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**An interdisciplinary, outcome assessor blinded, randomised 12 week parallel group rehabilitation study comparing physical function, HRQoL, fatigue and survival rates among primary glioma patients - a protocol study.**

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Complete List of Authors:	Hansen, Anders; Odense University Hospital, Rehabilitation Department Rosenbek Minet, Lisbeth; University of Southern Denmark, Institute of Clinical Research Søgaard, Karen; University of Southern Denmark, Institute of Sports Science and Clinical Biomechanics Jarden, Jens; Herlev University Hospital, Department of Neurology
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Title page

**An interdisciplinary, outcome assessor blinded, randomised 12 week parallel group rehabilitation study comparing physical function, HRQoL, fatigue and survival rates among primary glioma patients - a protocol study.**

Corresponding author:  
Anders Hansen Master of Health Science, Rehabilitation Unit, Odense University Hospital, Denmark.  
[anders.hansen@rsyd.dk](mailto:anders.hansen@rsyd.dk) – [www.ouh.dk](http://www.ouh.dk)  
Tlf: +45 2029 4467 / +45 6138 2536, fax: not relevant  
Odense University Hospital  
Sdr. Boulevard 29, entrance 108, 5000 Odense C  
Denmark

Co-authors:  
Lisbeth Kirstine Rosenbek Minet PT PhD, Rehabilitation Unit, Odense University Hospital, Denmark

Karen Sjøgaard Professor, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark

Jens Ole Jarden Neurologist Physician, Department of Neurology, Herlev University Hospital, University of Copenhagen, Denmark.

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## Abstract:

**Introduction:** Gliomas are among the biggest challenges in the field of neuro-rehabilitation and oncology and optimising treatment by improving function and cognition is of major clinical importance in this population. Though inpatient rehabilitation in brain tumor patients results in improved functional measures, rehabilitation efforts are still not emphasized in this patient group and the literature lacks randomised studies investigating the impact of functional measures, HRQoL or survival rates of a standardised outpatient interdisciplinary rehabilitation program for glioma patients.

**Method:** This study protocol (phase I) describes a randomised 12 week parallel group rehabilitation study investigating an outpatient interdisciplinary rehabilitation program. The study includes a (phase II) feasibility study with the perspective of determining safety, suitability, timing, intensity and type of rehabilitation programme. The intervention consists of 6 weeks of intensive physiotherapy as groups exercise followed by 6 weeks of individual training in a gym, in conjunction with 0-12 weeks of individual occupational therapy if need is indicated. The aim of this paper is to describe the design of the upcoming RCT. The results of the RCT will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer and primary brain tumors.

**Ethics and dissemination:** According to the national Research Ethics Committee, approval was not needed for the phase I and II study. Ethical approval of phase III will be sought when content of the intervention program has been proven feasible. Dissemination will occur through presentation and findings will be published in peer-reviewed journals.

A key strength of this study is the randomised design, and it is the first study investigating a standardised outpatient interdisciplinary rehabilitation programme for glioma patients. A potential limitation is the uncertainty and risk of side-effects to the concomitant treatment as well as the threat of a progression in tumor growth, which enhances the risk of dropout.

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## Background

Primary brain tumor is a complicated condition due to complex diagnostic and treatment regimes. It is progressive in nature and has a poor prognosis. The condition imposes physical, psychological, cognitive disabilities and participatory limitations that call for an interdisciplinary approach to increase functional capacity and health related quality of life (HRQoL)<sup>1,2</sup>. Gliomas are among the biggest challenges in the field of neuro-rehabilitation and oncology<sup>3,4</sup> and optimising treatment by improving function and cognition is of major clinical importance in this population. Primary brain tumors is the cause of 2% of all cancer-related deaths<sup>5,6</sup> and can in accordance with the World Health Organization be divided into low-grade glioma (LGG) (WHO grades I/II) and high-grade glioma (HGG) (WHO grades III/IV)<sup>7</sup>. The median survival for glioblastoma patients (WHO IV) has since 2005, with the addition of Temozolomide to radiotherapy been associated with a 14.6<sup>8</sup> months survival, and has one of the lowest 5-year survival rates among all human cancers<sup>9</sup>. LGG is characterised by a slow growth and is estimated to have a median survival rate between 5 and 10 years<sup>10,11</sup>. Factors including age, performance status, cognitive function, histology, tumor grade and size, prior

progression, resection, radiation and chemotherapy are independent predictors of survival<sup>11-15</sup>. Brain tumor patients often have neurological deficits such as sensory motor, cognitive, functional deficits (hemiparesis, dysphasia, ataxia) and psychosocial factors related to the condition<sup>16-18</sup>, as well as side effects to the medical treatment including (severe muscle weakness, fatigue, headache, vomiting and insomnia)<sup>4 19-21</sup>. The majority of patients have multiple impairments often resulting in great suffering and low HRQoL<sup>1 19 20</sup>.

