starts. The primary study aim is to demonstrate a reduced individual need for supportive care at the end of the first-line cancer treatment. To this extend, patients will be analyzed by a multi-dimensional assessment program to evaluate the physical, nutritional and quality of life status before and the end of the intervention as well as up to one year after study inclusion.

2. Methods

2.1. Study protocol design

The INTEGRATION trial is planned as a multicenter, randomized controlled study with pre-interim-post measurements. Patients will be randomized into one of two arms: A) intervention arm (INTEGRATION study: integrated, personalized, and needs-adapted nutrition and exercise therapy), or B), the control arm, providing standard of care (provision of nutrition counseling and physiotherapy following current healthcare practices). The study design, patient flow and the inclusion and exclusion criteria are shown in Figure 1. In this trial, personalized exercise and nutrition interventions will last over a minimum of four months and will be conducted in parallel to the systemic first-line treatment of patients with newly diagnosed cancer and a life-expectancy of at least 18 months. Therefore, inclusion into the trial within the first two weeks of the cancer treatment will be mandatory, as well as the protocol will require the cancer treatment to be predominantly planned in an outpatient setting and for a duration of at least four months.

Consenting patients will be randomly assigned (1:1) to one of the two treatment groups by block randomization with variable block length to ensure balance between the INTEGRATION group and the usual care group. Balancing of the two study arms will be performed by stratification with regard to three criteria: i) center, ii) mGPS (0 or 1 versus 2), and iii) Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) (Figure 1). Patients randomized into the control arm will receive a patient-oriented manual with dedicated information on nutrition and physical exercise recommendations during their cancer treatment. Also, these patients will receive prescriptions to physiotherapy and contact nutrition counseling as current clinical standard. At every visit, patients of both study arms will be therefore asked for their activities especially obtaining extra-curricular nutrition support and/or doing additional physical exercise training. All extra activities will be documented in the eCRFs to improve controlling of both study arms. The INTEGRATION study consortium will consist of 12 sites across Germany: University Hospital Bonn, University Hospital Heidelberg, University Hospital Freiburg, University Hospital Schleswig-Holstein, University Hospital Leipzig, University

