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The Yinota-O-trial: Efficacy of an online yoga-intervention in high-grade glioma patients and their caregivers – patient-reported outcomes and serum stress parameters - a study protocol of a randomized controlled trial

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Introduction: High-grade glioma patients and their caregivers often suffer from distress and a lower quality of life. Results from studies with patients with mixed cancer entities suggest that yoga can be an effective support. However, it is unclear whether this also applies to high-grade glioma patients and their caregivers. This study aims to investigate the effects of mindfulness-based online yoga for patients and their caregivers on emotional distress, quality of life and stress-associated physiological parameters compared to a waiting control group (WCG).

Methods & analysis: The study is designed as a multicenter randomized controlled trial. Adult glioma patients (CNS WHO grades 3 & 4) and their caregivers will be recruited. Examined yoga instructors deliver the intervention (1 h/week) in a synchronous format over 8 weeks via video conferencing. The WCG will receive standard care during the 8-week waiting period. Data will be collected before and after the end of the intervention and another 3 months later using questionnaires as well as blood serum and hair samples to evaluate biochemical stress parameters. Primary outcome is self-reported generalized anxiety and secondary outcomes are self-reported progression anxiety, depression, quality of life as well as BDNF, DHEA/DHEAS, Ferritin and hair cortisol. We hypothesize better outcomes in the intervention group (IG) compared to the WCG at all measurement points. 70 patients and 70 caregivers will be recruited consecutively. Primary endpoints are significant effect detections in the Generalized Anxiety Disorder Scale-7 of patients and caregivers at the end of the intervention. Analyses of covariance will be performed to analyze treatment effects.

Ethics and dissemination: The Ethics Committee of the University of Würzburg approved the YINOTA-O study on 26.10.2021 (No.185/18-me). Results will be presented at conferences and published in peer-reviewed journals.

Trial registration: German Clinical Trials Register (No. DRKS00029554, 08/2022).

Strengths and limitations of this study

- At the current time, this is the first RCT to analyze the effectiveness of mindfulness-based online yoga for high-grade glioma patients and their caregivers in a synchronous format

- The additional collection of biochemical stress markers could support the validity of self-reports of emotional distress
- The online format provides glioma patients and caregivers of different clinics access to the intervention and could also be beneficial for the target group after covid-19 pandemic
- A limitation is that the inclusion criteria regarding the type of disease (glioma patients CNS WHO grades 3 & 4) and the phase of the disease (diagnosis or recurrence) may induce higher variance of the experienced symptoms among the participants

Introduction

The most recent version of the WHO Classification of Tumors of the Central Nervous System [1] reflects the rapid advances in the understanding of these tumor types [2]. Although a better knowledge of the pathophysiology of these tumors may have a positive impact on the treatment [3], the treatment options for high-grade gliomas remain limited.

Already at the time of diagnosis, glioma patients often report cognitive deficits, seizures, headaches, dizziness, and motor deficits [4]. In addition, during the course of the disease drowsiness, dysphagia, confusion and aphasia are among the most common symptoms [4]. Each of these symptoms might reduce the patients´ autonomy [5]. Therefore, family members frequently provide caregiving, conducting “physically, emotionally, socially and/or financially demanding” tasks [6]. All this suggests an increased burden and a reduced quality of life for patients and caregivers.

Ståhl and colleagues examined the extent of anxious and depressive symptoms (Hospital Anxiety and Depression Scale) as well as health-related quality of life (SF-36) in both glioblastoma patients and their caregivers before surgery [7]. Caregivers reported significantly inferior health-related quality of life, more anxiety and more depressive symptoms than the patients did. These findings are consistent with those of previous studies [e.g. 8]. They imply that high-grade glioma patients as well as their caregivers should be offered support to deal with disease-related psychological distress.

In recent years, several meta-analyses evaluated the effectiveness of yoga on anxiety and depression in cancer patients [9, 10]. Lin et al. reported a standardized mean difference in favor of yoga of -0.76 (95% CI: -1.34 to -0.19) for anxiety and -0.95 for depression (95% CI: -1.55 to -0.36) [9]. Although, the yoga-styles applied in the analyzed studies varied widely, most yoga-interventions examined in the meta-analyses by Gonzalez et al. were based on Hatha yoga [10]. Yoga interventions had significant effects on depressiveness (N=1.486, g=−0.419, 95% CI=−0.558 to −0.281) and anxiety of cancer patients (N=977, g=−0.347, 95% CI=−0.473 to −0.221) compared to the control conditions (mainly “no specific therapy”) [10]. Sub-group analyses of different cancer populations were not possible, because the majority of studies was conducted with breast cancer patients. Meanwhile, only one of the included studies examined glioma-patients [11].

Milbury et al. studied the feasibility of a dyadic yoga program for high-grade glioma patients and their caregivers during radiotherapy as well as its effects on cancer-related symptoms [11]. Comparing the intervention group (IG, n=10) and the waiting control group (WCG, n=10), patients in the IG had significantly lower levels of depressiveness (d=0.71) and a significantly higher mental quality of life (d=0.69) at post-assessment. Interestingly, in the

caregivers' IG (IG: n=10, WCG n=10) treatment effects were even larger (depressiveness: d=1.12; mental quality of life: d=0.89).

Although these results are promising, seizures can limit the patients' mobility and thereby impede their participation in supportive services on site. Therefore, services, which can be attended from home, might facilitate access to supportive care for the target group. Nevertheless, only few studies were published examining online yoga interventions [12, 13]. The evaluation of a 12-week asynchronous yoga intervention for myeloproliferative neoplasm patients (n=48) revealed small effects on anxiety and moderate effects on depression at post-assessment [12]. Addington et al. examined a 12-week yoga intervention for breast cancer patients delivered in a synchronic format [13]. Based on qualitative interviews, recommendations for internet-based yoga research were presented.

Beyond subjective indications for the effectiveness of yoga, there is limited evidence in the literature regarding correlation of yoga and stress-associated physiological parameters [12, 14, 15, 16]. However, most of these studies investigated non-cancer patients.

In summary, there is consensus that high-grade glioma patients and their caregivers are highly distressed and that they report reduced quality of life. On-site yoga interventions have positive effects on self-reported emotional well-being of cancer patients. Nevertheless, at this time we are aware of only one American research group investigating the effects of yoga intervention specifically for high-grade glioma patients and their caregivers [11, 17]. Hence, there are still little findings regarding feasibility and efficacy of yoga interventions for high-grade glioma patients and their caregivers, especially if the program is offered online.

To address this research gap, a monocentric on-site pilot study to test feasibility and efficacy of a mindfulness-based yoga intervention for high-grade glioma patients and their caregivers

was started in 2020 and then adapted to an online format due to the COVID-19 pandemic [18]. The initial on-site yoga intervention was already investigated in previous randomized controlled studies in cancer patients with mixed tumor entities and treatment effects on emotional symptoms have been demonstrated [19, 20]. In the pilot study, participants filled questionnaires on disease-related psychological symptoms and quality of life and blood serum and saliva samples were taken. Participants were asked to rate their satisfaction with various course features. When it comes to the online-intervention, known technical problems were reported. However, patients and caregivers' satisfaction with the course was very high. The instructor's guidance was rated most positively. No adverse effects occurred. Overall, the pilot study implies that the online mindfulness-based yoga course is feasible and attractive for the target group, even when offered online and even without previous experience with yoga. The study will continue in a multicenter setting described here to achieve the predefined group size in a timely manner and to reduce the waiting time between recruitment and the start of the intervention. This was difficult to achieve in the monocentric pilot study, because of the rarity of the disease. To measure cortisol, more reliable hair samples will be collected.

Based on the research presented, in this study the following research questions will be examined:

1. Primary research question

a) Does an 8-week online yoga intervention for high-grade glioma patients and their caregivers reduce self-reported generalized anxiety symptoms directly after the intervention compared to a WCG? *We hypothesize that compared to participants in*

the WCG, participants in the IG report significantly fewer generalized anxiety symptoms after the end of the intervention.

2. Secondary research questions

a) Does such an intervention reduce self-reported fear of progression directly after the intervention compared to a WCG?

b) Does such an intervention reduce self-reported depressive symptoms directly after the intervention compared to a WCG?

c) Does such an intervention improve self-reported quality-of-life directly after the intervention compared to a WCG?

d) Does such an intervention have a positive effect on stress-associated physiological parameters (BDNF, DHEA/DHEAS, ferritin, hair cortisol) compared to the WCG?

e) Which changes in self-reported psychological symptoms, quality of life and stress-associated physiological parameters can be observed 3 months after the end of the online yoga intervention?

We hypothesize that the outcomes of participants in the intervention group will be superior to those of participants in the WCG in all aspects (2a-2d) at the end of the intervention.

Methods

Participants

Eligible for the study are adult (≥ 18 years) patients with glioma CNS WHO grades 3 & 4 (initial diagnosis or recurrence) treated in participating hospitals in Germany and their caregivers. Patients are eligible to participate at any time point of treatment, but we recommend joining the yoga program not earlier than six weeks after surgery. Prerequisite for participation is regular access to a mobile device with internet access. Exclusion criteria are insufficient German language skills and serious cognitive, affective, or physical impairments. The study physicians and staff consider exclusion criteria during the recruitment process.

Study centers

Study centers were only eligible to participate in this study if they have the ability to process blood serum samples and store them in a deep-freezer at -80 degrees. In addition, a positive ethics vote by the clinic's own ethics committee was necessary.

Study design and measurement points in time

This is a multicentric randomized controlled trial with an IG and a WCG. First, the IG receives the 8-week online yoga intervention delivered by videoconference (Zoom Video Communications). Subsequently, the WCG receives the same intervention. During the waiting period, the WCG receives the medical standard of care and if necessary additional psychological and supportive care. Measurement points for the IG are: Before randomization (T1), at the end of the intervention (T2) and 3 months after the last scheduled yoga class (T4). Measurement points for the WCG are: Before randomization (T1), at the end of the intervention of the IG/before the start of the intervention of the WCG (T2), at the end of the intervention (T3) and 3 months after the last scheduled yoga class (T5). At each

measurement point in time, questionnaire data as well as a blood serum and hair samples will be collected (Fig. 1)