Advances in neurosurgical techniques and medical treatment have resulted in increased survival time<sup>8 21-24</sup> and a further need for rehabilitation. There is strong evidence in favor of interdisciplinary rehabilitation in neurological conditions like multiple sclerosis, acquired brain injury and stroke<sup>1</sup>. Likewise, several studies have shown that brain tumor patients receiving inpatient rehabilitation acquire significant functional gains similar to patients with traumatic brain injuries or stroke<sup>1 6 17 25-27</sup>. Inpatient rehabilitation in brain tumor patients results in improved functional measures<sup>1 4 17 18 28-31</sup> including ADL, mobility, cognition as well as HRQoL and Karnofsky performance score (KPS)<sup>27 32-34</sup>. Despite this, rehabilitation efforts are still not emphasised in this patient group<sup>26 28 30</sup>. Available data on inpatient rehabilitation of brain tumor patients are often limited by small sample size studies<sup>26 28 33</sup>, heterogeneous diagnostic groups with histologically mixed tumor types<sup>18 26</sup> and missing details concerning resection and characteristics of the tumor including tumor size, location, neurological deficits or treatment to date<sup>6 18</sup>. Though evidence supports the fact that rehabilitation interventions enhance cognitive and functional outcome and improves HRQoL<sup>1</sup>, a Cochrane review recently concluded, that no well-designed clinical trials have investigated the effect of multidisciplinary rehabilitation in brain tumor patients<sup>1</sup>. In the present study, interdisciplinary rehabilitation is defined as the coordinated distribution of interdimensional rehabilitation (such as physiotherapy, occupational therapy, nursing, psychology and other allied health interventions) to improve symptoms, maximising functional independence and participation by using a holistic bio psychosocial model (covering physical and psychosocial aspects) of care, as defined by The International Classification of Functioning, Disability and Health (ICF)<sup>35</sup>. Little is known of the functional trajectory of patients with glioma in the outpatient rehabilitation phase. To our knowledge no randomised studies have investigated functional impact, HRQoL or survival rates of a standardised outpatient interdisciplinary rehabilitation programme for glioma patients. This study will include a feasibility study with the perspective of determining safety, suitability, timing, intensity and type of the rehabilitation programme. The final programme aims to improve functional capacity, HRQoL and reduce symptom burden of glioma patients undergoing radiation and chemotherapy. The results of the present RCT study will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer or LGG.

**Research hypothesis**

We hypothesise that an interdisciplinary rehabilitation programme of intensive specialised physiotherapy and occupational therapy can maintain or delay regression in physical function (defined as muscle strength, VO<sub>2</sub>, balance, gait function, activity levels and physical activity levels), improve HRQoL and reduce fatigue. Further, survival rate is expected to be higher in the intervention group at 6 months follow-up compared with the control group receiving standard care.

**Objectives**

The primary objective is to investigate if a structured rehabilitation programme of intensive specialised physiotherapy and occupational therapy versus standard care of primary glioma patients (WHO grades I, II,

III, and IV) has an effect on physical function. Secondary objective is to investigate if the rehabilitation programme has an effect on HRQoL, fatigue and median survival rate between the groups.

### **Trial design**

The trial is designed as a randomised, controlled, outcome assessor blinded, interdisciplinary exploratory trial with parallel groups.

### **Study setting**

The first part of the intervention is conducted at Odense University Hospital (OUH) in the Region of Southern Denmark. With a regional population of 1.2 million annually 90 patients newly diagnosed with glioma (WHO grades I-IV) is estimated at OUH.

### **Eligibility criteria**

Patient eligibility for randomisation and inclusion must comply with: (i) diagnosis of primary glioma (WHO grades I-IV), (ii) age  $\geq 18$ , reference with diagnosis or treatment at Odense University Hospital, (iii) Karnofsky performance score (KPS)  $\geq 70$  and (iiii) ability to understand Danish. Exclusion criteria are (i) pregnancy or breastfeeding, (ii) known psychiatric diagnosis or substance abuse and (iii) heart problems excluding intense exercise (NYHA gr. III and IV). The reason for excluding KPS  $< 70$  is to ensure inclusion of patients able to conduct the physical training at an active and independent level, having cognitive ability to complete questionnaires and socially able to interact with others.

### **Intervention**

The intervention consists of 6 weeks of intensive physiotherapy followed by 6 weeks of standardised training on their own in a gym, in conjunction with 0-12 weeks of occupational therapy if need is indicated. The physiotherapy intervention contains supervised group exercise of 90 minutes three times a week in groups of four patients with continuous inclusion. Exercise includes individually tailored strength training of main muscle groups at intensities ranging from 15 to 8 repetition maximum (RM) (leg press, arm flexion, arm extension, knee flexion and knee extension), cardio training (20 min. of cycling or treadmill with intensities ranging from 60% to 80% of the heart rate reserve), body awareness training or relaxation (training of proprioception or postural control tailored to personal needs). Every session starts with 5 to 10 minutes of warm-up. The strength training workload is calculated based on baseline tests and patients follow a training log with instructions on progression. The cardiovascular training is monitored by pulse and the workload is monitored by means of a wireless heart rate transmitter worn by the patients. The first 6 weeks of group training is located at OUH facilities 3 times a week, and the last 6 weeks of individual training is performed in a gym of their own choice following a logbook.