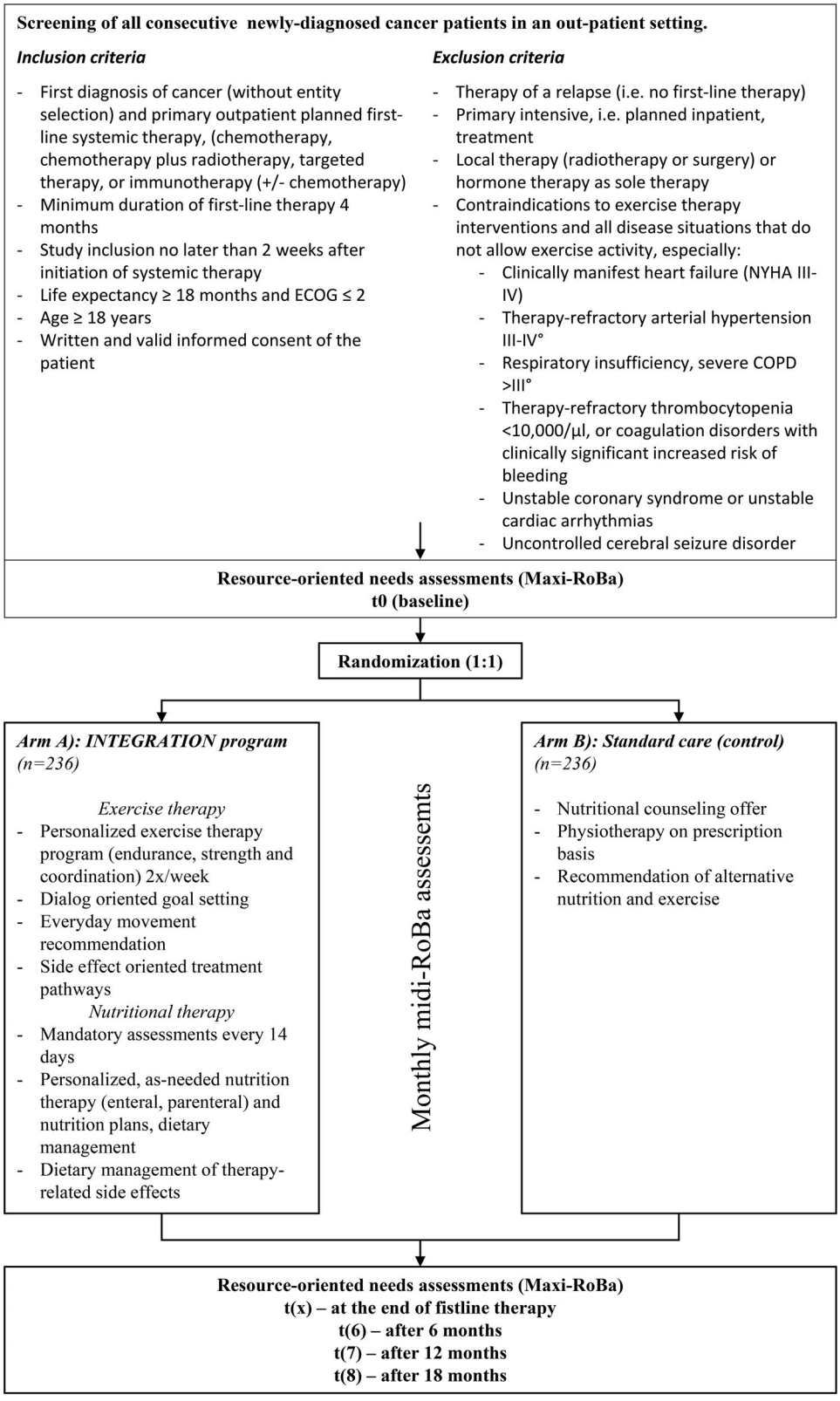

Figure 1. Study flow diagram.
At all study sites, consecutive patients with newly diagnosed cancer are screened for inclusion into the study. Baseline multimodal assessment (t0, maxi-RONA) precedes randomization into one of the study arms with stratification based on study site, ECOG performance status, and the modified Glasgow Prognostic Index (mGPS).

Hospital Halle-Wittenberg, Hospital of Bremen-Mitte, Hospital Northwest Frankfurt a.M., University Hospital Hamburg-Eppendorf, LMU University Hospital Munich, TUM University Hospital Munich, and the Institute for Epidemiology at the University of Regensburg. In addition, two health insurances are involved: AOK Rheinland/Hamburg, Düsseldorf, Germany on behalf of seven other cooperating AOK regional associations and the Deutsche Angestelltenversicherung (DAK), Hamburg, Germany, to provide health insurance data for secondary analyses. However, in accordance with treatment contracts as stipulated by §630 a BGB of the German Civil Code, patients with other health insurance providers are also eligible for inclusion in the study.

To ensure equal conditions and consistent trial activities across all study sites, we will install the same analysis tools and devices (e.g., spiro-ergometers, bioelectrical impedance analyzers and hand-grip analyzers) at all study sites. Also, we will use standard operating procedures (SOP) for all study assessments and interventions. The study personal from all sites will obtain central trainings before study initiation and also regularly during the study period.

The trial has been registered with the German Clinical Trial Register (ID: DRKS00020208). A SPIRIT 2013 Checklist reporting on the recommended items to address in a clinical trial protocol and related documents is shown in Supplemental Figure 1.

2.2. Sample size calculation and statistical analysis plan

Sample size calculation is based on an expected number of 50% patients that usually have an increased need for supportive care at the end of their cancer treatment (tx). In this study, will employ twelve validated tools, tests or questionnaires to assess the patients' physical fitness, nutritional status and quality of life before and after the intervention period. Details on this multi-dimensional assessment termed "resource-oriented needs assessments (RONA)" are outlined below and in (Table 1). To meet the primary endpoint, the intervention arm A) needs to demonstrate a 15% reduction of patients with an increased need for supportive care defined by a RONA score ≥ 9. To reach a statistical power of 90% and incorporating an estimated drop-out rate of 15%, a total of 472 patients need to be included into the trial in order to reach an minimum of $n = 200$ patients in each of the two study arms (calculated by Fisher's one-sided test with a power of 90% at a significance level of 5%). This sample size will also allow to detect a small to moderate Cohen's d of 0.25 for quantitative endpoints with 80% power. The power calculation was performed using G*Power [25].