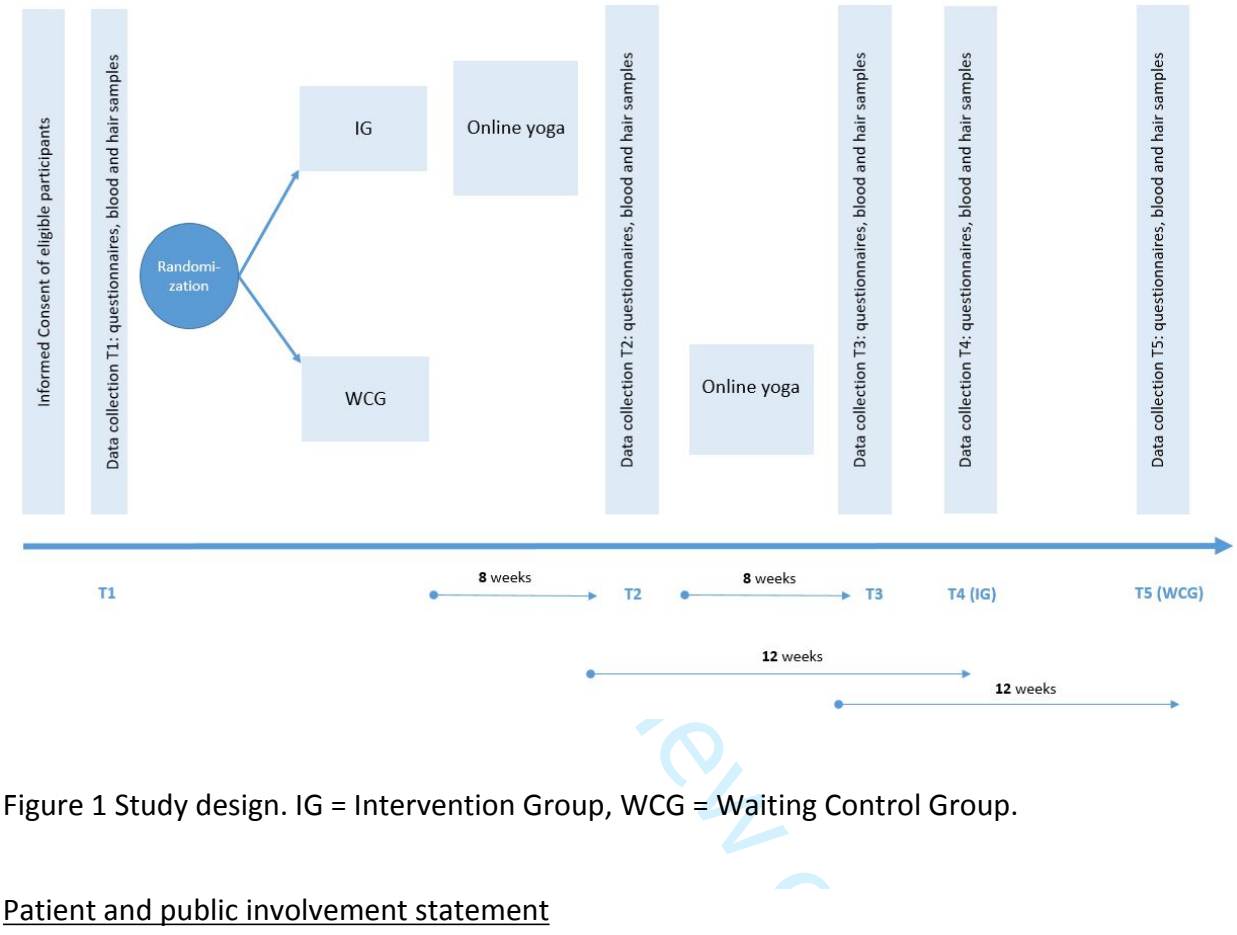

Figure 1 Study design. IG = Intervention Group, WCG = Waiting Control Group.

Patient and public involvement statement

The study was inspired by the positive experiences of a relative of a brain tumor patient with yoga during the disease and developed in exchange with her. Feedback from participants after the pilot study was considered in the multicenter study.

Yoga-intervention

Participation in the study should be consulted with a physician in advance. Yoga classes are held once a week for 60 minutes. Patients and caregivers will be taught successively in separate groups of 10 participants per group to ensure that caregivers are potentially nearby

in case patients require support. As recommended in the literature [13], the groups will be closed groups. The intervention is based on the mindfulness-based hatha yoga described by Jon Kabatt-Zinn [21]. The intervention is carried out by examined yoga instructors (>200 units). The classes consist of a sequence of breathing exercises (pranayama), physical exercises (asanas) and meditation, which is repeated in each lesson. The exercises were selected in such a way that even patients with advanced disease can perform them with a mindful practice. The intervention is described in detail in Zetzl et al. [20]. For the sake of standardization of the yoga classes, yoga instructors are trained in advance by video-support, demonstrating all the exercises provided. In addition, a booklet is available, describing all exercises and providing important information on possible cancer-specific and cancer non-specific contraindications.

Sample-size calculation

Based on previous research [9], a Standardized Mean Difference (SMD) of 0.76 is expected for generalized anxiety in favor of the IG when comparing the IG to the control group. Consequently, a case number of n=29 per group (α =0.05 and beta=0.20) will be determined for a two-tailed independent samples t-test. A low proportion of dropouts is expected at the post-intervention time point. Therefore, 70 patients and 70 relatives will be recruited.

Recruitment

Physicians and research staff of participating study centers will identify potential participants utilizing the centers' electronic medical record systems. Suitable persons will be informed about the study either during outpatient consultation in the policlinics or by phone. If patients and/or their caregivers are interested in study participation, they will receive the

written participation information and the consent form. They approve their participation by signing the latter and sending it by mail to the study coordinator.

Randomization and allocation concealment

Participants will be consecutively enrolled in the study and randomly assigned to the IG or WCG. Utilizing a computer-generated list of random numbers ensures a close balance of the group sizes at any time during the trial by external blocked randomization. The list is generated and managed by an employee who is not involved in the study. If both patients and their caregivers participate in the intervention, they are randomized as a pair. For every block of 20 patients and 20 caregivers, 20 participants (10 patients, 10 caregivers) will be allocated to each arm of the trial.

Data collection, management, and analysis

Data collection

An online questionnaire, blood serum samples and hair samples are used to collect the required data. The online questionnaire is created and administered using the EvaSys evaluation software. Participants can access it via a web-link. On the first page of the online questionnaire, participants are instructed to enter their assignment code, which they received in advance per e-mail.

Primary outcomes

Self-reported generalized anxiety: The German version of the Generalized Anxiety Scale (GAD-7) (22) is used to assess anxious symptoms. Participants are asked to indicate the frequency of perceived impairment by seven symptoms on a 4-point Likert scale (0="not at all" to 4="almost every day") in the last two weeks. The internal consistency is

Cronbachs α = 0.85, indicating high reliability [23]. A sum value is calculated from all items (range: 0-21). The higher the value, the greater the severity of the anxiety.

Secondary outcomes

Self-reported fear of progression: The patient questionnaire contains a short form of the Fear of Progression Questionnaire (FoP-Q-SF) with 12 items (PA-F-KF). The answers are given on a five-point Likert scale (1="never"; 5="very often"). Good reliability (Cronbachs α =0.87) and validity were demonstrated in a German sample of breast cancer patients [24]. For analysis, a sum value is calculated from all items (range: 12-60). The higher the value, the greater the severity of the anxiety.

Self-reported depression: The Patient Health Questionnaire-9 (PHQ-9) consists of nine items regarding the impairment due to depressive symptoms in the past two weeks. A 4-point Likert scale is used (0="not at all" to 3="almost every day"). Good reliability (Cronbachs α = 0.89) and validity were demonstrated in a sample of patients with different medical conditions [25]. For analysis, a sum score is calculated from all items. The higher the value, the greater the severity of depression (range: 0-27).

Self-reported Qualify of Life: The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire C30 (QLQ-C30) plus brain module (BN20) are used to assess quality of life. The EORTC QLQ-C30 consists of 30 questions that can be assigned to ten subscales. Two items assessing overall health and overall quality of life in the last week, both of which were scored from 1="very poor" to 7="excellent". The appropriateness of the other items is assessed on a 4-point Likert scale (1="not all" to 4="very much"). The validity and reliability of the questionnaire could be

demonstrated [26]. Although this is a cancer-specific questionnaire, norm values are also available for a healthy German sample [27].

The brain module is recommended for use in conjunction with the EORTC QLQ-C30 [28]. It consists of additional 20 items that can be assigned to seven single-item scales and four multi-item scales. A standardized point value is calculated by linear transformation. Scores range from 0-100. A higher score for the function scales indicates better functionality, and a higher score for the symptom scales indicates greater symptom burden. Adequate psychometric properties were demonstrated [28].

Stress parameters: To assess stress-associated physiological parameters, the study physicians or the study nurses collect blood serum samples from the participants (20 ml EDTA blood) and pencil-thick strands of hair (2cm, refers to the area of the scalp, length at least 1cm) from the back of the head [29]. The sample procurement points in time for blood serum and hair samples (hair length up to 7 cm) correspond to the time of the questionnaire assessments. For long hair (7 cm or more), one single pencil thick strand of hair will be collected at the last blood serum collection appointment. Hair sampling will not be performed in case of TTFields- or cortisone-treatment.

Sociodemographic and health data: As possible covariates and for sample description, participants will be asked at T1 to provide information regarding marital status, education and occupation, previous experiences with yoga and expectations regarding the classes as well as mental illnesses. In addition, at each measurement point in time, questions are asked about medication, actual treatment and the course of the disease. Patients' routine medical data (type and stage of disease, time of diagnosis, treatment) will be collected from the electronic patient file of the respective clinic by responsible study staff. For the continuous

development of the intervention, participants will be asked about their general and specific satisfaction with individual features of the intervention at the end of the intervention (selected exercises, duration of a single yoga class, and instruction of the exercises, group size, and atmosphere in the class).

Data management

All questionnaire data as well as all blood serum and hair samples are marked with a pseudonym instead of the participant's name and a password-protected digital allocation list is used. The allocation list includes the participant's first and last name, date of birth, the clinic where the participant was recruited, the e-mail address under which the participant would like to be contacted, and whether the participant is a patient or a caregiver. This data is taken from the consent form. The study coordinator, who is responsible for the assignment list, creates a pseudonymization code for each participant according to a predefined procedure. This is required to retrieve the data needed for sample description from the hospital information system as well as to process the blood serum and hair samples. During the period of the assignment, the research data will be considered “personal data” and data protection laws will be complied with.

At the end of data collection, the questionnaire data will be exported from the online platform used for the survey by the study coordinator and saved password-protected on a computer at the University Hospital of Würzburg. After that, the questionnaire data is deleted from the online platform. The site coordinators transmit the selected routine medical data of the participating patients to the study coordinator in accordance with data protection regulations. After data analysis, the assignment lists as well as the consent declarations are deleted. Deletion of the site-specific assignment lists provided will be

confirmed in writing by the site coordinators. The raw data of the study will be destroyed after 10 years in accordance with data protection regulations. To prevent loss of study data, the study coordinator performs a regular backup. Hair samples are enclosed in aluminum foil after collection and the part close to the root is fixed with a paper clip. Samples are stored dry and dark at room temperature in a cardboard box/large envelope. The blood and serum samples, if not completely consumed for molecular stress marker determination, will be stored frozen at -80°C for the duration of the study. After completion of data collection, the samples will be picked up from the participating centers by the medical study management of the University Hospital Würzburg and brought to the laboratory of the Section Experimental Neurosurgery of the Department of Neurosurgery, University Hospital Würzburg. All sample remnants will be destroyed after completion of the study.

Analysis

The data of the patients and the relatives are analyzed separately. To test for group differences (hypotheses 1a – 2d) covariance analyses with adjustment for baseline values of outcome variables will be performed. We use eta² as the effect size calculated in covariance analyses. Eta²=0.0099 was assessed as a small effect, eta²=0.0588 as a medium effect, and eta²=0.1379 as a large effect according to Cohen. To answer hypothesis 2e, a two-tailed t-test is performed. Standardized mean differences are used to calculate the effect size. A p-value of <0.05 is considered significant. Data analysis is performed using International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) Statistics for Windows version 22. The study results will be published by the participating centers as joint publications in peer-reviewed journals after completion of the data analysis.

