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Effect of early palliative care for patients with glioblastoma (EPCOG): a randomised phase III clinical trial protocol

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ABSTRACT

Introduction Randomised controlled trials (RCTs) have shown a positive effect of early integration of palliative care (EIPC) in various advanced cancer entities regarding patients' quality of life (QoL), survival, mood, caregiver burden and reduction of aggressiveness of treatment near the end of life. However, RCTs investigating the positive effect of EIPC for patients suffering from glioblastoma multiforme (GBM) are lacking. After modelling work identifying the specific needs of GBM patients and their caregivers, the aim of this study is to investigate the impact of EIPC in this particular patient group.

Methods and analysis The recruitment period of this multicenter RCT started in May 2019. GBM patients (n=214) and their caregivers will be randomly assigned to either the intervention group (receiving proactive EIPC on a monthly basis) or the control group (receiving treatment according to international standards and additional, regular assessment of QoL ('optimised' standard care)).

The primary outcome is QoL assessed by subscales of the Functional Assessment of Cancer Therapy for brain tumour (FACT-Br) from baseline to 6 months of treatment. Secondary outcomes are changes in QoL after 12 (end of intervention), 18 and 24 months (end of follow-up), the full FACT-Br scale, patients' palliative care needs, depression/anxiety, cognitive impairment, caregiver burden, healthcare use, cost-effectiveness and overall survival.

Ethics and dissemination The study will be conducted in accordance with the Declaration of Helsinki and has been approved by the local ethics committees of the University Clinics of Cologne, Aachen, Bonn, Freiburg and Munich (LMU). Results of the trial will be submitted for publication in a peer-reviewed, open access journal and disseminated through presentations at conferences.

Trial registration number German Register for Clinical Studies (DRKS) (DRKS00016066); Pre-results.

Strengths and limitations of this study

- For the first time the effect of a well-articulated, manualised palliative care intervention is being studied in a randomised controlled trial in a patient group (glioblastoma multiforme) with a wide range of neurological, psychological and psychiatric symptoms.
- Patients and caregivers are studied thoroughly over a period of 24 months, allowing for an observation period throughout the entire disease phase (for the majority of the patients).
- Missing values will be minimised by joint and proxy assessments should the patients' self-assessment not be possible.
- Permission of proxy assessment may cause a certain bias.
- Blinding of the researcher conducting the outcome measurements depends mainly on discretion of study participants.

INTRODUCTION

Background

Glioblastoma multiforme (GBM) is a highly malignant primary brain tumour. It can be regarded as a model for a rapidly progressive cancer with a wide range of fast-developing, life-changing symptoms encompassing neurological, psychological, psychiatric symptoms, as well as unpredictable personality changes, leading to loss of autonomy.[1–8] The burden is mainly related to the psychosocial dimension in contrast to other advanced cancer entities.[9–11]

Previous randomised controlled trials (RCTs) in various advanced cancer groups other than GBM have shown a positive effect

of early integration of palliative care (EIPC) in these patient groups.[12–18] The palliative care (PC) approach aims to relieve physical, psychological, social and spiritual symptoms and problems as well as to enhance the quality of life (QoL) of the patients and of their next to kin (unit of care) suffering from progressive incurable diseases. According to the WHO definition, PC uses a team approach and should be applied early in the course of illness.[19] Overall, the positive effects of EIPC in the aforementioned studies[12–18] were improvement of QoL, survival, mood, caregiver burden and reduction of aggressiveness of treatment near end of life (EOL). The 'EVI project' in Germany evaluates whether EIPC can be implemented into the everyday clinical practice of Comprehensive Cancer Centers.[20] Patients included in that study are those suffering from non-small cell lung cancer, metastatic oesophageal carcinoma, metastatic stomach carcinoma and non-endocrine pancreas carcinoma but without a special focus on GBM. A cohort study on GBM patients[21 22] found a positive impact of a multiprofessional and interdisciplinary home care team on GBM patients and on the hospitalisation rate. Also, the costs of the hospitalisation were significantly reduced compared with standard care. However, PC professionals were not involved, just as in RCTs testing rehabilitative and supportive care interventions in patients with high-grade gliomas and their caregivers.[23] In summary, we conclude that EIPC has the potential to benefit patients with several oncological entities as well as their caregivers. Nevertheless, the effect of EIPC on GBM patients in their highly complex situation and on their caregivers has yet to be evaluated. We, therefore, aim to investigate whether the benefit of EIPC on systemic cancers[12–18] can also be found and confirmed in GBM.