The occupational therapy intervention consists of individual training 60 minutes twice a week for patients having deficits in activity or participation levels measured by the Assessment of Motor and Process Skills (AMPS). The training focuses on bettering the patients functional capacity, body, activity and participation level by adapting activities, regaining or developing activity abilities and/or rebuilding and developing patient skills<sup>36</sup>. The occupational therapy is terminated before the 12th week if the patient has no functional gain from the training. The training is conducted at OUH facilities for the first 6 weeks supported by delivery of structured tasks or training over telephone by an occupational therapist for the last 6 weeks.

The control group receives usual standard of care (e.g. no training, individual training or group training in the municipality). The amount of training in this group is based on a questionnaire at the follow-up trials.

*Safety*

Prior to each physical training session the project study nurse assesses each individual patient for the following conditions: diastolic blood pressure <45 or > 95, pulse >100, temperature above 38°C<sup>37 38</sup>, and if a condition is found, the patients will be excluded from the physical workout on that specific day and a neurologist will be informed. All patients are instructed to interrupt or stop training at any time if they feel faint or unwell.

*Feasibility study*

Before initiating the RCT study, a feasibility study on 24 patients is conducted, aiming to determine the feasibility, safety and possible benefits of the structured interdisciplinary rehabilitation programme. The feasibility will be used to inform the intensity and the progression in the final programme and secure that the training is well tolerated by this specific group of patients. Further, it serves the purpose of estimating the benefit of the home training as it may be expected that compliance in these 6 weeks will be considerably lower than in the first 6 weeks.

**Criteria for discontinuing allocated intervention for a given trial participant**

It is to be expected that some patients will experience side effects to their concomitant treatment with radiation, chemotherapy or cortisone. Some patients will experience a progression in tumor growth. For a given patient, the assigned study intervention will be discontinued at the discretion of the trial investigators, if the healthcare staff notices a change behavior occurring in the patient. If so, a specialised nurse and neurologist will determine the further involvement. Regardless of any decision to modify or discontinue the assigned intervention, the patient is retained in the trial whenever possible to enable follow-up data collection and prevent missing data. Patients are informed that they can retrieve their consent at any time without any consequences regarding their relationship with the staff or the content of their medical treatment.

**Adherence**

To enhance validity of data, multiple methods are used to assess participant adherence assisted by a training log. For patients receiving radiation treatment the timing of the intervention and radiation session is coordinated to ensure a minimum of waiting time. Further, patients are transported between facilities by assistant staff if needed.

**Concomitant care**

In conjunction with the already mentioned treatment, patients are often treated with antiepileptic medication and followed by a neurologist. In the trial all medication will be registered for both the intervention and control group.

**Outcomes**

All outcome measures will be gathered at baseline (FU-0) at the end of the 6th week of intervention (FU-1), at the end of the 12th week of intervention (FU-2) and at a 6 month (FU-3) follow-up. At baseline, descriptive variables for each subject in terms of gender, age, weight, height, resection, type of treatment (radiation, Temozolomide, radiation plus Temozolomide) tumor location, tumor size and neurological deficits are extracted. A summary of primary and secondary outcomes is found in Table 1.

Extend of resection is assessed through imaging definitions by the Response Assessment in Neuro-Oncology (RANO) criteria as either: 1) no contrast-enhancing residual tumor, 2) no measurable residual tumor (<10mm<sup>2</sup>) or 3) measurable residual tumor (≥10mm<sup>2</sup>)<sup>39 40</sup>. Resection variables are considered binary: (1)

high resection (if no contrast-enhancing residual tumor or no measurable residual tumor is achieved) or (2) low resection (if measurable residual tumor is detected or only biopsy was conducted).

Primary outcome is isometric maximum strength (MVC) and rate of force development (RFD) of M. Quadriceps femoris.

Secondary outcomes are 1) physical capacity defined as: estimated maximum muscle strength (knee extension, knee flexion, arm flexion and arm extension),  $VO_2$  peak, balance, gait velocity, activity levels and physical activity, 2) HRQoL, 3) fatigue and 4) median survival rate.

### PASTE table 1

#### Sample size

The sample size was calculated on the basis of the primary hypothesis. Expecting an “effect size” of 15% increase in the strength capacity on primary outcome and statistical power of 0.8, 64 trial participants are required in each arm. Based on 90 new cases annually in the Region, an expected 80% fulfillment of inclusion criteria and high acceptance rate (90%) approximately 64 patients will be included per year. Enrollment is thus expected to extend for 24 months.