Monitoring

The yoga instructors will document adverse effects, such as injuries, in writing immediately after each class, including necessary adjustments to the exercises.

Ethics and dissemination

The Ethics Committee of the University of Würzburg approved the described study protocol on 26.10.2021 (No.185/18-me). Important changes in the protocol will be passed on to the responsible ethics committee as well as the German Register of Clinical Trials and will be described in study reports. The investigation conforms to the principles outlined in the Declaration of Helsinki. Potential study participants will be informed about all relevant aspects of the study (goals, processes, data protection). This information will be provided verbally and in writing by the research staff. In particular, the voluntary nature of the study participation as well as the possibility of discontinuing the study at any time without giving reasons and without any disadvantages for the treatment are emphasized. In the consent form, interested participants are specifically asked for their consent to provide blood serum and hair samples. They can consent either to provide both samples, to donate blood serum samples or hair samples only, or refuse to give such samples. Even without providing samples, participation in the study is possible. The consent form also asks for an e-mail address for further contact. Participation in the study is only possible with written consent.

Discussion

The disease and its treatment often stress high-grade glioma patients and their caregivers. Depressive and anxious symptoms and reduced quality of life are frequently reported in the literature [7, 8]. Sometimes the emotional health of the caregivers is worse than that of the patients [8]. This multicenter study will offer high-grade glioma patients and their caregivers

a mindfulness-based yoga course by examined yoga instructors, which has already proven helpful in previous studies with patients with mixed cancer entities [19, 20]. However, due to the heterogeneous sample characteristics of these previous studies, it remains unclear whether this yoga intervention is also helpful for improving emotional well-being and quality of life of high-grade glioma patients. In addition, the effectiveness of a mindfulness-based yoga intervention has not yet been studied for caregivers. Generally, yoga studies that exclusively include patients with high-grade glioma and their caregivers are rare [17]. Therefore, in this study the intervention will be provided exclusively for glioma patients CNS WHO grades 3 and 4 and their caregivers.

The aim of this randomized controlled study is to investigate whether significant changes of self-reported anxious and depressive symptoms and in quality of life are detectable after the intervention in the IG compared to the WCG. As in previous yoga studies [e.g. 10], self-report questionnaires will be used for this purpose. Furthermore, stress-associated physiological parameters extracted from blood and hair samples are also evaluated in this study. A possible demonstration of the effects of mindfulness-based online yoga therapy on a biochemical level could highlight the value of yoga in the supportive therapy of cancer patients and should be further investigated in future studies. Although the inclusion criteria regarding the type of disease (glioma patients CNS WHO grades 3 & 4) and the phase of the disease (diagnosis or recurrence) facilitate timely recruitment of the participants, they may also induce higher variance of the experienced limitations among the participants. In favor of greater homogeneity, specification of inclusion criteria regarding characteristics of the tumors based on the updated WHO Classification [1] is considered for this and recommended for future studies.

Due to the Covid-19 pandemic the yoga intervention, which we planned originally as an in-person course was adapted to an online format. Today, we expect this to actually bring other advantages for the vulnerable target group in comparison to on-site yoga. The participation in the online course may increase the sense of autonomy of patients with reduced mobility, as they do not need to be driven to class by family members. It also conserves caregivers' limited time resources due to caregiving and may reduce stress from travel. For this reason, the online yoga therapy if proven effective could be an attractive treatment approach for high-grade glioma patients and their caregivers even beyond the Covid-19 pandemic.

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Footnotes

Ethics approval and consent to participate

The study conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Würzburg on 26.10.2021 (No.185/18-me). In addition, the study is registered in the German Register of Clinical Trials (No. DRKS00029554, 08/2022). Any changes to the study protocol must be approved by the responsible ethics committee and reported to the German Clinical Trials Registry. Potential participants will be informed about the study verbally and in writing. Written informed consent must be given for study participation.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

EJ is the psychological study director and AK is the medical study director. CH and JS will supervise the collection of the biomarkers and analyze them. AR is responsible for the implementation and the coordination of the study. All authors read and approved the final manuscript.

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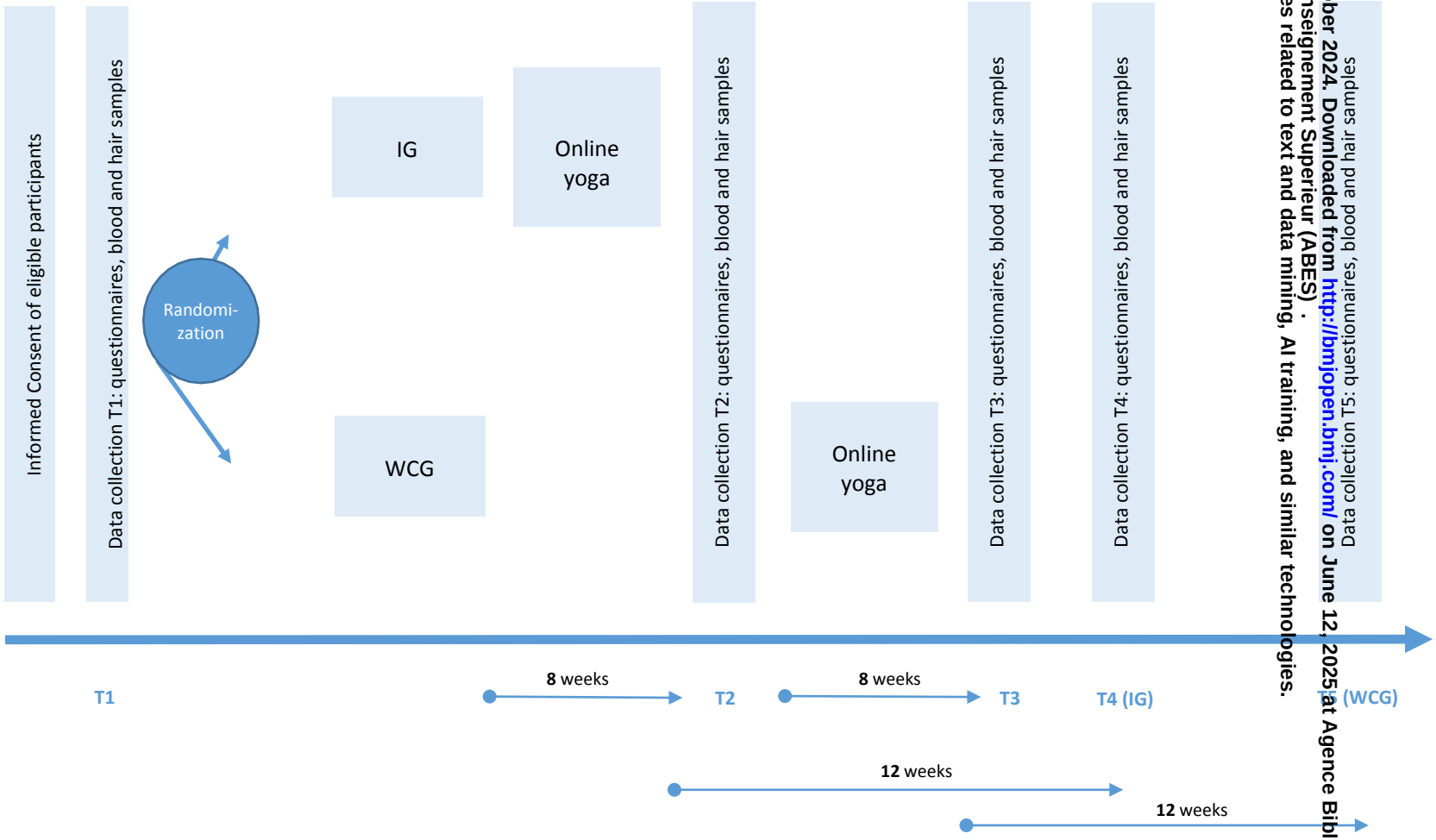

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Study protocol for a multicenter randomized controlled trial evaluating the efficacy of an online yoga-intervention in high-grade glioma patients and their caregivers: The YINOTA-O-trial

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Study protocol for a multicenter randomized controlled trial evaluating the efficacy of an online yoga-intervention in high-grade glioma patients and their caregivers: The YINOTA-O-trial

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Introduction: High-grade glioma patients and their caregivers often suffer from distress and a lower quality of life. Results from studies with patients with mixed cancer entities suggest that yoga can be an effective support. However, it is unclear whether this also applies to high-grade glioma patients and their caregivers. This study aims to investigate the effects of mindfulness-based online yoga for patients and their caregivers on emotional distress, quality of life and stress-associated physiological parameters compared to a waiting control group (WCG).

Methods & analysis: The study is designed as a multicenter randomized controlled trial. Adult glioma patients (CNS WHO grades 3 & 4) and their caregivers will be recruited. Examined yoga instructors deliver the intervention (1 h/week) in a synchronous format over 8 weeks via video conferencing. The WCG will receive standard care during the 8-week waiting period. Data will be collected before and after the end of the intervention and another 3 months later using questionnaires as well as blood serum and hair samples to evaluate biochemical stress parameters. Primary outcome is self-reported generalized anxiety and secondary outcomes are self-reported progression anxiety, depression, quality of life as well as BDNF, DHEA/DHEAS, Ferritin and hair cortisol. We hypothesize better outcomes in the intervention group (IG) compared to the WCG at all measurement points. 70 patients and 70 caregivers will be recruited consecutively. Primary endpoints are significant effect detections in the Generalized Anxiety Disorder Scale-7 of patients and caregivers at the end of the intervention. Analyses of covariance will be performed to analyze treatment effects.

Ethics and dissemination: The Ethics Committee of the University of Würzburg approved the YINOTA-O study on 26.10.2021 (No.185/18-me). Results will be presented at conferences and published in peer-reviewed journals.

Trial registration: German Clinical Trials Register (No. DRKS00029554, 08/2022).

Strengths and limitations of this study

- Simultaneous collection of subjective questionnaire data and objective physiological parameters
- Implementation of a tailored yoga intervention designed specifically to meet the unique needs of cancer patients

- The inclusion in the study without pre-screening for the identification of distressed patients and caregivers may influence the detection of treatment effects
- The inclusion criteria regarding the type of disease (glioma patients CNS WHO grades 3 & 4) and the phase of the disease (diagnosis or recurrence) may induce higher variance of the experienced symptoms among the participants

Introduction

The most recent version of the WHO Classification of Tumors of the Central Nervous System [1] reflects the rapid advances in the understanding of brain tumors [2]. While a better understanding of the pathophysiology of these tumors may have a positive impact on the treatment [3], the treatment options for high-grade gliomas remain limited.