Secondary outcome parameters will be evaluated exploratively. Differences between treatment arms will be statistically tested as follows: qualitative characteristics will be evaluated using the chi-square test or Fisher's test, event analytic variables such as mortality and morbidity will be analyzed using Kaplan-Meier and log-rank test, and quantitative characteristics will be assessed using the Welch test or Mann-Whitney-U test.

2.3. Data management and data monitoring committee (DMC)

Pseudonymized data will be centrally collected and managed using the Research Electronic Data Capture (REDCap) tools hosted at the University of Regensburg's computing center for the Department of Epidemiology and Preventive Medicine, University of Regensburg, Germany [26,27]. All severe adverse events will be centrally recorded and evaluated by the sponsor. A DMC is not planned for this trial since it does not fall under German AMG, GMP regulations.

3. Measurements and outcomes

3.1. Multidimensional resource-oriented needs assessment (RONA)

The primary objective of the INTEGRATION study will be to assess the patients' needs for nutritional and exercise support and their personal resources at the end of their first-line cancer treatment. Needs and resources with regard to three patient-oriented dimensions, i.e., physical status, nutritional status and quality of life, will be comprehensively assessed by a battery of twelve validated and published tools, termed as resource-oriented needs assessment (RONA) (Table 1). Each of the three dimensions consists of four equally weighted validated tools, resulting in twelve assessments of the full panel (termed Maxi-RONA). Patients in both arms will undergo full assessments by the Maxi-RONA score at four major timepoints: t0 (at study inclusion), tx and/or t6 (at the

Table 1. Multimodal resource-oriented needs assessment (RONA score).

Dimension	Parameter	Assessment	RONA subscore	References
Physical status	Strength	Handgrip [kg]	0: >25th percentile 1: >10th - ≤25th percentile 2: ≤10th percentile per age and gender based on a norm cohort	[35]
	Endurance	Spiroergometry [$VO2_{max}$]	0: fair 1: poor 2: very poor per age and gender based on a norm cohort	[36]
	Balance	Unipedal stance [sec]	0: >Mean-1xSE 1: >Mean-2xSE and ≤ Mean-1xSE 2: ≤Mean-2xSE per age and gender based on a norm cohort	[37]
	Physical activity behavior	Accelerometry [Time spent in MVPA min/ week]	0: >300 min/week 1: 150–300 min/week 2: <150 min/week	[38]
Nutritional status	Anthropometry	Body Mass Index [kg/ m^2]	0: ≥20.0–24.9 1: ≥25.0 OR <20.0 without weight loss(1) 2: <18.5 OR <20.0 kg/m^2 with weight loss(1)	[39]
	Body composition	Bioelectrical impedance analysis [Phase angle]	0: >Mean-1xSD 1: ≤Mean-1xSD and > Mean-2xSD 2: <Mean-2xSD per age and gender based on a norm cohort	[40,41]
	Inflammation and metabolism	mGPS [Serum CRP mg/l & Albumin g/l]	0: CRP ≤10 and Albumin ≥35 1: CRP >10 and Albumin ≥35 2: CRP >10 and Albumin <35	[42]
	Nutritional status	PG-SGA (questionaire)	0: A (well nourished) 1: B (moderately malnourished/ suspected malnutrition) 2: C (severely malnourished)	[43]
Quality of life	Fatigue	MFI-20 (questionaire)	0: <75th percentile 1: ≥75th percentile and <90th percentile 2: ≥90th percentile per age and gender based on a norm cohort	[44]
	Therapy induced polyneuropathy	FACT/GOG-Ntx (questionaire)	0: 0–11 (item score) 1: 12–22 (item score) 2: >22 (item score)	[45]
	Anxiety and depression	HADS (questionaire)	0: 0–13 1: 14–21 2: ≥21	[46]
	Quality of life	EORTC QLQ-C30 (questionaire)	0: >Mean-1xSD 1: ≤Mean-1xSD and > Mean-2xSD 2: <Mean-2xSD per age and gender based on a norm cohort	[47]

All twelve assessments will be used to calculate the Maxi-RONA score. For calculation of a smaller scoring system, termed Midi-RONA, only assessments in the shaded rows will be used. BMI = Body Mass Index; WtHR = Waist to hip ratio; PG-SGA = Patient-Generated Subjective Global Assessment; MFI = Multidimensional Fatigue Inventor; FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity; HADS = Hospital anxiety and depression scale; EORTC = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; MVPA = Moderate to Vigorous Physical Activity. (1)Significant underweight is defined as a BMI <18.5 kg/m^2, or BMI < 20kg/m^2 AND unintentional weight loss of >5% of baseline weight in the previous 3–6 months.