#### Recruitment

On a daily basis the administration list from neurological- and neurosurgical departments is screened for potential study participants by the project nurse or project leader. Concurrently, a nurse from the neurosurgical department supplies information on planned cerebral tumor operations. The project leader or project nurse approaches eligible patients at the first post-operative day with written information about the project. They estimate a KPS score and ask permission to pass information on to a neurology specialist for histological assessment of inclusion/exclusion criteria. Before discharge (typically at the 3<sup>rd</sup> or 4<sup>th</sup> postoperative day) the patient is approached a second time for oral information with the opportunity for relatives to be present. After 24 hours (or the nearest weekday) post-discharge the project leader/study nurse contacts the patient by telephone and gets accept or refusal for study participation. If accepted, the patient will receive a formal invitation for baseline assessing through mail. Patients are carefully followed by their coordinating nurse from the neurooncology clinic until intervention starts. For HGG this is simultaneously with the start of the radiation treatment approximately 4 weeks after discharge from the neurosurgical unit. For LGG patients not offered radiation treatment, the start of intervention is likewise 4 weeks after discharge from the neurosurgical unit. Informed consent is obtained at the baseline test.

#### Randomisation

Participants are randomly assigned to a control or intervention group (with a 1:1 allocation) by block randomisation stratified by tumor grade. The block size will not be disclosed to sustain concealment. Consecutively, closed, opaque, numbered envelopes containing assembly allocation are prepared by an assistant outside the study group. The envelopes are stored securely in a locked container. After baseline assessment tests the randomisation is performed by a secretary with no interest in the outcome of the study. The nurse will open the envelope and reveal the allocation for the patient.

### Figure 1: overview of the study design

#### Blinding

Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are instructed not to reveal the allocation status of the participant at the follow-up assessments. The testing personnel are blinded to which intervention the patients have received. An employee outside the research

team will feed data into the computer in separate datasheets so that the researchers can analyse data without having access to information about the allocation.

**Data collection methods**

Primary outcome of MVC and RFD of m. Quadriceps femoris are measured as knee extension against strain gauge dynamometer at a knee angle of 90 degrees in a setup previously described by Jensen et al.<sup>41</sup>.

*Secondary outcome*

Indirect 1 RM test will be assessed by a 4-6 Repetition Maximum test<sup>42</sup> using the procedure described by Kraemer and Fry<sup>43</sup>. A warm-up/familiarisation series of 10 to 12 repetitions with an affordable load will be applied. The patient is told to perform repetitions until the resistance is impossible to be sustained. Loads will initially be estimated based on the test personnel's experience and answers from a dialogue relating to training experience. If a patient has to repeat a given repetition as a result of ease in obtaining the desired repetitions or failure to attain the repetition number, a 3-minute pause will be given, and an adjusted load attempted. The tester will strictly observe each repetition and only trials completed with proper form through the full range of motion will be counted<sup>43</sup>. Subjects are encouraged to complete repetitions consecutively and verbal motivation is standardised using a protocol during all testing sessions. An equation proposed by Brzycki will be used to estimate 1 RM:  $1\text{-RM} = 100 * \text{load rep} / (102.78 - 2.78 * \text{rep})$  where

- load rep: workload value of repetitions performance, expressed in kg.
- rep: number of repetitions performed<sup>42</sup>.

Measuring VO<sub>2</sub> max directly is considered the gold standard but requires refined equipment, skilled technicians, time and money. It is also for a number of subjects associated with discomfort<sup>44</sup>. There are no validated submaximal fitness tests for these patients, but the Åstrand-Rhyming one-point test is considered the best choice for safety reasons, when a maximum test is associated with risk. The Åstrand-Rhyming test estimates maximal oxygen uptake (fitness indicators) from workload and pulse rate as per protocol by Åstrand<sup>45</sup>. The participant cycles for 6 minutes at 50-60 rpm with a load that stabilises the pulse in the range of 110-170 beats /minute, at the last of the six minutes.

Balance is assessed by sway test. Laboratory-based assessment using measures of center of pressure (COP) recorded from a force platform is considered the gold standard measure of balance<sup>46</sup>. The Wii Balance Board (WBB) is a valid and low-cost system for assessing standing balance<sup>46</sup>. Good-to-excellent test-retest reproducibility has been demonstrated during a static bilateral stance in thirty young individuals by extracting raw vertical force data from the WBB<sup>46</sup>. The WBB makes it possible to obtain non-invasive data on subjects by four piezoelectric strain gauges built into the corners of the device. The outputs of these gauges assess force distribution and the resultant movements in COP through a Bluetooth connection<sup>47</sup>. Sway measurements are assessed after the same protocol as performed in previous studies<sup>48</sup>.

Gait velocity and step frequency will be assessed by 10 meter walk test (10MWT) as per protocol of Vos-Vromans DC. 10MWT is a valid and reliable quantitative test to measure walking ability<sup>49</sup>. The patient will be asked to walk 10 meters from a standing position at a preferred speed. Patients are allowed to use a preferred aid if needed. Time will be recorded using a stopwatch and the number of steps taken will be counted. Mean time score and mean number of steps will be calculated.

