

BMJ Open Study protocol for a multicentre randomised 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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ABSTRACT

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 with a waiting control group (WCG).

Methods & analysis The study is designed as a multicentre randomised controlled trial. Adult glioma patients (central nervous system WHO grades 3 and 4) and their caregivers will be recruited. Examined yoga instructors deliver the intervention (1 hour per 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 generalised anxiety and secondary outcomes are self-reported fear of progression, depression and quality of life as well as brain-derived neurotrophic factor (BDNF), dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS), ferritin and hair cortisol. We hypothesise better outcomes in the intervention group compared with the WCG at all measurement points. 70 patients and 70 caregivers will be recruited consecutively. Primary endpoints are significant effect detections in the Generalised Anxiety Disorder scale-7 of patients and caregivers at the end of the intervention. Analyses of covariance will be performed to analyse the treatment effects.

Ethics and dissemination The Ethics Committee of the University of Würzburg approved the YINOTA-O (Yoga-Intervention bei Neuroonkologischen Tumorpateinten und deren Angehörigen - Online) study on 26 October 2021 (No.185/18-me). Results will be presented at conferences and published in peer-reviewed journals.

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 prescreening 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 central nervous system WHO grades 3 and 4) and the phase of the disease (diagnosis or recurrence) may induce a higher variance of the experienced symptoms among the participants.

Trial registration number German Clinical Trials Register No. DRKS00029554.

INTRODUCTION

The most recent version of the WHO Classification of Tumours of the Central Nervous System (CNS)¹ reflects the rapid advances in the understanding of brain tumours.² While a better understanding of the pathophysiology of these tumours 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 symptoms⁴ 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 anxiety 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 (eg,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 recognised 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 with 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 programme for high-grade glioma patients and their caregivers during radiotherapy as well as its effects on cancer-related symptoms.¹² Comparing the intervention group (IG) and the waiting control group (WCG), patients in the IG showed significantly lower levels of depression and a significantly higher mental quality of life at post-assessment. In the caregivers' IG 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, for example, in an online format, could facilitate access to 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 generalised to brain tumour patients as they have brain tumour-specific symptoms like motor deficits⁴ 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 the 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^{16–18} 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 programme 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 eightweek online yoga intervention for high-grade glioma patients and their caregivers reduce self-reported generalised anxiety symptoms directly after the intervention compared to a WCG, and do these improvements persist three months after the intervention? *We hypothesise that compared with participants in the WCG, participants in the IG will report significantly fewer generalised anxiety symptoms both immediately postintervention and at the 3-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 hypothesise that the outcomes of participants in the IG will be superior to those of participants in the WCG in all aspects both immediately postintervention and at the 3-month follow-up.*

METHODS

Participants

Eligible for the study are adult (≥ 18 years) patients with glioma CNS WHO grades 3 and 4 (initial diagnosis or recurrence) treated in participating hospitals in Germany (University Hospital Würzburg, University Hospital Mannheim, Aschaffenburg-Alzenau Hospital, University Hospital Essen and University Hospital Augsburg) and their caregivers. Patients are eligible to participate at any time during treatment, but we recommend joining the yoga programme not earlier than 6 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 centres

Study centres 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°C . Moreover, a positive ethics approval from the hospital's internal ethics committee and the execution of a cooperation agreement are mandatory.

Study design and measurement points in time

This is a multicentric randomised 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 (eg, 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 randomisation (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 randomisation (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 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 2-week timeframe before the start and after the 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 was April 2024 and the expected end of the study is April 2026. This trial is at protocol V.4, dated 05 July 2021. table 1 shows the study workflow.

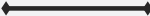
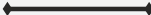
Patient and public involvement statement

The study was inspired by the positive experiences of a relative of a brain tumour patient with yoga during the disease and developed in exchange with her. Feedback from participants after the pilot study¹⁵ was considered in the multicentre 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 min. Patients and caregivers will be taught successively in separate groups of 10 participants per group to ensure that caregivers are potentially nearby

Table 1

	Enrolment	Before allocation	Post-allocation				
TIMEPOINT	-T ₁	T1	After 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
Generalised 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

BDNF, Brain-derived neurotrophic factor; DHEA, Dehydroepiandrosterone ; DHEAS, Dehydroepiandrosterone Sulfate.

BDNF, Brain-derived neurotrophic factor; DHEA, Dehydroepiandrosterone ; DHEAS, Dehydroepiandrosterone Sulfate.

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 Kabat-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 by Zetzl *et al.*²⁰ For the sake of standardisation 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 minimise the 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 standardised mean difference (SMD) of 0.76 is expected for generalised anxiety in favour of the IG when comparing the IG to the control group. Consequently, a case number of $n=29$ per group ($\alpha=0.05$ 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 centres will search for potential participants via the centres' 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.

Randomisation and allocation concealment

Participants will be consecutively enrolled in the study and randomly assigned to the IG or WCG. Using a computer-generated list of random numbers ensures a close balance of the group sizes at any time during the trial by external blocked randomisation (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 randomised as a pair. For every block of 20 patients and 20 caregivers, 20 participants (10 patients and 10 caregivers) will be allocated to each arm of the trial. The study coordinator will request the results of the randomisation 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, randomisation 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 email.

Primary outcomes

Self-reported generalised anxiety: The German version of the Generalised Anxiety Disorder-7 (GAD-7)²¹ is used to assess symptoms of anxiety. 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 2 weeks. The internal consistency is Cronbachs $\alpha=0.85$, 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 with 12 items (FoP-Q-SF). The answers are given on a five-point Likert scale (1='never' to 5='very often'). Good reliability (Cronbachs $\alpha=0.87$) 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 2 weeks. A 4-point Likert scale is used (0='not at all' to 3='almost every day'). Good reliability (Cronbachs $\alpha=0.89$) 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 quality of life: The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire C30 (QLQ-C30) plus brain module (BN20) are used to assess the quality of life. The EORTC QLQ-C30 consists of 30 questions that can be assigned to 10 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 at 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 standardised point value is calculated by linear transformation. Scores range from 0 to 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 (2 cm, refers to the area of the scalp, length at least 1 cm) 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 the case of Tumor Treating Fields (TTFs) 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 and 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 and the email 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 pseudonymisation 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 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 aluminium 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 centres 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 analysed 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 η^2 as the effect size calculated in covariance analyses. $\eta^2=0.0099$ was assessed as a small effect, $\eta^2=0.0588$ as a medium effect and $\eta^2=0.1379$ as a large effect according to Cohen. To analyse the changes between postintervention and follow-up two-tailed t-tests are performed. SMDs are used to calculate the effect size. A p-value of <0.05 is considered significant. Missing values due to drop-out will be analysed by pairwise deletion.

Data analysis is performed using International Business Machines Corporation Statistical Package for Social Sciences Statistics for Windows V.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 October 2021 (No.185/18-me). Important changes in the protocol will be passed on to the responsible ethics committee as well as to 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 and 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 emphasised. 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 the samples, participation in the study is possible. The consent form also asks for an email 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. The use of professional writers is not intended.

DISCUSSION

The disease and its treatment often stress high-grade glioma patients and their caregivers. Depressive symptoms, as well as anxiety 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 multicentre 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 randomised controlled study is to investigate whether significant changes of self-reported anxiety, depressive symptoms and quality of life are detectable after the intervention in the IG compared with the WCG. As in previous yoga studies (eg,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 and 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 favour of greater homogeneity, specification of inclusion criteria regarding characteristics of the tumours based on the updated WHO Classification¹ 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.

Trial registration data set

See online supplemental 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 October 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 online supplemental file 2).

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

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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