end of systemic cancer treatment (tx) and/or six months after inclusion (t6) whichever comes first),12 months (t7) and 18 months (t8) after inclusion into the trial (Figure 1). A shorter assessment panel consisting of two tools per dimension (termed Midi-RONA) will be conducted every four weeks during the intervention phase (Table 1). We were able to confirm the validity of each assessment and the RoBa score in an independent cohort of 62 cancer patients with corresponding inclusion and exclusion criteria of the here proposed study. Here, we found each of the twelwe assessments to maintain single-tool validity, as well as we found significant correlations with the combined RoBa score (manuscript in preparation).

Nutritional status assessment includes variables such as nutritional status (evaluated using the Patient-Generated Subjective Global Assessment, PG-SGA), weight progression (including Body Mass Index, BMI, and Waist-to-Hip-ratio, WtHR), body composition (assessed through bio-impedance analysis, Bioimpedance analysis, BIA), and blood/serum parameters (considering the modified Glasgow Prognostic Score (mGPS), inflammatory and metabolic status, catabolism, protein synthesis, and electrolyte levels). The assessment of exercise status is based on variables including strength (measured using the handgrip test), endurance (assessed through spiro-ergometry and the 30/15 Intermittent Fitness Test), coordination (determined by the single-leg stand test), and physical movement behavior (monitored using an accelerometer). Quality of life status is

determined through factors such as signs of fatigue (measured with MFI-20), chemotherapy-induced polyneuropathy (assessed using FACT/GOG-Ntx), anxiety and depression (evaluated with the Hospital Anxiety and Depression Scale, HADS), and health-related quality of life (measured using EORTC QLQ-C30 and SF-36) (see Table 1).

The results of each assessment will be categorized into one of three categories: 0 points (no or low needs), 1 point (medium needs), or 2 points (high needs). The categorization from 0 to 2 within each assessment is derived from the originally published tools, questionnaires and internationally recognized reference values or guidelines. The maxi-RONA can therefore result in a minimum of 0 points to a maximum of 24 points, and higher point numbers represent increased needs for supportive care. An elevated overall need for supportive care is defined when the total RONA score is ≥9.

3.2. Primary endpoint

The primary combined endpoint of the study will be the reduction of the proportion of patients with an increased need for supportive care - defined as a RONA score ≥ 9—at the end of the first-line oncologic therapy (tx), or- if the cancer treatment is planned for a longer period of time—at 6 months (t6) from study inclusion.

3.3. Secondary endpoints

A number of secondary outcome parameters will be also evaluated:

- Feasibility of the INTEGRATION study within the clinical routine
- Overall survival (disease specific mortality and non-cancer related mortality)
- Disease-specific progression-free survival in subgroups
- Morbidity (organ dysfunction, fatigue, polyneuropathy, pain, cachexia)
- Exercise status: exercise behavior, exercise capacity (strength, endurance, balance).
- Nutritional status: body composition (phase angle, body-mass-index, waist-to-hip- ratio), weight loss, malnutrition
- Quality of life
- Chronic inflammation and metabolism (modified Glasgow Prognostic Score)
- Therapy adherence and treatment per initially planned protocol, dose modifications
- Rehabilitation potential (cumulative days of sick note)
- Treatment costs, hospitalization frequency, cumulative hospital days
- Consumption of supportive medications (e.g. pain killers, antiemetic drugs, anti-depressives)

4. Interventions

In both study arms, treatment will follow standardized operating procedures of the trial protocol. Specifically, patients in the experimental arm A) will receive personalized integrated supportive care following the INTEGRATION study. In the control arm B), patients will receive general recommendations for physical exercise and physiotherapy prescriptions upon request, as well as offers for nutritional counseling. These life-style recommendations are summarized in a booklet that patients in arm B) will receive after study inclusion. To better control extra activities of the patients randomized into the control arm, we will monitor and document additional exercise or nutrition therapies beyond the provided life-style recommendations at each study visit.