Changes in activity and performance status are assessed by an AMPS test which is a globally recognised assessment of everyday function. The AMPS is an observational, standardised performance-based assessment that obtains information on the quality of an individual's performance of activity of daily living (ADL) tasks<sup>50</sup>. According to AMPS, a higher score indicates an increased level of independence, increased safety in the community, and increased efficiency of performance<sup>50</sup>.

Physical activity level is calculated using a metabolic equivalent (MET) questionnaire<sup>51</sup>. MET is a concept used to measure physical activity according to intensity and energy costs as well as exercise performance<sup>52</sup>. MET level imitates the energy costs of physical activity as a multiple of resting energy expenditure<sup>52</sup>.

HRQoL is assessed by means of the questionnaire EORTC-QLQ-30<sup>53</sup> with the addition of the questionnaires QLQ-BN20<sup>54</sup> and EQ-5D. Questionnaires are handed out at baseline tests to be completed at the venue.

The EORTC QLQ-C30 consists of single and multi-item scales. There are 30 items of which 24 aggregate into nine multi-item scales representing various HRQoL dimensions: five functioning scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain and nausea) and a global health status. There are six single item scales that assess treatment-related symptoms: dyspnea, loss of appetite, sleep disturbance, constipation, diarrhea and perceived financial consequences of the treatment. High scores indicate better perceived HRQoL for the global health status and functioning scales, and worse HRQoL for the treatment-related symptom scale<sup>53 54</sup>. This is supplemented by a module designed for brain tumor patients. The QLQ-BN20 consists of four multi-item scales that address four items of future uncertainty, three items of visual disorder, three items of motor dysfunction and three items of communication deficit. Seven single items assess headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control<sup>55</sup>. All scores of the EORTC-QLQ-C30 and QLQ-BN20 are linearly changed to a 0–100 scale

EQ-5D is a standardised measurement of health status. It consists of a descriptive system (EQ-5D) and a visual analogue scale (EQ VAS)<sup>56</sup>. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems or severe problems. The EQ VAS registers the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'<sup>56</sup>.

Median survival time will be assessed using the charts. Survival time is defined as the period from time of resection to time of death or the last follow-up date for patients still alive. The overall survival time will be calculated in months for all patients. Within the PhD project the 6 months status will be used. However, the study will form a cohort that can be followed up after 12 months and 5 years.

Prior to the study inter-tester reliability of the physical tests is examined (isometric maximum strength and RFD of M. Quadriceps femoris, 1 RM estimation test of knee flexion, arm flexion and extension and leg press, sway test, 10 m walking test and Åstrand-Rhyming cycle test). All test personnel for the AMPS test is certified and calibrated.

#### Retention

Once a patient is randomised the study staff will make every effort to follow the patient for the entire study period. The staff is accountable for developing and implementing standard operating procedures to

maximise level of follow-up limiting participant burden related to visits and procedures. Before each follow-up the patient will receive a telephone call from the project leader or nurse and receive a formal invitation through mail. The nurse will give the project group an update on the patient's health status. If a patient has experienced a heavy disease progression and is not physically or mentally able to participate, the patient will be lost to follow-up in order to protect safety. Participants may withdraw from the study for any reason at any time without any effect on the primary treatment.

**Statistical method**

The intervention group will be compared with the controls for all primary analysis. We will use  $\chi^2$  test for binary outcomes and T-test or Mann Whitney for continuous outcomes. For subgroup analyses, we will use regression methods with appropriate interaction terms (respective subgroup  $\times$  treatment group). Multivariable analyses will be based on logistic regression for binary outcomes and linear regression for continuous outcomes. Mortality is calculated using Kaplan-Meier survival analysis followed by multivariable Cox proportional hazards model for adjusting for baseline variables. Relative Risk (RR) and RR Reductions (RRR) are calculated with corresponding 95% confidence intervals to compare dichotomous variables, and difference in means will be used for additional analysis of continuous variables. All analyses are conducted using SPSS. For all tests 1-sided p-values with  $\alpha = < 0.05$  level of significance are used. A Bonferroni method is used to appropriately adjust the overall level of significance for multiple primary and secondary outcomes. Data are analysed by the 'intention-to-treat' principle and per-protocol analysis is made.

**Missing data**

Intention-to-treat analyses are performed to avoid effects of dropout, which may break the random assignment to the treatment groups in the study. Therefore simple imputation such as carry forward and backward will be performed to allow an intention-to-treat analysis.

**Confidentiality**

All study-related information will be stored securely at the study site in accordance with the Danish Data Protection Agency. All participant information will be stored in locked file cabinets in areas with limited access. All reports, data collection, process and administrative forms will be identified by a coded ID number to maintain participant confidentiality. All records containing names or other personal identifiers, such as informed consent forms are stored separately from study records identified by code number. All local databases will be secured with password-protected access systems.