At the time of diagnosis, glioma patients often report cognitive deficits, seizures, headaches, dizziness, and motor deficits [4]. As the disease progresses, drowsiness, dysphagia, confusion, and aphasia expand the list of symptoms [4] and can reduce the patients´ autonomy [5]. Family members frequently take on the role of caregivers, conducting “physically, emotionally, socially and/or financially demanding” tasks [6]. Thus the diagnosis of a high grade glioma imposes a burden and significant reduction in quality of life for both the patients and their caregivers. Ståhl and colleagues examined the extent of anxious and depressive symptoms as well as health-related quality of life in both glioblastoma patients and their caregivers before surgery [7]. Caregivers reported significantly inferior health-related quality of life, more anxiety, and more depressive symptoms than the patients did. These findings are consistent with those of previous studies [e.g. 8]. They imply that high-grade glioma patients as well as their caregivers should be offered support to deal with disease-related psychological distress.

Yoga is increasingly recognized as a complementary therapy for improving quality of life and cancer-related symptoms [9]. In recent years, several meta-analyses evaluated the effectiveness of yoga on anxiety and depression in cancer patients [10, 11]. Lin et al. as well as Gonzalez et al. reported significant medium effects of yoga on anxiety and significant medium to large effects on depression compared to the control conditions [10,11]. Most studies were conducted with breast cancer patients which is why no meta insights can be derived for the glioma patient population.

One referenced study examined a yoga intervention for glioma patients in an on-site setting [12]. Milbury et al. studied the feasibility of a dyadic yoga program for high-grade glioma patients and their caregivers during radiotherapy as well as its effects on cancer-related symptoms [12]. Comparing the intervention group and the waiting control group, patients in the intervention group showed significantly lower levels of depression and a significantly higher mental quality of life at post-assessment. In the caregivers' intervention group treatment effects were even more pronounced with a large effect size for improvement in depression. These results are encouraging but due to the on-site course format, require the physical presence of participants at the course location. Seizures can limit the patients' mobility and thereby impede their participation in supportive services on site. Alternatively, services, which can be attended from home, e.g. in an online format, could facilitate access supportive care for the target group. To date, only few studies were published examining online yoga interventions [13, 14]. None of them concern the group of glioma patients. The initial indications of feasibility cannot be generalized to brain tumor patients as they have brain tumor-specific symptoms like motor deficits [4] that need to be dealt with. In order to provide individual support from the yoga teachers, a synchronous online format seems appropriate for the target group but has not yet been investigated. It allows interaction with

the instructor as well as simultaneous supervision. To evaluate the feasibility of such an intervention for both patients and their caregivers, a monocentric pilot study was conducted in 2020, demonstrating its practicality and participant satisfaction [15].

The use of subjective measurement tools for assessing potential effects of yoga interventions on anxiety and depression seems appropriate, given the subjective nature of these criteria. Nonetheless, it remains unclear whether intervention effects are also detectable at the biological level. Initial indications of the effects of yoga interventions on biological parameters are derived from studies involving non-clinical populations [16, 17, 18] as well as patients with myeloproliferative neoplasms [13]; evidence for glioma patients and their caregivers is missing.

Based on the research presented, in this study the following research questions will be examined:

1. Primary research question

   Does an eight-week online yoga intervention for high-grade glioma patients and their caregivers reduce self-reported generalized anxiety symptoms directly after the intervention compared to a WCG? *We hypothesize that compared to participants in the WCG, participants in the IG will report significantly fewer generalized anxiety symptoms after the end of the intervention.*

2. Secondary research question

   Does such an intervention reduce self-reported fear of progression, depressive symptoms, quality of life and stress-associated physiological parameters (BDNF, DHEA/DHEAS, ferritin, hair cortisol) directly after the intervention compared to a

WCG? *We hypothesize that the outcomes of participants in the intervention group will be superior to those of participants in the WCG in all aspects at the end of the intervention.*

Moreover, employing an explorative approach, the changes in self-reported psychological symptoms, quality of life and stress-associated physiological parameters 3 months after the end of the online yoga intervention should be investigated.

Methods

Participants

Eligible for the study are adult (≥ 18 years) patients with glioma CNS WHO grades 3 & 4 (initial diagnosis or recurrence) treated in participating hospitals in Germany (University Hospital Würzburg, University Hospital Mannheim, Aschaffenburg-Alzenau Hospital, University Hospital Augsburg) and their caregivers. Patients are eligible to participate at any time point of treatment, but we recommend joining the yoga program not earlier than six weeks after surgery. Prerequisite for participation is regular access to a mobile device with internet access. Exclusion criteria are insufficient German language skills and serious cognitive, affective, or physical impairments. The study physicians and staff consider exclusion criteria during the recruitment process. Participants are advised not to concurrently engage in other supportive interventions for psychological distress throughout the duration of the study.

Study centers

Study centers were only eligible to participate in this study if they have the ability to process blood serum samples and store them in a deep-freezer at -80 degrees. Moreover, a positive ethics approval from the hospital's internal ethics committee and the execution of a

cooperation agreement were mandatory. Other clinics in Germany, excluding those mentioned, are still in the process of fulfilling these requirements.

Study design and measurement points in time

This is a multicentric randomized controlled trial with an IG and a WCG. First, the IG receives the 8-week online yoga intervention delivered by videoconference (Zoom Video Communications). Subsequently, the WCG receives the same intervention. During the waiting period, the WCG receives the medical standard of care and if necessary additional psychological and supportive care. The latter was determined for ethical reasons. Measurement points for the IG are: Before randomization (T1), at the end of the intervention (T2) and 3 months after the last scheduled yoga class (T4). Measurement points for the WCG are: Before randomization (T1), at the end of the intervention of the IG/before the start of the intervention of the WCG (T2), at the end of the intervention (T3) and 3 months after the last scheduled yoga class (T5). At each measurement point in time, questionnaire data as well as a blood serum and hair samples will be collected (Fig. 1). Study staff will supervise the status of data collection and, if necessary, contact participants by telephone if assessments are missing. The planned start of the study is January 2024 and the expected end of the study is January 2026. Table 1 shows the study workflow.

Table 1. Schedule of enrolment, interventions, and assessments, according to Spirit 2013 guidelines

	Enrolment	**Before allocation**	**After T1**	**Post-allocation**			
TIMEPOINT	**$-T_1$**	**T1**		***T2***	***T3***	***T4***	***T5***

					(only WCG)	*(only IG)*	*(only WCG)*
ENROLMENT:							
Eligibility screen	x						
Informed consent	x						
Allocation			x				
INTERVENTIONS:							
Online Yoga (IG)			←	—			
Online Yoga (WCG)				→			
ASSESSMENTS:							
socio-demographic data		x					
Medical data		x		x	x	x	x
Generalized anxiety		x		x	x	x	x
Fear of progression (only patients)		x		x	x	x	x
Depression		x		x	x	x	x
Quality of Life Questionnaire + Brain Module (only patients)		x		x	x	x	x
BDNF, DHEA/DHEAS, ferritin, hair cortisol		x		x	x	x	x
Evaluation						x	x

Patient and public involvement statement

The study was inspired by the positive experiences of a relative of a brain tumor patient with yoga during the disease and developed in exchange with her. Feedback from participants after the pilot study [15] was considered in the multicenter study.

Yoga intervention

Participation in the study should be consulted with a physician in advance. Yoga classes are held once a week for 60 minutes. Patients and caregivers will be taught successively in separate groups of 10 participants per group to ensure that caregivers are potentially nearby in case patients require support. As recommended in the literature [14], the groups will be closed groups. The intervention is based on the mindfulness-based hatha yoga described by Jon Kabatt-Zinn [19]. The intervention is carried out by examined yoga instructors (>200 units). The classes consist of a sequence of breathing exercises (pranayama), physical exercises (asanas) and meditation, which is repeated in each lesson. The exercises were selected in such a way that even patients with advanced disease can perform them with a mindful practice. The intervention is described in detail in Zetzl et al. [20]. For the sake of standardization of the yoga classes, yoga instructors are trained in advance by video-support, demonstrating all the exercises provided. Alternative variations of the exercises will be discussed during the training session for participants who may face challenges in performing certain exercises due to impairments. In addition, a booklet is available, describing all exercises and providing important information on possible cancer-specific and cancer non-specific contraindications. To minimize technical difficulties, participants will be offered a technical rehearsal, and they will receive instructions on using the video platform.

Sample-size calculation

Based on previous research [10], a Standardized Mean Difference (SMD) of 0.76 is expected

for generalized anxiety in favor of the IG when comparing the IG to the control group. Consequently, a case number of n=29 per group (α =0.05 and beta=0.20) will be determined for a two-tailed independent samples t-test. A low proportion of dropouts is expected at the post-intervention time point. Therefore, 70 patients and 70 relatives will be recruited.

Recruitment

Physicians and research staff of participating study centers will identify potential participants utilizing the centers' electronic medical record systems. Suitable persons will be informed about the study either during outpatient consultation in the policlinics or by phone. If patients and/or their caregivers are interested in study participation, they will receive the written participation information and the consent form. They approve their participation by signing the latter and sending it by mail to the study coordinator. Recruitment will be concluded once the required sample size is reached.

Randomization and allocation concealment

Participants will be consecutively enrolled in the study and randomly assigned to the IG or WCG. Utilizing a computer-generated list of random numbers ensures a close balance of the group sizes at any time during the trial by external blocked randomization (allocation rate 1:1). The list is generated and managed by an employee of the University Hospital Würzburg who is not involved in the study. If both patients and their caregivers participate in the intervention, they are randomized as a pair. For every block of 20 patients and 20 caregivers, 20 participants (10 patients, 10 caregivers) will be allocated to each arm of the trial. The study coordinator will request the results of the randomization after the initial survey is completed and convey it to the participants. Participants are then no longer blinded. If there is a likelihood of missing two sessions, randomization will be delayed.

Data collection, management, and analysis

Data collection

An online questionnaire, blood serum samples and hair samples are used to collect the required data. The online questionnaire is created and administered using the EvaSys evaluation software. Participants can access it via a web-link. On the first page of the online questionnaire, participants are instructed to enter their assignment code, which they received in advance per e-mail.

Primary outcomes

Self-reported generalized anxiety: The German version of the Generalized Anxiety Scale (GAD-7) [21] is used to assess anxious symptoms. Participants are asked to indicate the frequency of perceived impairment by seven symptoms on a 4-point Likert scale (0="not at all" to 4="almost every day") in the last two weeks. The internal consistency is Cronbachs α = 0.85, indicating high reliability [22]. A sum value is calculated from all items (range: 0-21). The higher the value, the greater the severity of the anxiety.

Secondary outcomes

Self-reported fear of progression: The patient questionnaire contains a short form of the Fear of Progression Questionnaire (FoP-Q-SF) with 12 items (PA-F-KF). The answers are given on a five-point Likert scale (1="never"; 5="very often"). Good reliability (Cronbachs α =0.87) and validity were demonstrated in a German sample of breast cancer patients [23]. For analysis, a sum value is calculated from all items (range: 12-60). The higher the value, the greater the severity of the anxiety.

Self-reported depression: The Patient Health Questionnaire-9 (PHQ-9) consists of nine items regarding the impairment due to depressive symptoms in the past two weeks. A 4-point Likert scale is used (0="not at all" to 3="almost every day"). Good reliability (Cronbachs α = 0.89) and validity were demonstrated in a sample of patients with different medical conditions [24]. For analysis, a sum score is calculated from all items. The higher the value, the greater the severity of depression (range: 0-27).