Rationale

Temel *et al*[12] found in their landmark RCT involving patients with non-small cell lung cancer that EIPC leads to improvement of QoL and depression, to a reduction in aggressive treatment near the EOL and even to an increased life expectancy. Similar results could be confirmed for other advanced cancers.[13–18] However, there are no data about the effect of EIPC in patients with GBM and they are less likely to receive PC than other cancer patients.[1 24] Their disease-specific needs are probably not met by a 'one-size-fits-all' generic PC approach as they suffer from unique, serious, fast-developing, neuropsychiatric life-changing symptoms with a high caregiver burden[1–11] as also shown in own studies.[1–3 7] Therefore, this study aims to evaluate whether EIPC is efficacious (1) in a patient group with very different needs, (2) in medical disciplines not very experienced in PC yet, such as neurosurgery/neuro-oncology and (3) within the practicability of the German healthcare system. Following Temel *et al*,[12] we will use QoL as a primary endpoint and an EIPC team as the intervention adapted to the special needs of GBM patients (PC physician and PC social worker instead of PC physician and PC nurse). For the individual patient we expect that EIPC results in better symptom control and improved QoL, reduced caregiver burden, improved co-ordination of care, more efficient and appropriate use of healthcare services and less unnecessary emergency admissions at the EOL. EIPC will help to clarify treatment plans early in the course of the disease which are often non-existent in this patient group.[6] EIPC is constructed in a way that (1) the visits with specialised PC are face to face and/or via telephone, (2) specialised PC should serve as a mediator between patients and already existing services and (3) the caregivers' view and assessment plays a crucial role especially if patients are unable to self-assess any longer. All these strategies are resource-oriented, focus on clinical reality and practicability and have an economic impact. If this design proves to be successful, it could be used as a future strategy improving the level of care for GBM patients throughout the course of the disease until the EOL in Germany.

In spite of the positive results of EIPC in systemic cancer[12–18] we do not know how EIPC affects GBM patients, if such an effect will be sustainable and when to integrate PC in the care of this patient group. Therefore, our proposed design involves a wide range of GBM patients (initial diagnosis, recurrence, rural and urban areas) for a long period of time (12 months intervention, 12 months follow-up), in most cases, probably until death (median survival of GBM patients is between 15 and 17 months).[25–27] This means that EIPC effects on this patient group will be studied comprehensively and will answer our study questions using a prospective clinical study design. What justifies a confirmatory clinical trial at this time point? Following the Medical Research Council (UK)in its current version from 2008,[28] we believe that the development phase of our complex intervention can be based on numerous studies including own modelling work identifying the specific needs of GBM patients and their caregivers[1–11] and also the efficacy of EIPC.[12–18] A potential intervention for GBM patients can be modelled on this existing evidence and our clinical experience. We have conducted two feasibility studies on prospective ongoing patient-reported outcome measurement (PROM) data collection from diagnosis to death[2] and on assessing PC needs of GBM patients and caregiver burden.[3] Our results demonstrated that prospective ongoing PROM data collection is feasible but that the importance of caregivers' external assessment increases[2 3] with disease progression and that this did not bias our results significantly.[2] Therefore, in this trial, we will involve proxies in the assessment, if patients should be unable to participate themselves. Our previous studies also demonstrated the challenges of recruitment and attrition in this patient group with a recruitment rate of almost 30% of all GBM patients in the field and a considerably high attrition rate of 10%–79%[2 3] depending on the presence of assessment personnel. High attrition in PC trials is well-known,[29–31] thus to assure sufficient recruitment rates, a study nurse will at least partly be engaged at the neurosurgery/neuro-oncological departments at each site

(usually neurosurgery, depending on the study site neuro-oncology (Bonn)). The study nurse will carefully identify all eligible patients (inpatient/outpatient), provide and explain trial information to all potential study participants (patients and respective caregivers), contact the responsible neurosurgery/neuro-oncology physician, organise the contacts between eligible patients and the neurosurgery/neuro-oncology physician and guide study participants through the clinical trial process. Our own experiences and results[1–3 7] combined with the results of other existing studies[4–6 9 10 21 22] lead to the next step of evaluating EIPC intervention for GBM patients including an assessment of efficacy.[12–17 23]

The study period is from November 2018 to October 2023, while patient recruitment began in May 2019 and the last patient will be visited in April 2023.