4.1. Nutritional intervention

In the experimental arm A), nutrition consultations are obligatory every two weeks and follow national and international current clinical guidelines to detect early signs of malnutrition and develop personalized nutritional interventions [8,9]. In case of an inconspicuous clinical course, this 2-week rhythm is maintained. In case of signs of malnutrition or new risk symptoms nutritional counseling will be intensified to weekly consultations. In case of nutritional deficits, systematic nutrition therapy following the German Nutrition Care Process

(G-NCP) will be applied to the individual. The G-NCP was introduced in 2003 and is a process model for quality assurance used in nutrition-related health promotion and prevention as well as in nutrition therapy [28,29]. According to the above-mentioned clinical guidelines, nutrition interventions will focus on:

- the normalization, improvement, or stabilization of food intake, weight, physical performance, and immuno-metabolic status [30].
- the adaptation/offering of special foods and nutritional solutions (incl. parenteral nutrition) in the case of restrictions in enteral food intake to meet energy as well as substrate requirements

4.2. Exercise intervention

Exercise therapy is conducted twice per week, with each session lasting a maximum of 60 minutes. At the beginning of each training session, a brief anamnesis is performed to record any deficits, side effects, or therapy management considerations. In cases of typical therapy-associated side effects such as polyneuropathy, fatigue, or pain, personalized interventions following study SOP guidelines are applied to alleviate these symptoms. Individual exercise programs will take into account the specific cancer entity, the oncologic treatment protocol and drug-specific risks, and the patient's physical capabilities. This comprehensive assessment generates an individual risk-resources profile, from which the trained exercise therapist collaborates with the patient to formulate the therapy goal, ensuring patient shared decision-making. The basis for the exercise therapy of the INTEGRATION study is the modular intervention program known as "personalized oncological training and exercise therapy (OTT)", originally established at the University Hospital Cologne [31].

The core of the exercise program combines strength and endurance training using equipment. The characteristics of aerobic exercises are determined based on $Watt_{max}$ from prior endurance testing, planned training intensity, and the Borg scale. For strength exercises, the exercise weight is derived from a preceding submaximal strength test (hypothetical one-repetition maximum test), planned training intensity, and the Rate of Perceived Exertion (RPE) scale. Depending on individually defined training goals, the physical activity target level varies between "near strenuous" and "strenuous" training" defined by the Borg scale (Borg 13–16, RPE 6–8). However, patients typically start with moderate training for the first 2–4 weeks before transitioning to more intensive training. If patients do not tolerate the "near strenuous" or "strenuous" training, they are allowed to switch back to "moderate training" (Borg scale: 11–13, RPE 5–6). The training intensity is continuously monitored during each training session through in dialogue with the patient, using the RPE and Borg scales, and adjusted as needed to ensure safety and effectiveness.

To address existing or anticipated side effects of medical therapy most effectively, the exercise program incorporates additional module content tailored to specific side effects. These supplementary modules include sensor motoric, vibration, or sphincter muscle training.

To ensure the safety of exercise therapy, particularly during intense exercise sessions, the following contraindications are applicable for each exercise session:

- Acute, clinically significant bleeding
- Platelet values <10,000/µl or 10,000–20,000/µl with signs of bleeding
- Significant anemia (haemoglobin <8g/dl and anemia-related symptoms)
- Acute infections or fever (> 38.3 °C)
- Same day of cardiotoxic therapy (e.g., anthracyclines, trastuzumab)
- Acute cardiac arrhythmia or acute shortness of breath

5. Ethics and dissemination

The institutional review board of the University Hospital Cologne and all study sites approved the study protocol (No. 20-1044_1, Institutional Review Board, University Hospital Cologne, Cologne, Germany). The trial sponsor and consortium lead is the University Hospital Cologne, Kerpener Str. 62, 50937 Köln, Germany. The protocol follows the Declaration of Helsinki and from all patients written informed consent is obtained before study inclusion.

The trial protocol is registered at the German Clinical Trial Register (DRKS, ID: DRKS00020208). Data of the trial will published after final evaluation. Additional data can be provided with legitimated interest and upon request to the corresponding authors. The SPIRIT 2013 checklist providing more details on data availability and dissemination of this trial can be found in the supplemental material to this article (Suppl. Fig. 1).