Self-reported Qualify of Life: The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire C30 (QLQ-C30) plus brain module (BN20) are used to assess quality of life. The EORTC QLQ-C30 consists of 30 questions that can be assigned to ten subscales. Two items assessing overall health and overall quality of life in the last week, both of which were scored from 1="very poor" to 7="excellent". The appropriateness of the other items is assessed on a 4-point Likert scale (1="not all" to 4="very much"). The validity and reliability of the questionnaire could be demonstrated [25]. Although this is a cancer-specific questionnaire, norm values are also available for a healthy German sample [26].

The brain module is recommended for use in conjunction with the EORTC QLQ-C30 [27]. It consists of additional 20 items that can be assigned to seven single-item scales and four multi-item scales. A standardized point value is calculated by linear transformation. Scores range from 0-100. A higher score for the function scales indicates better functionality, and a higher score for the symptom scales indicates greater symptom burden. Adequate psychometric properties were demonstrated [27].

Stress parameters: To assess stress-associated physiological parameters, the study physicians or the study nurses collect blood serum samples from the participants (20 ml EDTA blood) and pencil-thick strands of hair (2cm, refers to the area of the scalp, length at least 1cm) from the

back of the head [28]. The sample procurement points in time for blood serum and hair samples (hair length up to 7 cm) correspond to the time of the questionnaire assessments. For long hair (7 cm or more), one single pencil thick strand of hair will be collected at the last blood serum collection appointment. Hair sampling will not be performed in case of TTFields- or cortisone-treatment.

Sociodemographic and health data: As possible covariates and for sample description, participants will be asked at T1 to provide information regarding marital status, education and occupation, previous experiences with yoga and expectations regarding the classes as well as mental illnesses. In addition, at each measurement point in time, questions are asked about medication, actual treatment and the course of the disease. Patients' routine medical data (type and stage of disease, time of diagnosis, treatment) will be collected from the electronic patient file of the respective clinic by responsible study staff. For the continuous development of the intervention, participants will be asked about their general and specific satisfaction with individual features of the intervention at the end of the intervention (selected exercises, duration of a single yoga class, and instruction of the exercises, group size, and atmosphere in the class).

Data management

All questionnaire data as well as all blood serum and hair samples are marked with a pseudonym instead of the participant's name and a password-protected digital allocation list is used. The allocation list includes the participant's first and last name, date of birth, the clinic where the participant was recruited, the e-mail address under which the participant would like to be contacted, and whether the participant is a patient or a caregiver. This data is taken from the consent form. The study coordinator, who is responsible for the assignment list,

creates a pseudonymization code for each participant according to a predefined procedure. This is required to retrieve the data needed for sample description from the hospital information system as well as to process the blood serum and hair samples. During the period of the assignment, the research data will be considered “personal data” and data protection laws will be complied with.

At the end of data collection, the questionnaire data will be exported from the online platform used for the survey by the study coordinator and saved password-protected on a computer at the University Hospital of Würzburg. After that, the questionnaire data is deleted from the online platform. The site coordinators transmit the selected routine medical data of the participating patients to the study coordinator in accordance with data protection regulations. After data analysis, the assignment lists as well as the consent declarations are deleted. Deletion of the site-specific assignment lists provided will be confirmed in writing by the site coordinators. The raw data of the study will be destroyed after 10 years in accordance with data protection regulations. To prevent loss of study data, the study coordinator performs a regular backup. Hair samples are enclosed in aluminum foil after collection and the part close to the root is fixed with a paper clip. Samples are stored dry and dark at room temperature in a cardboard box/large envelope. The blood and serum samples, if not completely consumed for molecular stress marker determination, will be stored frozen at -80°C for the duration of the study. After completion of data collection, the samples will be picked up from the participating centers by the medical study management of the University Hospital Würzburg and brought to the laboratory of the Section Experimental Neurosurgery of the Department of Neurosurgery, University Hospital Würzburg. The analysis of the biological data is blinded. All sample remnants will be destroyed after completion of the study.

Analysis

Intent-to-treat as well as per protocol analyses should be performed. Participants who attended at least six out of the eight sessions are considered completers. The data of the patients and the relatives are analyzed separately. To test for group differences covariance analyses with adjustment for baseline values of outcome variables will be performed. We use eta² as the effect size calculated in covariance analyses. Eta²=0.0099 was assessed as a small effect, eta²=0.0588 as a medium effect, and eta²=0.1379 as a large effect according to Cohen. To analyze changes between post-intervention and follow-up two-tailed t-tests are performed. Standardized mean differences are used to calculate the effect size. A p-value of <0.05 is considered significant. Missing values due to drop-out will be analyzed by pair-wise deletion.

Data analysis is performed using International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) Statistics for Windows version 22.

Monitoring

The yoga instructors will document adverse effects, such as injuries, in writing immediately after each class, including necessary adjustments to the exercises. The documentation of presence is used to calculate the adherence rate.

Ethics and dissemination

The Ethics Committee of the University of Würzburg approved the described study protocol on 26.10.2021 (No.185/18-me). Important changes in the protocol will be passed on to the responsible ethics committee as well as the German Register of Clinical Trials and will be described in study reports. The investigation conforms to the principles outlined in the Declaration of Helsinki. Potential study participants will be informed about all relevant aspects of the study (goals, processes, data protection). This information will be provided verbally and

in writing by the research staff. In particular, the voluntary nature of the study participation as well as the possibility of discontinuing the study at any time without giving reasons and without any disadvantages for the treatment are emphasized. In the consent form, interested participants are specifically asked for their consent to provide blood serum and hair samples. They can consent either to provide both samples, to donate blood serum samples or hair samples only, or refuse to give such samples. Even without providing samples, participation in the study is possible. The consent form also asks for an e-mail address for further contact. Participation in the study is only possible with written consent. After completion of the study, a joint publication of the study results has been contractually agreed between the participating clinics. There are no publication restrictions. No professional writers are planned.

Discussion

The disease and its treatment often stress high-grade glioma patients and their caregivers. Depressive and anxious symptoms and reduced quality of life are frequently reported in the literature [7, 8]. Sometimes the emotional health of the caregivers is worse than that of the patients [8]. This multicenter study will offer high-grade glioma patients and their caregivers a mindfulness-based yoga course by examined yoga instructors, which has already proven helpful in previous studies with patients with mixed cancer entities [20, 29]. However, due to the heterogeneous sample characteristics of these previous studies, it remains unclear whether this yoga intervention is also helpful for improving emotional well-being and quality of life of high-grade glioma patients. In addition, the effectiveness of a mindfulness-based yoga intervention has not yet been studied for caregivers. Generally, yoga studies that exclusively include patients with high-grade glioma and their caregivers are rare [12]. Therefore, in this study the intervention will be provided exclusively for glioma patients CNS WHO grades 3 and 4 and their caregivers.

The aim of this randomized controlled study is to investigate whether significant changes of self-reported anxious and depressive symptoms and in quality of life are detectable after the intervention in the IG compared to the WCG. As in previous yoga studies [e.g. 11], self-report questionnaires will be used for this purpose. Furthermore, stress-associated physiological parameters extracted from blood and hair samples are also evaluated in this study. A possible demonstration of the effects of mindfulness-based online yoga therapy on a biochemical level could highlight the value of yoga in the supportive therapy of cancer patients and should be further investigated in future studies. Although the inclusion criteria regarding the type of disease (glioma patients CNS WHO grades 3 & 4) and the phase of the disease (diagnosis or recurrence) facilitate timely recruitment of the participants, they may also induce higher variance of the experienced limitations among the participants. In favor of greater homogeneity, specification of inclusion criteria regarding characteristics of the tumors based on the updated WHO Classification [1] is considered for this and recommended for future studies.

Due to the Covid-19 pandemic the yoga intervention, which we planned originally as an in-person course was adapted to an online format. Today, we expect this to actually bring other advantages for the vulnerable target group in comparison to on-site yoga. The participation in the online course may increase the sense of autonomy of patients with reduced mobility, as they do not need to be driven to class by family members. It also conserves caregivers' limited time resources due to caregiving and may reduce stress from travel. For this reason, the online yoga therapy if proven effective could be an attractive treatment approach for high-grade glioma patients and their caregivers even beyond the Covid-19 pandemic.

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Trial status

This trial is at protocol version 4, dated 05.07.2021.

Trial registration data set

See Supplementary file 1.

Ethics approval and consent to participate

The study conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Würzburg on 26.10.2021 (No.185/18-me). In addition, the study is registered in the German Register of Clinical Trials (No. DRKS00029554, 08/2022). Any changes to the study protocol must be approved by the responsible ethics committee and reported to the German Clinical Trials Registry. Potential participants will be informed about the study verbally and in writing. Written informed consent must be given for study participation (see Supplementary file 2).

Consent for publication

Not applicable.

Availability of data and materials

Only members of the research team will have access to the final data set. There are no data sharing plans.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

EJ is the psychological study director and AK is the medical study director. CH and JS will supervise the collection of the biomarkers and analyze them. AR is responsible for the implementation and the coordination of the study. All authors read and approved the final manuscript.

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Table 2. Trial registration data

Data category	Information
Primary registry and trial identifying number	DRKS-ID: DRKS00029554
Date of registration in primary registry	22 August 2022
Source(s) of monetary or material support	University Hospital Würzburg, Comprehensive Cancer Center Mainfranken; institutional budged/no external funding
Primary sponsor	University Hospital Würzburg, Comprehensive Cancer Center Mainfranken
Contact for public queries	Dr. Elisabeth Jentschke (Jentschke_E@ukw.de)
Contact for scientific queries	Dr. Elisabeth Jentschke (Jentschke_E@ukw.de)
Public and scientific title	Efficacy of an online yoga-intervention in patients with a brain-derived tumor of WHO grades 3 & 4 and their caregivers
Countries of recruitment	Germany
Health condition(s) or problem(s) studied	Brain-derived tumors (WHO grades 3 & 4)
Intervention(s)	Study group: online yoga intervention
	Waiting control group: online yoga intervention after eight weeks of waiting
Key inclusion and exclusion criteria	Inclusion criteria: Patients with a brain-derived tumor (WHO grades 3 &4, initial diagnosis and/or recurrent disease, 6 weeks after surgery at the earliest) and their caregivers, male and female, age of 18-years or older, regular access to a computer with internet access
	Exclusion criteria: Lack of German language abilities, severe cognitive, affective and physical limitations
Study type	Interventional
	Allocation: randomized
	Primary purpose: supportive care
Date of first enrolment	Enrollment is scheduled for the first quarter of 2024
Target sample size	140
Recruitment status	Recruiting planned
Primary outcome(s)	Anxiety (GAD-7) after intervention
Key secondary outcomes	Progression anxiety (PA-F-KF), quality of life (EORTC QLQ C30 + BN20), depression (PHQ-9), BDNF, DHEA/DHEAS, ferritin and hair cortisol after intervention and 3 months after the end of the intervention

Comprehensive Cancer Center Mainfranken

Einwilligungserklärung zur Teilnahme an der YINOTA-O-Studie

(Yoga-Intervention bei Neuroonkologischen Tumorpatienten und deren Angehörigen - Online)

„Erforschung der Wirksamkeit einer Online-Yogatherapie bei Patient:innen mit hirneigenem Tumor WHO Grade 3 und 4 und deren Angehörigen“

für Patient:innen

Name:…….