Objective

Primary objective

The primary objective of this trial is to determine the efficacy of proactive early specialised PC tailored to patients with GBM to improve QoL. The changes in patients' QoL will be measured by the Trial Outcome Index (TOI, see the Measurements section) from baseline to 6 months.

It has been controversially discussed whether QoL is an appropriate measurement in PC and EOL care.[32] However, QoL measures are widely used in PC studies, including the landmark study by Temel *et al*.[12] The first statement about PC in the WHO definition is 'Palliative care is an approach that improves the QoL of patients and their families…', so changes in QoL are of crucial importance to evaluate a PC intervention. Temel *et al*[12] measured QoL, defined as their primary endpoint, using the validated Functional Assessment of Cancer Therapy (FACT). As our study is strongly influenced by the study of Temel *et al*,[12] we also chose QoL as primary endpoint but using the specific module for brain tumour patients (FACT-Br).[33]

Secondary objectives

Secondary endpoints will be changes in patients' QoL measured by the TOI from baseline to 12 months (end of intervention), at 18 and 24 months of follow-up (to evaluate maintenance/sustainability of effect), full FACT-Br scale,[33] patients' PC needs, patients' depression and anxiety, patients' cognitive impairment, caregiver burden, each outcome measurement being validated and cost-effectiveness (costs per FACT-Br-unit) from the societal perspective including direct medical and direct non-medical costs.[34] Moreover, data on overall survival and compliance will be collected.

METHODS

Trial design and study setting

The study is a multicenter, randomised, confirmatory, phase III, rater-blinded, controlled, parallel-group, clinical trial testing the efficacy of proactive early specialised PC tailored to patients with GBM to improve QoL.

The trial is conducted at the Departments of Palliative Care and the Departments of Neurosurgery of the University Hospitals of Cologne, Aachen, Bonn (here, additionally Department of Neurooncology), Freiburg and Munich, Germany (list of study sites: please see DRKS00016066).

Recruitment

The neurosurgery/neuro-oncology study nurse of each site will see all patients potentially fulfilling predefined inclusion criteria (see the Eligibility criteria section) (outpatient and inpatient). The study nurse will provide information material about the study to each potentially eligible patient and caregiver. These patients and caregivers will be referred to the treating neurosurgery/neuro-oncology physicians who will make the final decision on eligibility, explain the study and obtain informed written consent prior to enrolment or document why GBM patients or their caregivers could not be recruited into the study (inclusion criteria do not fit or refusal of study participation). Time between diagnosis of first or recurrent GBM and study inclusion may not exceed 4 weeks. The neurosurgery/neuro-oncology study nurse will co-ordinate further steps of the study (eg, baseline assessment, randomisation, start and further steps of intervention/follow-up). After obtaining written informed consent (see online supplementary file 1 for model consent form), the baseline visit will be carried out by the 'assessment researcher' (researcher being responsible for the assessment) either on the ward, in the outpatient clinic or at patients' home/whereabouts (see figure 1). Afterwards, patients will be randomly assigned to either the control or the EIPC group (see the Randomisation section).

Assessment visits and data collection

At all study sites, the blinded assessment researcher will collect patients' and caregivers' data during personal meetings at the patient's home/whereabouts, commencing at study inclusion (baseline) and then every 3 months until month 12. These visits will be scheduled slightly delayed to routine clinical visits (time frame allowed +2 weeks), where patients of both groups will receive an 'optimised' standard care (OSTC) (for more information, see the Treatment arms section). Face-to-face data collection at patient's home/whereabouts will be pursued to minimise the degree of burden for study participants (they do not have to come in for another clinic appointment), to establish a confidential relationship and to increase the number of patients' self-assessment as strategies can be used which are not possible during a telephone assessment. To promote participant retention and to complete follow-up, caregivers may complete the questionnaires as an external assessment should patients feel overburdened.