**Ethical considerations**

This study poses no serious ethical issues in general. All procedures involved in this study are conducted in accordance with the Helsinki Declaration and the Danish Data Protection Agency (J. no.2008-58-0035). In accordance with the national Research Ethics Committee an approval was not needed (ID: s-20130003) for the pilot study. However ethical approval will be sought and obtained for the RCT.

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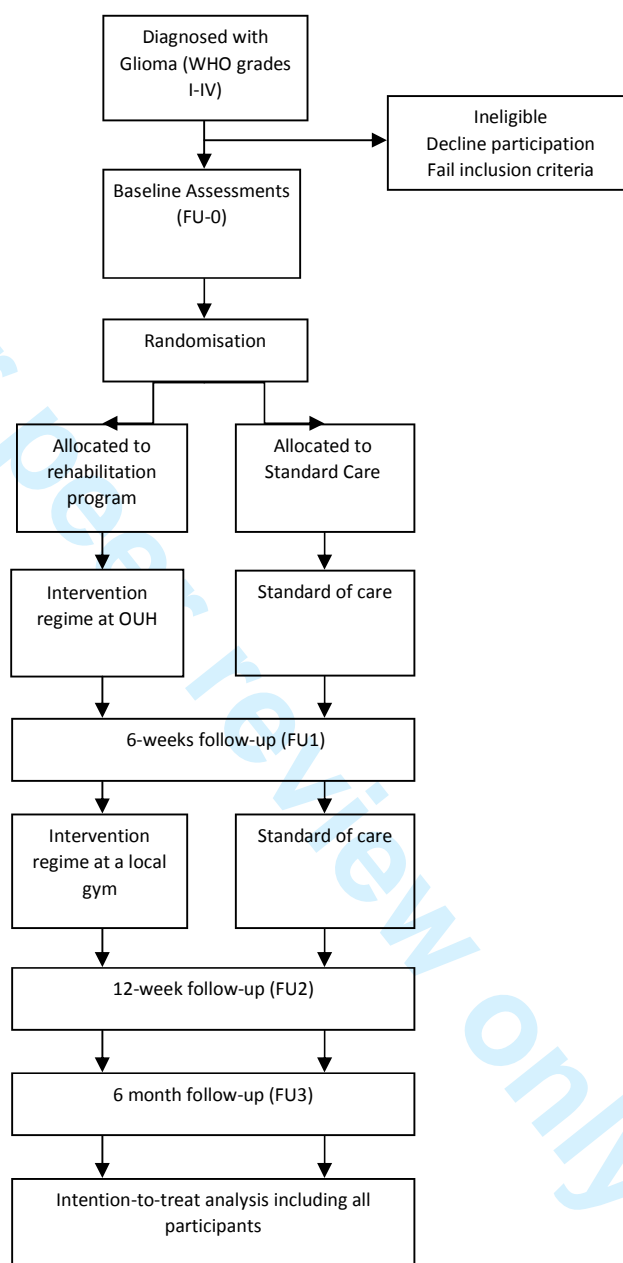
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Table 1: Outcomes

Variable	Details	Unit
<b>Primary Outcome</b>		
Isometric maximum strength and rate of force development of M. Quadriceps femoris	Knee extension against strain gauge dynamometer at a knee angle of 90 degrees	Kg
<b>Secondary Outcomes</b>		
Estimated maximum muscle strength of leg press	4-6 RM	Kg
Estimated maximum muscle strength of knee flexion	4-6 RM	Kg
Estimated maximum muscle strength of arm flexion	4-6 RM	Kg
Estimated maximum muscle strength of arm extension	4-6 RM	Kg
Peak oxygen uptake (Vo2peak)	Åstrand-Rhyming cycle test	ml. O2/min/kg
Standing balance	Sway test	%
Gait velocity	10 Meter Walk Test (10MWT)	sek.
Number of steps	10 Meter Walk Test (10MWT)	steps
Activity levels	The Assessment of Motor and Process Skills (AMPS)	score
Physical activity levels	Metabolic equivalent	MET
HRQoL	EORTC-QLQ-30 with the addition of EQ-5d	score
Symptom burden	EORTC-QLQ-30 with the addition of BN-20	score
Fatigue	EORTC-QLQ-30	score
Survival	Chart extract	months

Figure 1: Overview of the study design



# BMJ Open

## The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among primary glioma patients – an RTC study protocol

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Title page

**The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among primary glioma patients – an RTC study protocol**

Corresponding author:  
Anders Hansen Master of Health Science, Rehabilitation Unit, Odense University Hospital, Denmark.  
[anders.hansen@rsyd.dk](mailto:anders.hansen@rsyd.dk) – [www.ouh.dk](http://www.ouh.dk)  
Tlf: +45 2029 4467 / +45 6138 2536  
Odense University Hospital  
Sdr. Boulevard 29, entrance 108, 5000 Odense C  
Denmark

Co-authors:  
Lisbeth Kirstine Rosenbek Minet PT PhD, Rehabilitation Unit, Odense University Hospital, Denmark  
  
Karen Sjøgaard Professor, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark

Jens Ole Jarden, M.D., D.MSci., Department of Neurology, Herlev University Hospital, University of Copenhagen, Denmark.