Vorname:……...

Geburtsdatum:……..

E-Mail-Adresse:…..……..

Ich bin von Herrn / Frau ……..über den Inhalt der Studie „Erforschung der Wirksamkeit einer Online-Yogatherapie bei Patient:innen mit hirneigenem Tumor WHO Grade 3 und 4 und deren Angehörigen“ informiert worden.

Alle meine Fragen sind zu meiner Zufriedenheit beantwortet worden. Ich hatte ausreichend Zeit, um meine Entscheidung zur Studienteilnahme zu überdenken und frei zu treffen. Die Studie wird von Dr. Elisabeth Jentschke von der Universitätsklinik Würzburg geleitet.

Eine schriftliche Teilnehmerinformation wurde mir ausgehändigt. Darin wurde mir versichert, dass

- die Teilnahme freiwillig ist,
- ich die Teilnahme jederzeit ohne Angabe von Gründen und ohne Nachteile abbrechen kann,
- keine personenbezogenen Angaben (Name, Geburtsdatum, Adresse) an Dritte weitergegeben werden,
- meine Angaben anonym ausgewertet werden,
- die geltenden Datenschutzbestimmungen eingehalten werden und eine unbefugte Weitergabe oder Veröffentlichung meiner persönlichen Daten nicht zulässig ist,
- die erhobenen Daten an der Uniklinik Würzburg zusammengeführt und verarbeitet werden - in einer Form, in der Rückschlüsse auf meine Person nicht mehr möglich sind.

Ich bin bereit, während des Studienzeitraums je nach Gruppenzuteilung insgesamt 3- bzw. 4-mal (1x vor der Zuordnung, 1x vor dem Kurs, 1x zum Ende des Kurses sowie 3 Monate nach Ende des Kurses) je 20 ml Blut- sowie eine Haarprobe abzugeben, die im Labor auf molekulare Stressmarker untersucht werden.

O nein O ja, beides O nur Haarproben O nur Blutproben

Ort, Datum Unterschrift der/s Teilnehmerin/s

Comprehensive Cancer Center Mainfranken

Teilnehmer:in

Ich bin damit einverstanden, dass medizinische Daten, wie in der Patienteninformation angegeben aus der Klinikakte entnommen werden. Ich möchte die Studie unterstützen und willige daher in die Teilnahme ein.

Ort, Datum Unterschrift der/s Teilnehmerin/s

Aufklärende Person

Der/die Teilnehmer:in wurde von mir im Rahmen eines Gesprächs über das Ziel und den Ablauf der Studie sowie über die Risiken aufgeklärt. Ein Exemplar der Informationsschrift und der Einwilligungserklärung wird an den/die Teilnehmer:in ausgehändigt.

Ort, Datum Unterschrift der aufklärenden Person

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	Item No	Description	Addressed on page number
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	Supplementary file 1
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	21
	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	21
	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)	9, 13

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	3-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5-6
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)	7, 9, 5
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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	7, 10-12, 14
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)	7

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9,13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	See 17a
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	10-13
	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	7

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	12-13
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	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	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)	14
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	n/a. The research team itself takes on the regular monitoring of the data, reducing the need for a separate committee (see page 7)
	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	9
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

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a. The members of the study team monitor and discuss all processes. No external auditing is mandatory for this trial
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a. No ancillary studies.
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	12-13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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	13-14

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	n/a (The risks of harm to participants in this study are minor and no compensation for harm is necessary)
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	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2 (German)
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	13-14

*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.

BMJ Open

Study protocol for a multicenter randomized controlled trial evaluating the efficacy of an online yoga-intervention in high-grade glioma patients and their caregivers: The YINOTA-O-trial

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Study protocol for a multicenter randomized controlled trial evaluating the efficacy of an online yoga-intervention in high-grade glioma patients and their caregivers: The YINOTA-O-trial

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Introduction: High-grade glioma patients and their caregivers often suffer from distress and a lower quality of life. Results from studies with patients with mixed cancer entities suggest that yoga can be an effective support. However, it is unclear whether this also applies to high-grade glioma patients and their caregivers. This study aims to investigate the effects of mindfulness-based online yoga for patients and their caregivers on emotional distress, quality of life and stress-associated physiological parameters compared to a waiting control group (WCG).

Methods & analysis: The study is designed as a multicenter randomized controlled trial. Adult glioma patients (CNS WHO grades 3 & 4) and their caregivers will be recruited. Examined yoga instructors deliver the intervention (1 h/week) in a synchronous format over 8 weeks via video conferencing. The WCG will receive standard care during the 8-week waiting period. Data will be collected before and after the end of the intervention and another 3 months later using questionnaires as well as blood serum and hair samples to evaluate biochemical stress parameters. Primary outcome is self-reported generalized anxiety and secondary outcomes are self-reported progression anxiety, depression, quality of life as well as BDNF, DHEA/DHEAS, Ferritin and hair cortisol. We hypothesize better outcomes in the intervention group (IG) compared to the WCG at all measurement points. 70 patients and 70 caregivers will be recruited consecutively. Primary endpoints are significant effect detections in the Generalized Anxiety Disorder Scale-7 of patients and caregivers at the end of the intervention. Analyses of covariance will be performed to analyze treatment effects.

Ethics and dissemination: The Ethics Committee of the University of Würzburg approved the YINOTA-O study on 26.10.2021 (No.185/18-me). Results will be presented at conferences and published in peer-reviewed journals.

Trial registration: German Clinical Trials Register (No. DRKS00029554, 08/2022).

Strengths and limitations of this study

- Simultaneous collection of subjective questionnaire data and objective physiological parameters
- Implementation of a tailored yoga intervention designed specifically to meet the unique needs of cancer patients

- The inclusion in the study without pre-screening for the identification of distressed patients and caregivers may influence the detection of treatment effects
- The inclusion criteria regarding the type of disease (glioma patients CNS WHO grades 3 & 4) and the phase of the disease (diagnosis or recurrence) may induce higher variance of the experienced symptoms among the participants

Introduction

The most recent version of the WHO Classification of Tumors of the Central Nervous System [1] reflects the rapid advances in the understanding of brain tumors [2]. While a better understanding of the pathophysiology of these tumors may have a positive impact on the treatment [3], the treatment options for high-grade gliomas remain limited.

At the time of diagnosis, glioma patients often report cognitive deficits, seizures, headaches, dizziness, and motor deficits [4]. As the disease progresses, drowsiness, dysphagia, confusion, and aphasia expand the list of symptoms [4] and can reduce the patients´ autonomy [5]. Family members frequently take on the role of caregivers, conducting “physically, emotionally, socially and/or financially demanding” tasks [6]. Thus the diagnosis of a high grade glioma imposes a burden and significant reduction in quality of life for both the patients and their caregivers. Ståhl and colleagues examined the extent of anxious and depressive symptoms as well as health-related quality of life in both glioblastoma patients and their caregivers before surgery [7]. Caregivers reported significantly inferior health-related quality of life, more anxiety, and more depressive symptoms than the patients did. These findings are consistent with those of previous studies [e.g. 8]. They imply that high-grade glioma patients as well as their caregivers should be offered support to deal with disease-related psychological distress.

Yoga is increasingly recognized as a complementary therapy for improving quality of life and cancer-related symptoms [9]. In recent years, several meta-analyses evaluated the effectiveness of yoga on anxiety and depression in cancer patients [10, 11]. Lin et al. as well as Gonzalez et al. reported significant medium effects of yoga on anxiety and significant medium to large effects on depression compared to the control conditions [10,11]. Most studies were conducted with breast cancer patients which is why no meta insights can be derived for the glioma patient population.

One referenced study examined a yoga intervention for glioma patients in an on-site setting [12]. Milbury et al. studied the feasibility of a dyadic yoga program for high-grade glioma patients and their caregivers during radiotherapy as well as its effects on cancer-related symptoms [12]. Comparing the intervention group and the waiting control group, patients in the intervention group showed significantly lower levels of depression and a significantly higher mental quality of life at post-assessment. In the caregivers' intervention group treatment effects were even more pronounced with a large effect size for improvement in depression. These results are encouraging but due to the on-site course format, require the physical presence of participants at the course location. Seizures can limit the patients' mobility and thereby impede their participation in supportive services on site. Alternatively, services, which can be attended from home, e.g. in an online format, could facilitate access supportive care for the target group. To date, only few studies were published examining online yoga interventions [13, 14]. None of them concern the group of glioma patients. The initial indications of feasibility cannot be generalized to brain tumor patients as they have brain tumor-specific symptoms like motor deficits [4] that need to be dealt with. In order to provide individual support from the yoga teachers, a synchronous online format seems appropriate for the target group but has not yet been investigated. It allows interaction with

the instructor as well as simultaneous supervision. To evaluate the feasibility of such an intervention for both patients and their caregivers, a monocentric pilot study was conducted in 2020, demonstrating its practicality and participant satisfaction [15].

The use of subjective measurement tools for assessing potential effects of yoga interventions on anxiety and depression seems appropriate, given the subjective nature of these criteria. Nonetheless, it remains unclear whether intervention effects are also detectable at the biological level. Initial indications of the effects of yoga interventions on biological parameters are derived from studies involving non-clinical populations [16, 17, 18] as well as patients with myeloproliferative neoplasms [13]; evidence for glioma patients and their caregivers is missing.

The purpose of this study is to explore the potential benefits of mindfulness-based yoga for high-grade glioma patients and their caregivers. It aims to determine if participating in an 8-week online intervention program can significantly reduce emotional distress and improve the quality of life and stress-associated physiological parameters. In this regard, the following research questions will be examined:

1. Primary research question

   Does an eight-week online yoga intervention for high-grade glioma patients and their caregivers reduce self-reported generalized anxiety symptoms directly after the intervention compared to a WCG, and do these improvements persist three months after the intervention? *We hypothesize that compared to participants in the WCG, participants in the IG will report significantly fewer generalized anxiety symptoms both immediately post-intervention and at the three-month follow-up.*

2. Secondary research question

Does such an intervention reduce self-reported fear of progression, depressive symptoms, quality of life and stress-associated physiological parameters (BDNF, DHEA/DHEAS, ferritin, hair cortisol) directly after the intervention compared to a WCG, and do these improvements persist three months after the intervention? *We hypothesize that the outcomes of participants in the intervention group will be superior to those of participants in the WCG in all aspects both immediately post-intervention and at the three months follow-up.*

Methods

Participants

Eligible for the study are adult (≥ 18 years) patients with glioma CNS WHO grades 3 & 4 (initial diagnosis or recurrence) treated in participating hospitals in Germany (University Hospital Würzburg, University Hospital Mannheim, Aschaffenburg-Alzenau Hospital, University Hospital Augsburg) and their caregivers. Patients are eligible to participate at any time point of treatment, but we recommend joining the yoga program not earlier than six weeks after surgery. Prerequisite for participation is regular access to a mobile device with internet access. Exclusion criteria are insufficient German language skills and serious cognitive, affective, or physical impairments. The study physicians and staff consider exclusion criteria during the recruitment process. Participants are advised not to concurrently engage in other supportive interventions for psychological distress throughout the duration of the study.