Patients at all study sites live not only in the respective town but also in larger catchment areas. In our study, we will intentionally include patients from these catchment

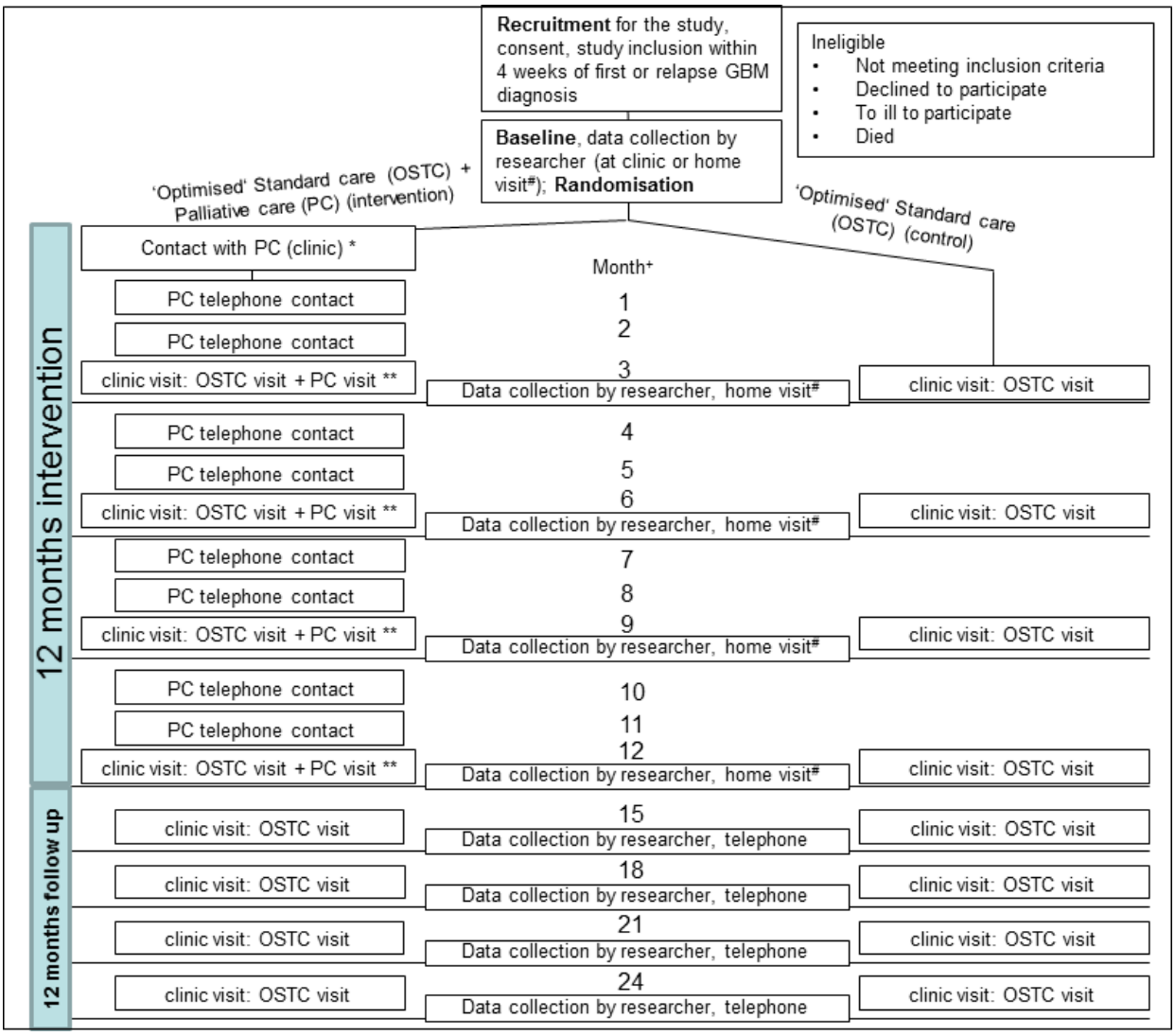

Figure 1 Trial flow chart. #Home visit means: the assessment researcher visits the patient for data collection at home or his/her whereabouts. +All visits are allowed to be scheduled within a time frame of ±1 week except for the assessment visits for data collection at patient's home/whereabouts every 3 months. These assessment visits must be scheduled after the respective clinic visit (and PC visit, intervention group, only) within a time frame of +2 weeks. *After randomisation and before first PC contact by telephone (no later than 4 weeks after study inclusion): first contact of PC physician and PC social worker (EIPC team) with patients/caregivers to introduce themselves (not yet an EIPC visit but solely serves the purpose of getting acquainted with each other before the first EIPC contact by telephone). **If patient is too ill for clinic visit telephone contact with EIPC team instead. EIPC, earlyintegration of palliative care; GBM, glioblastoma multiforme; OSTC, optimised standard care; PC, palliative care.