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## Abstract

**Introduction:** Gliomas are among the biggest challenges in neurological- and oncology rehabilitation and optimising treatment is of major clinical importance in this population. Though inpatient rehabilitation among glioma patients' results in improved functional measures, rehabilitation efforts are still not emphasized in this patient group and the literature lacks studies investigating the impact of outpatient rehabilitation.

**Method:** This protocol describes a randomised 6 week parallel group rehabilitation study investigating an outpatient interdisciplinary rehabilitation program. The intervention consists of 6 weeks intensive physiotherapy as groups exercise in conjunction with 0-6 weeks of individual occupational therapy if a need is present. The aim of this paper is to describe the design of the upcoming RCT. The results of the RCT will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer.

**Ethics and dissemination:** The project is approved by the Regional Scientific Ethical Committees for Southern Denmark under Project-ID: (S-20140108) and by the Danish Data Protection Agency (J. no.2008-58-0035). Dissemination will occur through presentation and findings will be published in peer-reviewed journals.

A key strength of this study is the randomised design and it is the first study to investigate a standardised outpatient interdisciplinary rehabilitation program among glioma patients. A potential limitation is the uncertainty and risk of side-effects to the concomitant treatment which enhances the risk of dropout.

**ClinicalTrials.gov Identifier:** NCT02221986

## Background

Primary brain tumor is a complicated condition due to complex diagnostic and treatment regimes. It has a progressive nature and a poor prognosis causing 2% of all cancer-related deaths<sup>1,2</sup>. Gliomas are the most frequent primary neoplasm in the CNS<sup>3</sup> and according to World Health Organization histologically categorized into low-grade glioma (LGG) (WHO grades I/II) or high-grade glioma (HGG) (WHO grades III/IV)<sup>4</sup>. Gliomas are among the biggest challenges in neurological- and oncology rehabilitation<sup>5,6</sup> and optimising treatment is of major clinical importance in this population. Patients often have neurological deficits such as sensory and motor, cognitive, functional deficits (hemiparesis, dysphasia, ataxia) and psychosocial (personality changes, loss of insight or empathy) factors due to tumor localisation or remote effects<sup>7,8</sup>. Not only does the damage to the brain tissue from tumor growth result in neurological impairment, the treatments can produce significant side-effects including severe muscle weakness, fatigue, headache, vomiting and insomnia<sup>9,10</sup>. The majority of patients have multiple impairments often resulting in great suffering and low health-related quality of life (HRQoL)<sup>7,9-11</sup>. Since the vast majority of patients cannot be cured outcome measures in clinical cancer research have traditionally focused on prolonging the overall survival, progression-free survival or response to the medical treatment<sup>12-15</sup>. Today there is a general agreement that HRQoL measures are increasingly important and The American Society of Clinical Oncology has suggested, that QoL measurements are an important primary endpoint in any Phase III study<sup>16</sup>. HRQoL plays a role in predicting survival or survival duration<sup>17</sup> among standard prognostic indicators such as histology and clinical stage. However, research on glioma patients' perception on HRQoL is sparse compared to other patient categories with neoplasms<sup>13,18</sup>. Advances in the neurosurgical techniques and medical treatment have resulted in an increased survival time<sup>19-23</sup>. This has led to a pronounced proportion of patients having a rehabilitation need<sup>24</sup>. Several studies indicate that glioma patients receiving inpatient rehabilitation acquire significant HRQoL, cognitive and

functional gains similar with those seen in patients with non-neoplastic neurological conditions<sup>2 6 8 9 25-33</sup>. Despite of this, rehabilitation efforts are still not emphasised in this patient group<sup>24 29 30 34 35</sup> and a Cochrane review recently concluded, that no well-designed clinical trials have investigated the effect of multidisciplinary rehabilitation in brain tumor patients<sup>9</sup>. Available data are often limited by small sample size studies<sup>27 30</sup>, heterogeneous diagnostic groups with histologically mixed tumor types<sup>29 32</sup> and missing details concerning resection and characteristics of the tumor including size and location or information regarding neurological deficits or treatment to date<sup>2 32</sup>. In the present study, interdisciplinary rehabilitation is defined as the coordinated distribution of interdimensional rehabilitation (such as physiotherapy, occupational therapy, nursing, psychology and other allied health interventions) to improve symptoms, maximising functional independence and participation by using a holistic bio psychosocial model (covering physical and psychosocial aspects) of care, as defined by The International Classification of Functioning, Disability and Health (ICF)<sup>36</sup>.

Little is known of the functional path of glioma patients in the outpatient rehabilitation phase and it has been suggested that prospective studies should test the effect of properly selected training interventions to avert and/or relieve dysfunction<sup>5 33</sup>. To our knowledge no randomised studies have investigated if a standardised outpatient interdisciplinary rehabilitation program among glioma patients has effect on HRQoL, symptom burden or physical function. The results of the present RCT study will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer.