6. Conclusions

Current data and literature strongly support the benefits of nutrition and exercise therapy across various patient groups, and this study protocol seeks to validate and strengthen the feasibility and efficacy of combined and personalized nutrition and physical exercise interventions in cancer patients in a clinical real-world setting. In this regard, the INTEGRATION study protocol represents to our knowledge the largest randomized, controlled trials analyzing personalized and integrated nutrition and exercise interventions in patients with newly diagnosed cancer, irrespective of the cancer entity, and in parallel to systemic first-line cancer treatment. In contrast, the majority of ongoing trials registered at the National Library of Medicine, USA, focus on either a specific cancer entity, do not combine nutrition counseling with exercise interventions, or address patients later and after the acute oncological treatment phase [32]. Because the INTEGRATION trial aims to prevent the development or worsening of deficits in cancer patients as early as possible, the primary study endpoint was defined as a clinically meaningful reduction of the needs for supportive care at the end of the oncological first line treatment and assessed in a multidimensional way by the RONA score. We hypothesize that early supportive interventions might also translate into clinical benefits during the follow-up phase. By instituting early personalized supportive care, the program aims to fully harness the potential of nutrition and exercise therapy while improving tolerability of the tumor therapy and effectively managing associated therapy-related side effects and long-term consequences (somatic, psychological, psychosocial).

Another key objective and long-term goal is to implement early and personalized supportive therapy in clinical routine care. This entails recognizing and addressing both inter- and intraindividual barriers, while also identifying the facilitating factors involved in this process. A significant challenge lies in the wide variation in how standard care is defined across different healthcare facilities. Standardizing protocols for nutritional and exercise therapy becomes pivotal to ensure quality and uniformity and is vital in addressing this diversity in care standards. Another challenge involves the early inclusion of patients in the program upon diagnosis, necessitating seamless collaboration, information exchange, and effective communication among all relevant disciplines within medical institutions. This interdisciplinary coordination is essential for ensuring that pertinent information related to treatment reaches therapists, enabling the safe design of supportive therapy plans and providing all patients with access to supportive therapy options. Patient education on the benefits of nutrition and exercise therapy also plays a pivotal role in enhancing compliance.

Additionally, the trial seeks to validate the feasibility of the RONA Score. If proven effective and efficient, it has the potential to guide patient needs assessment and enhance the organization of supportive therapy in routine clinical practice. While the comprehensive Maxi RONA-Score may not be suitable for daily clinical use, we aim to identify single assessments within the RONA Score that strongly correlate with patient needs, demonstrating their feasibility. In a broader context, we expect that the integration of personalized nutrition and exercise therapy, aligning with international recommendations, will prove feasible and effective within oncology practice [8,22,33]. Moreover, we anticipate that established components of nutrition and exercise therapy utilized in the INTEGRATION study will provide a robust foundation for developing new infrastructures incorporating these practices.

Our study will utilize secondary endpoints to validate real-world effectiveness of combined nutrition and exercise therapy on disease-specific morbidity and mortality. Additionally, the study aims to provide data on treatment costs, hospitalization frequency, cumulative hospital days and rehabilitation potential which will allow to impact on clinical decision makings regarding the adoption and reimbursement of personalized nutrition and exercise therapy in the clinical routine. The INTEGRATION study also aligns with the strong motivation of nearly all cancer patients and their families to contribute positively to successful cancer treatment [14,34].

We see two major challenges that might limit the trial outcomes. One is the heterogeneity of cancer entities and cancer treatment regimens that are allowed to be included, and the second is the extra supportive

care activities that every patient and especially those in the control group could take part of. We implemented controls to measure and document such extra activities already in our protocol and eCRFs, as well as we plan to analyze outcomes in cancer-specific subgroups. We expect the main cancer entities that are usually treated at our study sites, i.e., gastro-intestinal cancer and breast cancer, to be mainly represented in the INTEGRATION trial which would allow for such subgroup analyses.

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Author contributions

ST, TN, HB, CW, AT, ML and FTB developed the trial concept and wrote the study protocol. TJW, CR and MH contributed to the trial concept with helping to set up the data base structure for health insurance data. ISW, CG, KL, DF, PJ, JO, WJ, KG, JW, CF, NZ, MN, DK, HB, JA, HFB, AM, UH, RF, LPM, KF, GD, JvG, LS, IR, EJ, JM, MH, BM, VW, BS and NE helped to write standard operating procedures necessary for the trial conduction. All authors supported the implementation of the trial at their centers and reviewed the manuscript.

Disclosure statement

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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