areas as we want to offer all patients treated at the study sites the opportunity to participate. Therewith, the study covers the true distribution of GBM patients in rural and urban areas and the results will reflect 'real-world' settings of GBM patients in Germany. This inevitably entails time-consuming and cost-consuming data collection by the assessment researcher (travel times, time-consuming assessments due to severe disease). After the end of the intervention, patients and/or caregivers will be contacted by the already familiar assessment researcher via telephone 3-monthly up to 12 months to collect data on patients' and caregivers' current status or place and date of death (see figure 1). We opted for telephone calls at this point in time to keep study costs to a minimum. Data collected beyond 6 months of the intervention and after the end of the intervention will be used to evaluate the maintenance/sustainability of the effect. During the EIPC intervention, in the intervention group face-to-face PC visits (months 3, 6, 9, 12) and PC telephone contacts (months 1, 2, 4, 5, 7, 8, 10, 11) will be conducted according to a PC manual.

Eligibility criteria

Patients are eligible to participate in the EPCOG Trial if they have a newly diagnosed GBM within 4 weeks of diagnosis (histologically confirmed by biopsy or resection) as well as patients with a recurrent GBM within 4 weeks after diagnosis of recurrence (confirmed according to RANO

Table 1 Key inclusion and exclusion criteria

	Patients	Caregivers
Inclusion criteria	► Patients with newly diagnosed GBM (histologically confirmed by biopsy or resection) within 4 weeks of diagnosis or ► Patients with recurrent GBM within 4 weeks after diagnosis of recurrence.	► Caregiving persons (relatives or other closely related persons) of special importance for the patients, that is, they live with them or have face-to-face contact with them at least twice a week. Note: Patients can also be included if no such caregiver exists.
	and	
	► ECOG 0–2.* ► Age ≥18 years. ► Ability to understand, read and respond to the German language. ► Ability to give informed consent.	
Exclusion criteria	► Unwillingness to abide by the protocol. ► Being legally incapacitated. ► Ongoing drug abuse or alcohol abuse or a psychiatric condition that, in the opinion of the investigator, makes the patient or caregiver unsuitable for study participation. ► Any kind of dependency on the investigator or employed by the sponsor or investigator. ► Held in an institution by legal or official order.	

*ECOG performance status[51]: grade 0: fully active, able to carry on all pre-disease performance without restriction; grade 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; grade 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; grade 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours; grade 4: completely disabled, cannot carry on any self-care, totally confined to bed or chair; grade 5: dead.
ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma mulitforme.

criteria or if clinical and/or radiological deterioration leads to a change in oncological treatment (eg, re-surgery/stereotactic biopsy, re-irradiation and/or change in chemotherapy protocol or dosage, which is not based on side effects like thrombocytopenia) as indicated by the local investigator). Moreover, a caregiving person (caregiver; relatives or other closely related persons) can be included if of special importance for the patients, that is, they live with them or have face-to-face contact with them at least twice a week. Of note, patients can also be included if no such caregiver exists or is willing to participate in the study. Further inclusion and exclusion criteria for patients and caregivers are shown in table 1.

Randomisation

Patients who meet the eligibility criteria will be randomly assigned into the intervention or the control group. Randomisation will be done using a 24/7 readily accessible internet-based tool (ALEA; FormsVision BV, Abcoude, the Netherlands). Patients will be assigned to treatment groups (ratio 1:1) according to permuted blocks of varying length. Randomisation will be stratified by study site, time point of PC intervention (initial diagnosis or recurrence) and availability of a caregiver (ie, 20 strata altogether). Patients will be informed about their allocation to the trial arm by the study nurse.

Blinding

The randomisation will be carried out by an unblinded team member, for example, by the neurosurgery/neuro-oncology study nurse. Study participants will be asked not to tell the assessment researcher whether they are in the intervention or in the control group. The status of the researchers' blindness will be queried after each visit. The statistician performing the statistical analysis will be blinded as well.

Treatment arms

'Optimised' standard care

In the *control group*, GBM patients will receive OSTC that includes regular visits to the neurosurgery/neuro-oncology outpatient clinic every 3 months (±1 week) as well as treatment and routine assessments following international standards.[35] In addition, the 'optimisation' includes regular assessments of the patients' QoL measured using the FACT-Br.[33] This allows the primary treating physicians to detect and react on patients' current needs in a timelier and more frequent manner, including, if necessary, the integration of existing PC structures which is also allowed explicitly in the control group (reactive approach) (see figure 2). This format is chosen to weaken the argument that additional care and attention alone is sufficient to improve QoL and reduce PC needs.[36]

Proactive, early PC

In the *intervention group*, in addition to the OSTC, patients will be in regular, structured contact (according to a PC manual) with specialised PC, irrespective of their current needs ('proactive') (for further details, see the Interventions section).