Study centers

Study centers are only eligible to participate in this study if they have the ability to process blood serum samples and store them in a deep-freezer at -80 degrees. Moreover, a positive ethics approval from the hospital's internal ethics committee and the execution of a cooperation agreement are mandatory. Other clinics in Germany, excluding those mentioned, are still in the process of fulfilling these requirements.

Study design and measurement points in time

This is a multicentric randomized controlled trial with an IG and a WCG. First, the IG receives the 8-week online yoga intervention delivered by videoconference (Zoom Video Communications). Subsequently, the WCG receives the same intervention. During the waiting period, the WCG receives the medical standard of care and if needed additional psychological and supportive care. Psychological support is provided by the psycho-oncology service as the standard procedure, either following a positive result from a routine distress screening (for inpatients) or at the request of the patient or their relatives. Other support services (e.g. nutritional counselling) will also be provided at request. Brochures in the hospital provide information about the services and contact details. Measurement points for the IG are: Before randomization (T1), at the end of the intervention (T2) and 3 months after the last scheduled yoga class (T4). Measurement points for the WCG are: Before randomization (T1), at the end of the intervention of the IG / before the start of the intervention of the WCG (T2), at the end of the intervention (T3) and 3 months after the last scheduled yoga class (T5). At each measurement point in time, questionnaire data as well as a blood serum and hair samples will be collected (Table 1). Study staff will supervise the status of data collection. Participant data will be collected within a two-week timeframe before start and after end of the intervention. In case of missing data, participants will be reminded by telephone up to three times. This also

applies to the follow-up. The planned start of the study is April 2024 and the expected end of the study is April 2026. This trial is at protocol version 4, dated 05.07.2021. Table 1 shows the study workflow.

Table 1. Schedule of enrolment, interventions, and assessments, according to Spirit 2013 guidelines

	Enrolment	Before allocation	After T1	Post-allocation			
TIMEPOINT	**$-T_1$**	**T1**		***T2***	***T3 (only WCG)***	***T4 (only IG)***	***T5 (only WCG)***
ENROLMENT:							
Eligibility screen	x						
Informed consent	x						
Allocation			x				
INTERVENTIONS:							
Online Yoga (IG)			◆—	——			
Online Yoga (WCG)				◆—	——		
ASSESSMENTS:							
socio-demographic data		x					
Medical data		x		x	x	x	x
Generalized anxiety		x		x	x	x	x
Fear of progression (only patients)		x		x	x	x	x
Depression		x		x	x	x	x
Quality of Life Questionnaire +		x		x	x	x	x

Brain Module (only patients)							
BDNF, DHEA/DHEAS, ferritin, hair cortisol		x		x	x	x	x
Evaluation						x	x

Patient and public involvement statement

The study was inspired by the positive experiences of a relative of a brain tumor patient with yoga during the disease and developed in exchange with her. Feedback from participants after the pilot study [15] was considered in the multicenter study.

Yoga intervention

It is recommended that participation in the study is discussed with a physician in advance to determine if yoga is appropriate for the participant's medical condition and to address any specific concerns related to the participant's medical condition. Yoga classes are held once a week for 60 minutes. Patients and caregivers will be taught successively in separate groups of 10 participants per group to ensure that caregivers are potentially nearby in case patients require support. As recommended in the literature [14], the groups will be closed groups. The intervention is based on the mindfulness-based hatha yoga described by Jon Kabatt-Zinn [19]. The intervention is carried out by certified yoga instructors (>200 units). The classes consist of a sequence of breathing exercises (pranayama), physical exercises (asanas) and meditation, which is repeated in each lesson. The exercises were selected in such a way that even patients with advanced disease can perform them with a mindful practice. The intervention is described in detail in Zetzl et al. [20]. For the sake of standardization of the yoga classes, yoga instructors are trained in advance by video-support, demonstrating all the exercises provided.

Alternative variations of the exercises will be discussed during the training session for participants who may face challenges in performing certain exercises due to impairments. In addition, a booklet is available, describing all exercises and providing important information on possible cancer-specific and cancer non-specific contraindications. To minimize technical difficulties, participants will be offered a technical rehearsal, and they will receive instructions on using the video platform.

Sample-size calculation

Based on previous research [10], a Standardized Mean Difference (SMD) of 0.76 is expected for generalized anxiety in favor of the IG when comparing the IG to the control group. Consequently, a case number of n=29 per group (α =0.05 and beta=0.20) will be determined for a two-tailed independent samples t-test. Based on the dropout rates reported in the reference studies [12-13, 20], 70 patients and 70 relatives will be recruited.

Recruitment

Based on the defined inclusion criteria, physicians and research staff of participating study centers will search for potential participants via the centers' electronic medical record systems. Eligible persons will be informed personally about the study during their outpatient consultation by their doctor or a member of the study team. The patients' caregivers – if not present at the outpatient visit - will be informed by telephone. If patients and/or their caregivers are interested in study participation, they will receive the written participation information and the consent form. They approve their participation by signing the latter and sending it by mail to the study coordinator. Recruitment will be concluded once the required sample size is reached.

Randomization and allocation concealment

Participants will be consecutively enrolled in the study and randomly assigned to the IG or WCG. Utilizing a computer-generated list of random numbers ensures a close balance of the group sizes at any time during the trial by external blocked randomization (allocation rate 1:1). The list is generated and managed by an employee of the University Hospital Würzburg who is not involved in the study. If both patients and their caregivers participate in the intervention, they are randomized as a pair. For every block of 20 patients and 20 caregivers, 20 participants (10 patients, 10 caregivers) will be allocated to each arm of the trial. The study coordinator will request the results of the randomization after the initial survey is completed and convey it to the participants. Participants are then no longer blinded. If there is a likelihood of missing two sessions, randomization will be delayed.

Data collection, management, and analysis

Data collection

An online questionnaire, blood serum samples and hair samples are used to collect the required data. The online questionnaire is created and administered using the EvaSys evaluation software. Participants can access it via a web-link. On the first page of the online questionnaire, participants are instructed to enter their assignment code, which they received in advance per e-mail.

Primary outcomes

Self-reported generalized anxiety: The German version of the Generalized Anxiety Scale (GAD-7) [21] is used to assess anxious symptoms. Participants are asked to indicate the frequency of perceived impairment by seven symptoms on a 4-point Likert scale (0="not at all" to 4="almost every day") in the last two weeks. The internal consistency is

Cronbachs α = 0.85, indicating high reliability [22]. A sum value is calculated from all items (range: 0-21). The higher the value, the greater the severity of the anxiety.

Secondary outcomes

Self-reported fear of progression: The patient questionnaire contains a short form of the Fear of Progression Questionnaire (FoP-Q-SF) with 12 items (PA-F-KF). The answers are given on a five-point Likert scale (1="never"; 5="very often"). Good reliability (Cronbachs α =0.87) and validity were demonstrated in a German sample of breast cancer patients [23]. For analysis, a sum value is calculated from all items (range: 12-60). The higher the value, the greater the severity of the anxiety.

Self-reported depression: The Patient Health Questionnaire-9 (PHQ-9) consists of nine items regarding the impairment due to depressive symptoms in the past two weeks. A 4-point Likert scale is used (0="not at all" to 3="almost every day"). Good reliability (Cronbachs α = 0.89) and validity were demonstrated in a sample of patients with different medical conditions [24]. For analysis, a sum score is calculated from all items. The higher the value, the greater the severity of depression (range: 0-27).

Self-reported Qualify of Life: The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire C30 (QLQ-C30) plus brain module (BN20) are used to assess quality of life. The EORTC QLQ-C30 consists of 30 questions that can be assigned to ten subscales. Two items assessing overall health and overall quality of life in the last week, both of which were scored from 1="very poor" to 7="excellent". The appropriateness of the other items is assessed on a 4-point Likert scale (1="not all" to 4="very much"). The validity and reliability of the questionnaire could be demonstrated [25]. Although this is a cancer-specific questionnaire, norm values are also available for a healthy German sample [26].

The brain module is recommended for use in conjunction with the EORTC QLQ-C30 [27]. It consists of additional 20 items that can be assigned to seven single-item scales and four multi-item scales. A standardized point value is calculated by linear transformation. Scores range from 0-100. A higher score for the function scales indicates better functionality, and a higher score for the symptom scales indicates greater symptom burden. Adequate psychometric properties were demonstrated [27].

Stress parameters: To assess stress-associated physiological parameters, the study physicians or the study nurses collect blood serum samples from the participants (20 ml EDTA blood) and pencil-thick strands of hair (2cm, refers to the area of the scalp, length at least 1cm) from the back of the head [28]. The sample procurement points in time for blood serum and hair samples (hair length up to 7 cm) correspond to the time of the questionnaire assessments. For long hair (7 cm or more), one single pencil thick strand of hair will be collected at the last blood serum collection appointment. Hair sampling will not be performed in case of TTFields- or cortisone-treatment.

Sociodemographic and health data: As possible covariates and for sample description, participants will be asked at T1 to provide information regarding marital status, education and occupation, previous experiences with yoga and expectations regarding the classes as well as mental illnesses. In addition, at each measurement point in time, questions are asked about medication, actual treatment, and the course of the disease. Patients' routine medical data (type and stage of disease, time of diagnosis, treatment) will be collected from the electronic patient file of the respective clinic by responsible study staff. For the continuous development of the intervention, participants will be asked about their general and specific satisfaction with individual features of the intervention at the end of the intervention (selected exercises,

duration of a single yoga class, and instruction of the exercises, group size, and atmosphere in the class).

Data management

All questionnaire data as well as all blood serum and hair samples are marked with a pseudonym instead of the participant's name and a password-protected digital allocation list is used. The allocation list includes the participant's first and last name, date of birth, the clinic where the participant was recruited, the e-mail address under which the participant would like to be contacted, and whether the participant is a patient or a caregiver. This data is taken from the consent form. The study coordinator, who is responsible for the assignment list, creates a pseudonymization code for each participant according to a predefined procedure. This is required to retrieve the data needed for sample description from the hospital information system as well as to process the blood serum and hair samples. During the period of the assignment, the research data will be considered “personal data” and data protection laws will be complied with.

At the end of data collection, the questionnaire data will be exported from the online platform used for the survey by the study coordinator and saved password-protected on a computer at the University Hospital of Würzburg. After that, the questionnaire data is deleted from the online platform. The site coordinators transmit the selected routine medical data of the participating patients to the study coordinator in accordance with data protection regulations. After data analysis, the assignment lists as well as the consent declarations are deleted. Deletion of the site-specific assignment lists provided will be confirmed in writing by the site coordinators. The raw data of the study will be destroyed after 10 years in accordance with data protection regulations. To prevent loss of study data, the study coordinator performs a

regular backup. Hair samples are enclosed in aluminum foil after collection and the part close to the root is fixed with a paper clip. Samples are stored dry and dark at room temperature in a cardboard box/large envelope. The blood and serum samples, if not completely consumed for molecular stress marker determination, will be stored frozen at -80°C for the duration of the study. After completion of data collection, the samples will be picked up from the participating centers by the medical study management of the University Hospital Würzburg and brought to the laboratory of the Section Experimental Neurosurgery of the Department of Neurosurgery, University Hospital Würzburg. The analysis of the biological data is blinded. All sample remnants will be destroyed after completion of the study.