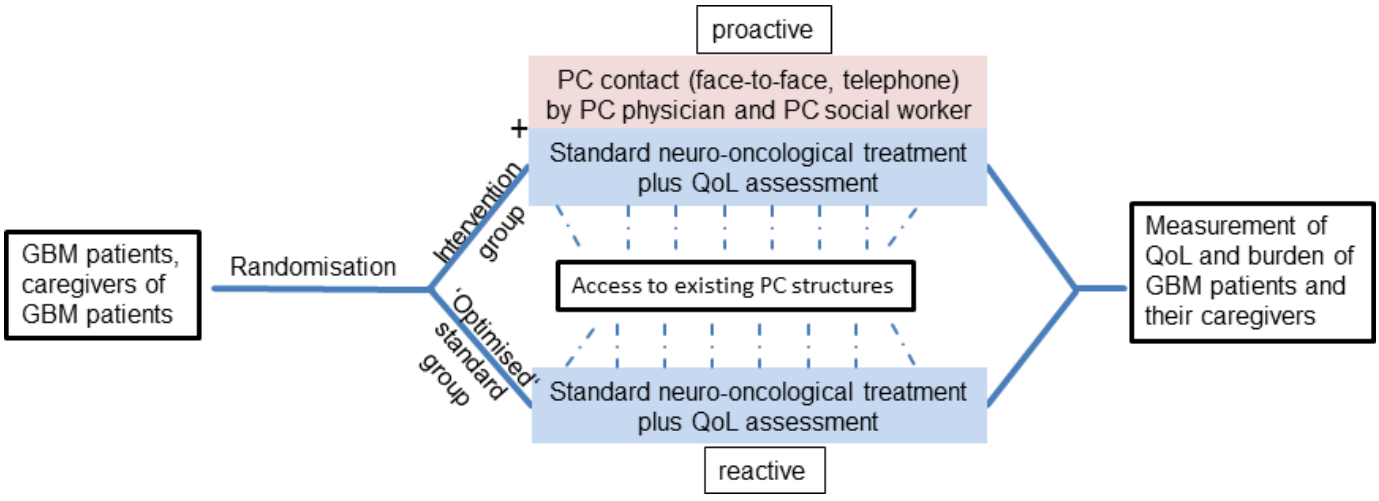

Figure 2 Intervention scheme. GBM, glioblastoma multiforme; PC, palliative care; QOL, quality of life.

Interventions

The EIPC intervention team consists of a PC physician and a PC social worker. The study plan schedules fixed face-to-face appointments with the EIPC team every 3 months, on the same day as the patients' appointment for their routine neurosurgery/neuro-oncology treatment at the clinic (feasible in clinical practice), that is, participants will not have to come to the clinic just because of the clinical trial. Between these quarterly visits, patients will be contacted monthly by the EIPC team by telephone. If patients are too ill for a clinic visit, a PC clinic contact may be compensated by a telephone PC contact or caregivers may be contacted instead.[2]

All staff members performing interventions will strictly follow a PC checklist/manual. Accordingly, the EIPC team will focus on pain and symptom management, psychosocial and spiritual support, assistance in treatment decisions and help in care planning during their fixed face-to-face/telephone contacts with study participants (see online supplementary file 2).