Analysis

Intent-to-treat as well as per-protocol analyses should be performed. Participants who attended at least six out of the eight sessions are considered completers. The data of the patients and the relatives are analyzed separately. To test for group differences covariance analyses with adjustment for baseline values of outcome variables will be performed. To calculate the adherence rate, the average number of sessions the participants attended will be calculated. We use eta² as the effect size calculated in covariance analyses. Eta²=0.0099 was assessed as a small effect, eta²=0.0588 as a medium effect, and eta²=0.1379 as a large effect according to Cohen. To analyze changes between post-intervention and follow-up two-tailed t-tests are performed. Standardized mean differences are used to calculate the effect size. A p-value of <0.05 is considered significant. Missing values due to drop-out will be analyzed by pair-wise deletion.

Data analysis is performed using International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) Statistics for Windows version 22.

Monitoring

The yoga instructors will document adverse effects, such as injuries, in writing immediately after each class, including necessary adjustments to the exercises. The documentation of presence is used to calculate the adherence rate.

Ethics and dissemination

The Ethics Committee of the University of Würzburg approved the described study protocol on 26.10.2021 (No.185/18-me). Important changes in the protocol will be passed on to the responsible ethics committee as well as the German Register of Clinical Trials and will be described in study reports. The investigation conforms to the principles outlined in the Declaration of Helsinki. Potential study participants will be informed about all relevant aspects of the study (goals, processes, data protection). This information will be provided verbally and in writing by the research staff. In particular, the voluntary nature of the study participation as well as the possibility of discontinuing the study at any time without giving reasons and without any disadvantages for the treatment are emphasized. In the consent form, interested participants are specifically asked for their consent to provide blood serum and hair samples. They can consent either to provide both samples, to donate blood serum samples or hair samples only, or refuse to give such samples. Even without providing samples, participation in the study is possible. The consent form also asks for an e-mail address for further contact. Participation in the study is only possible with written consent. After completion of the study, a joint publication of the study results has been contractually agreed between the participating clinics. There are no publication restrictions. No professional writers are planned.

Discussion

The disease and its treatment often stress high-grade glioma patients and their caregivers. Depressive and anxious symptoms and reduced quality of life are frequently reported in the literature [7, 8]. Sometimes the emotional health of the caregivers is worse than that of the patients [8]. This multicenter study will offer high-grade glioma patients and their caregivers a mindfulness-based yoga course by examined yoga instructors, which has already proven helpful in previous studies with patients with mixed cancer entities [20, 29]. However, due to the heterogeneous sample characteristics of these previous studies, it remains unclear whether this yoga intervention is also helpful for improving emotional well-being and quality of life of high-grade glioma patients. In addition, the effectiveness of a mindfulness-based yoga intervention has not yet been studied for caregivers. Generally, yoga studies that exclusively include patients with high-grade glioma and their caregivers are rare [12]. Therefore, in this study the intervention will be provided exclusively for glioma patients CNS WHO grades 3 and 4 and their caregivers.

The aim of this randomized controlled study is to investigate whether significant changes of self-reported anxious and depressive symptoms and in quality of life are detectable after the intervention in the IG compared to the WCG. As in previous yoga studies [e.g. 11], self-report questionnaires will be used for this purpose. Furthermore, stress-associated physiological parameters extracted from blood and hair samples are also evaluated in this study. A possible demonstration of the effects of mindfulness-based online yoga therapy on a biochemical level could highlight the value of yoga in the supportive therapy of cancer patients and should be further investigated in future studies. Although the inclusion criteria regarding the type of disease (glioma patients CNS WHO grades 3 & 4) and the phase of the disease (diagnosis or recurrence) facilitate timely recruitment of the participants, they may also induce higher variance of the experienced limitations among the participants. In favor of greater

homogeneity, specification of inclusion criteria regarding characteristics of the tumors based on the updated WHO Classification [1] is considered for this and recommended for future studies.

Due to the Covid-19 pandemic the yoga intervention, which we planned originally as an in-person course was adapted to an online format. Today, we expect this to actually bring other advantages for the vulnerable target group in comparison to on-site yoga. The participation in the online course may increase the sense of autonomy of patients with reduced mobility, as they do not need to be driven to class by family members. It also conserves caregivers' limited time resources due to caregiving and may reduce stress from travel. For this reason, the online yoga therapy if proven effective could be an attractive treatment approach for high-grade glioma patients and their caregivers even beyond the Covid-19 pandemic.

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Trial registration data set

See Supplementary file 1.

Ethics approval and consent to participate

The study conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Würzburg on 26.10.2021 (No.185/18-me). In addition, the study is registered in the German Register of Clinical Trials (No. DRKS00029554, 08/2022). Any changes to the study protocol must be approved by the responsible ethics committee and reported to the German Clinical Trials Registry. Potential participants will be informed about the study verbally and in writing. Written informed consent must be given for study participation (see Supplementary file 2).

Consent for publication

Not applicable.

Availability of data and materials

Only members of the research team will have access to the final data set. There are no data sharing plans.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EJ is the psychological study director and AK is the medical study director. CH and JS will supervise the collection of the biomarkers and analyze them. AR is responsible for the implementation and the coordination of the study. All authors read and approved the final manuscript.

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Table 1. Trial registration data

Data category	Information
Primary registry and trial identifying number	DRKS-ID: DRKS00029554
Date of registration in primary registry	22 August 2022
Source(s) of monetary or material support	University Hospital Würzburg, Comprehensive Cancer Center Mainfranken; institutional budged/no external funding
Primary sponsor	University Hospital Würzburg, Comprehensive Cancer Center Mainfranken
Contact for public queries	Dr. Elisabeth Jentschke (Jentschke_E@ukw.de)
Contact for scientific queries	Dr. Elisabeth Jentschke (Jentschke_E@ukw.de)
Public and scientific title	Efficacy of an online yoga-intervention in patients with a brain-derived tumor of WHO grades 3 & 4 and their caregivers
Countries of recruitment	Germany
Health condition(s) or problem(s) studied	Brain-derived tumors (WHO grades 3 & 4)
Intervention(s)	Study group: online yoga intervention
	Waiting control group: online yoga intervention after eight weeks of waiting
Key inclusion and exclusion criteria	Inclusion criteria: Patients with a brain-derived tumor (WHO grades 3 &4, initial diagnosis and/or recurrent disease, 6 weeks after surgery at the earliest) and their caregivers, male and female, age of 18-years or older, regular access to a computer with internet access
	Exclusion criteria: Lack of German language abilities, severe cognitive, affective and physical limitations
Study type	Interventional
	Allocation: randomized
	Primary purpose: supportive care
Date of first enrolment	Enrollment is scheduled for the first quarter of 2024
Target sample size	140
Recruitment status	Recruiting planned
Primary outcome(s)	Anxiety (GAD-7) after intervention
Key secondary outcomes	Progression anxiety (PA-F-KF), quality of life (EORTC QLQ C30 + BN20), depression (PHQ-9), BDNF, DHEA/DHEAS, ferritin and hair cortisol after intervention and 3 months after the end of the intervention

Comprehensive Cancer Center Mainfranken

Einwilligungserklärung zur Teilnahme an der YINOTA-O-Studie

(Yoga-Intervention bei Neuroonkologischen Tumorpatienten und deren Angehörigen - Online)

„Erforschung der Wirksamkeit einer Online-Yogatherapie bei Patient:innen mit hirneigenem Tumor WHO Grade 3 und 4 und deren Angehörigen“

für Patient:innen

Name:…….

Vorname:……...

Geburtsdatum:……..

E-Mail-Adresse:…..……..

Ich bin von Herrn / Frau ……..über den Inhalt der Studie „Erforschung der Wirksamkeit einer Online-Yogatherapie bei Patient:innen mit hirneigenem Tumor WHO Grade 3 und 4 und deren Angehörigen“ informiert worden.

Alle meine Fragen sind zu meiner Zufriedenheit beantwortet worden. Ich hatte ausreichend Zeit, um meine Entscheidung zur Studienteilnahme zu überdenken und frei zu treffen. Die Studie wird von Dr. Elisabeth Jentschke von der Universitätsklinik Würzburg geleitet.

Eine schriftliche Teilnehmerinformation wurde mir ausgehändigt. Darin wurde mir versichert, dass

- die Teilnahme freiwillig ist,
- ich die Teilnahme jederzeit ohne Angabe von Gründen und ohne Nachteile abbrechen kann,
- keine personenbezogenen Angaben (Name, Geburtsdatum, Adresse) an Dritte weitergegeben werden,
- meine Angaben anonym ausgewertet werden,
- die geltenden Datenschutzbestimmungen eingehalten werden und eine unbefugte Weitergabe oder Veröffentlichung meiner persönlichen Daten nicht zulässig ist,
- die erhobenen Daten an der Uniklinik Würzburg zusammengeführt und verarbeitet werden - in einer Form, in der Rückschlüsse auf meine Person nicht mehr möglich sind.

Ich bin bereit, während des Studienzeitraums je nach Gruppenzuteilung insgesamt 3- bzw. 4-mal (1x vor der Zuordnung, 1x vor dem Kurs, 1x zum Ende des Kurses sowie 3 Monate nach Ende des Kurses) je 20 ml Blut- sowie eine Haarprobe abzugeben, die im Labor auf molekulare Stressmarker untersucht werden.

O nein O ja, beides O nur Haarproben O nur Blutproben

Ort, Datum Unterschrift der/s Teilnehmerin/s

Comprehensive Cancer Center Mainfranken

Teilnehmer:in

Ich bin damit einverstanden, dass medizinische Daten, wie in der Patienteninformation angegeben aus der Klinikakte entnommen werden. Ich möchte die Studie unterstützen und willige daher in die Teilnahme ein.

Ort, Datum Unterschrift der/s Teilnehmerin/s

Aufklärende Person

Der/die Teilnehmer:in wurde von mir im Rahmen eines Gesprächs über das Ziel und den Ablauf der Studie sowie über die Risiken aufgeklärt. Ein Exemplar der Informationsschrift und der Einwilligungserklärung wird an den/die Teilnehmer:in ausgehändigt.

Ort, Datum Unterschrift der aufklärenden Person

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

Section/item	Item No	Description	Addressed on page number
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	Supplementary file 1
Protocol version	3	Date and version identifier	8
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	21
	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	N/A [see 5a-5b]
	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)	11, 14-15

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	3-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5-6
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)	5-7, 10
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	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)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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	11-15
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)	8

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	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
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	10
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	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A [see 17a]
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	11-14
	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	7

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	14-15
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	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A [No additional analyses are planned]
	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)	15
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	N/A [The research team itself takes on the regular monitoring of the data, reducing the need for a separate committee]
	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	N/A [Recruitment will be concluded once the required sample size is reached]
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	16

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A [The members of the study team monitor and discuss all processes. No external auditing is mandatory for this trial]
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
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)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A [No ancillary studies]
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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	21

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	N/A [The risks of harm to participants in this study are minor and no compensation for harm is necessary]
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	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset and statistical code	2, 21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2 (German)
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	13-15

*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.