Sample size calculation

The sample size calculation was performed by the Institute of Medical Statistics and Computational Biology, University of Cologne for the primary outcome TOI. Here, we assume an effect size of 0.5 for the comparison of the experimental treatment versus control as previously found by Temel *et al*.[12] Assuming a similar SD of 20 points for the change in TOI (≈11.6 {SD early palliative care group}*148{range TOI}/84{range TOI Temel *et al*[12]}), this medium effect size corresponds to a difference of 10 points in TOI, that is, about 4 points [≈10*56{range sum of subscales}/148{range TOI}] for the sum of the FACT-G/Br subscales physical and function. According to Cella *et al*,[37] a clinically relevant change for the sum of the FACT-G/Br subscales physical and function is derived as half the mean of the difference between ECOG PSR 0 to 1 and 1 to 2, that is, 4 ≈ ([{4.1+4.6} + {3.1+2.7}]/2)/2 points. Thus, by approximation, the expected effect size 0.5 corresponds to a clinically relevant change. The two-sample t-test requires 64 patients per treatment group to yield 80% power at two-sided significance level 5% (Stata V.14.1, StataCorp; power two means). Thus, cautiously, 128 evaluable patients need to complete the trial. Accounting for up to 40% dropout, 214 patients need to be included and randomised. Nota bene, power may be further increased by taking a baseline-adjusted mixed model for repeated measures (MMRM) approach for statistical analysis. Specifically, assuming (1) one baseline measurement, (2) two follow-up measurements after randomisation (at 3 and 6 months) and (3) a correlation of 0.5 between repeated measurements, 128 evaluable patients may be sufficient to detect an effect size as small as 0.35 with 80% power.[38]

Measurements

The primary outcome measure is the QoL as assessed by the FACT-Br following Temel *et al*.[12] The QoL will be analysed by the TOI (37 items scored 0–4, range 0–148) which is the sum of scores on the Br (Br1–21, NTX6, An10), and the physical well-being (GP1–7) and functional well-being (GF1–7) subscales of the FACT-Br-scale[33] from baseline to 6 months of treatment.

The maintenance/sustainability of EIPC will be measured by the TOI from baseline to 12 (end of intervention), 18 and 24 months (follow-up).

Moreover, the following outcome measures will be assessed at baseline and every 3 months with secondary endpoints at months 6 and 12 (end of intervention), as well as at months 18 and 24 (follow-up after treatment):

- PC needs: Integrated Palliative Care Outcome Scale (IPOS).[39 40]
- Depression and anxiety: Hospital Anxiety and Depression scale (HADS).[41 42]
- Cognitive screening: Montreal Cognitive Assessment (MoCA).[43–45]
- Caregiver burden: Zarit Burden Interview, short version (12 questions; ZBI-12)[46–48] adapted version according to Kühnel *et al*.[49]
- Overall survival.

- Use of healthcare and cost-effectiveness: type and number of contacts to healthcare structures; type, lengths and frequency of tumour therapies usual for GBM patients[34] (see online supplementary file 3).
- Case and data reporting form (see online supplementary files 4–7).

Data analysis plan

The change in QoL (as assessed by the TOI) from baseline to 6 months after randomisation will be evaluated by a MMRM over time (ARH1-structured covariance matrix). To account for and assess the impact of attrition multiple imputation approaches are taken, accounting for proxy measures and assuming specific missingness-not-at-random patterns. Time-to-event (eg, dropout or survival) distributions are summarised by the Kaplan-Meier method and compared by the (stratified) log-rank test. Secondary outcomes (ie, further time points and measures) are analysed along the same lines.

Subgroup analyses are done by study site, time point of PC intervention, availability of a caregiver and sex; interaction with treatment is investigated. No interim analysis is planned. The trial may be terminated prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable.

Data monitoring

A data monitoring committee is not applicable (non-AMG/non-MPG clinical trial). An internal trial steering committee was formed to monitor the progress of the trial, manage and supervise all trial procedures on a regular basis and reach majority decisions on upcoming questions. The internal trial steering committee is advised by an independent, interdisciplinary and multidisciplinary scientific advisory board, whose members are involved in planning, guiding and evaluation of the trial.

Patient and public involvement

To assure patients' perspectives in the study question, design and implementation, we directly invited the patient support organisation 'German Brain Cancer Aid e.V.' for support with this study. They have declared their willingness to support us by commenting on the study proposal and helping with dissemination on patient platforms. Moreover, we involved patient representatives of the University Hospital of Cologne to comment on the study proposal.

ETHICS AND DISSEMINATION

Ethical considerations

Protocol amendments will be submitted to the ethics committee and signed by all authors of the trial protocol. Amendments will be published in the online registration of the trial and in the trial paper.

The Clinical Trials Centre Cologne (CTCC) is an external party that will monitor the study in a risk-adapted way and ensure that the study follows GCP, that is, that all participants give informed written consent and that study-related materials are handled correctly.

Safety considerations

We do not expect Adverse Events in this non-AMG/non-MPG clinical trial. GBM patients' death and worsening in general conditions is expected during the trial as intervention and follow-up extend over a period of time in which GBM patients are expected to die due to the given disease course. The EIPC intervention applied in this clinical trial has been proven for other disease entities—though in modified form—not to harm but rather to improve QoL, reduce depression and decrease aggressive treatment to the EOL.[12–18] The EIPC intervention according to the PC checklist/manual is designed such that primary treating physicians will get a feedback on patients'/caregivers' complaints and the measures will be taken, so that they have the possibility to react to particularities unless not done by the EIPC team itself. In addition to this, the control group will also be 'optimised' by regularly measuring QoL using the FACT-Br.[33] Primary treating physicians can directly act on distress becoming obvious during FACT-Br assessment (eg, items ticked with the worst score) and react on patients' specific needs also apart from planning tumour-specific treatment. In both groups, all available healthcare structures are allowed to be integrated into the patients' care, if needed, including existing PC structures. Apart from the regular use of the FACT-Br,[33] study participants will be assessed every 3 months. Using the regular outcome measurements (FACT-Br,[33] IPOS,[39 40] HADS,[41 42] ZBI-12)[48] a distress score will be calculated every 6 months. Thereby potential distress will be detected. Forty-nine items (including the domains physical (pain, dyspnoea, vomiting and so on), psychological (anxiety, depression and so on), relationship (family, friends)) are regarded relevant for distress phenomena. Items ticked with the worst score possible are classified as critical, recoded items are summed up and the sum is divided by the number of answered items. Relevant items will be aggregated by category (by the principal coordinating investigator) and listed. The internal steering committee will regularly monitor any (aggregated) distress phenomena which can be extracted from the database.

Dissemination plan

Findings of this study will be disseminated broadly to participants, healthcare professionals, the public and other relevant groups. The study protocol and results of this study will be published open access in a peer-reviewed scientific journal and presented at national and international conferences.

Confidentiality

Patients and caregivers will be given a trial number so that personally identifying information cannot be linked to assessment or trial information. All investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing.

Documentation and quality assurance

All data relevant to the trial will be directly documented in the electronic case reporting form (eCRF) or soon after measurement by the investigator responsible (documentation of EIPC according to PC manual by PC physician and social worker). Entering data may be delegated to members of the trial team except for the assessment researcher who has to stay blinded.

The assessment researcher who visits the patients for data collection at home or their whereabouts will directly document the results of the outcome measurements in the database (eCRF). This comprises the data and case reporting forms (documenting the healthcare use), sociodemographic data, the caregiver form (ZBI-12) and all patient forms (Fact-Br, IPOS, HADS) besides from the MoCA. The latter must be filled out on paper, so that only the results of each cognitive domain are entered into the eCRF. In the follow-up phase, the MoCA will be administered by telephone (T-MoCA)[50], as no face-to-face assessment is planned during the follow-up phase. In case of technical failure (eg, missing internet connection), the assessment researcher will complete all measures on paper but transfer all acquired data into the eCRF right after the study appointment. The FACT-Br filled out during regular neurosurgery/neuro-oncology clinic visits (OSTC) will be kept in the patient's file. The database used, TrialMaster, is validated (Omni-Comm.com). Every correction made to the data is traceable. Only authorised persons have access to the programme and the data. Regular data backups will be made. The eCRFs are signed by the principal investigators of each trial centre.

Monitoring is conducted by the CTCC Cologne and will include written informed consent, as well as risk-based monitoring of all inclusion/exclusion criteria and source data. Other than initiation visits at the beginning of the study and close-out visits at the end of the study, monitoring visits will be scheduled based on the number of patients included at each study centre (first visit: after 15–20 patients or after 1 year).

Data management

The IT infrastructure and data management staff will be supplied by the CTCC. The trial database will be developed and validated before data entry according to standard operating procedures (SOPs) at the CTCC. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT-infrastructure and safety concept with a firewall and backup system. The data are backed up daily. At the study end or after premature termination after confirmed completion and cleaning of data, the database is locked and the data are exported for statistical analysis.

The data will be entered online at the trial sites. Plausibility checks are run during data entry, thereby detecting discrepancies immediately. The CTCC data management will conduct further checks (listed in a study-specific data review plan) for completeness and plausibility and will clarify any questions with the trial sites according to the SOPs via queries. These electronic queries have to be answered in a timely manner by the trial site.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The trial will be conducted in compliance with this study protocol, the Declaration of Helsinki and Good Clinical Practice. The trial has been approved by the local ethics committees of the University Clinics of Cologne, Aachen, Bonn, Freiburg and Munich (LMU).

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