**Research hypothesis**

We hypothesise that patients attending an interdisciplinary rehabilitation program of intensive specialised physiotherapy and occupational therapy will improve their perception of HRQoL, reduce symptom burden and maintain or delay regression in physical function (defined as muscle strength, VO<sub>2peak</sub>, balance, gait function and activity levels).

**Objectives**

The primary objective is to investigate if a structured rehabilitation program of intensive specialised physiotherapy and occupational therapy versus standard care has effect on HRQoL. Secondary objective is to investigate if the rehabilitation program can reduce the symptom burden and maintain or delay regression in physical function.

**Trial design**

This trial is designed as a randomised, controlled, outcome assessor blinded, interdisciplinary exploratory trial with parallel groups.

**Study setting**

The intervention is set to begin in September 2014 at Odense University Hospital (OUH) in the Region of Southern Denmark and end in early spring 2017. With a regional population of 1.2 million approximately 90 patients are annually diagnosed with glioma (WHO grades I-IV) at OUH.

**Eligibility criteria**

Patient eligibility for randomisation and inclusion must comply with: (i) diagnosis of primary glioma (WHO grades I-IV), (ii) age ≥ 18, reference with diagnosis or treatment at Odense University Hospital, (iii) Karnofsky performance score (KPS) ≥70 and (iiii) ability to understand Danish. Exclusion criteria are (i)

pregnancy, (ii) known psychiatric diagnosis or substance abuse, (iii) heart problems excluding intense exercise (NYHA group III and IV) and (IV) pronounced impressive or expressive aphasia. The reason for excluding KPS <70 is to ensure inclusion of patients able to conduct the physical training at an active and independent level, having cognitive ability to complete questionnaires and socially be able to interact with others.

### Intervention

The intervention consists of 6 weeks intensive outpatient physiotherapy in conjunction with 0-6 weeks of occupational therapy if need is indicated. The physical intervention contains supervised group exercise of 90 minutes three times a week in groups up to four patients included continuously. Exercise includes individually tailored strength training of main muscle groups with increasing load ranging from 15 to 10 repetition maximum (RM) (leg press, arm flexion, arm extension, knee flexion and knee extension), cardio training (20 minutes of cycling or treadmill with intensities ranging from 65% to 85% of the heart rate reserve), body awareness training or relaxation (training of proprioception, postural control or stability of the core muscles tailored to personal needs). Every session starts with 5 to 10 minutes of warm-up. The strength training workload is calculated based on baseline tests and patients follow a training diary with instructions to progression. The cardiovascular training is monitored by pulse through means of a wireless heart rate transmitter worn by the patients.

The occupational therapy intervention consists of individual training 60 minutes twice a week for patients having deficits in activity or participation levels measured by the Assessment of Motor and Process Skills (AMPS). The training focuses on bettering the patients functional capacity, body, activity and participation level by adapting activities, regaining or developing activity abilities and/or rebuilding and developing patient skills<sup>37</sup>. The occupational therapy is terminated before the 6th week if the patient has reached the appointed functional goals and follow-up assessments are conducted.

The control group receives usual standard of care (e.g. no training, individual training or group training in the municipality). The amount of training in this group is based on a questionnaire at the follow-up trials.

### Safety

Prior to each physical training session the study nurse assesses each individual patient for the following conditions: diastolic blood pressure <45 or >100, pulse >100, temperature above 38°C, respiration frequency at rest >20, infection requiring treatment with antibiotics, ongoing bleeding; fresh petechiae, bruises<sup>38</sup>, blood-leukocytes <5×10<sup>9</sup>/L and blood-thrombocytes <5 x 10<sup>3</sup>/μL. If a condition is found, the patients will be excluded from the physical workout on that specific day and a physician will be informed. All patients are instructed to interrupt or stop training at any time if they feel faint or unwell.

### Feasibility study

Before initiating the RCT-study a feasibility study on 24 patients has been conducted to (i) test the feasibility and safety of a twelve week interdisciplinary rehabilitation program of individually activity based training and physical exercise as a group intervention for patients with primary glioma, (ii) to assess the preliminary effects on HRQoL, symptom burden and physical function and (iii) to determine the effect sizes and sample needed for the RCT-study. The feasibility study also informed the intensity and progression in the final program and secured that the training was well tolerated by this specific group of patients.

### Criteria for discontinuing allocated intervention for a given trial participant

It is to be expected that some patients will experience side effects to their concomitant treatment with

radiation, chemotherapy or cortisone. For a given patient, the assigned study intervention will be discontinued at the discretion of the trial investigators if the healthcare-staff notices a change behaviour occurring in the patient or the symptom burden is too high. The Physical and emotional status of the patients are evaluated before every training session. If patients exceed the set of specified requirements, s/he is referred to the study nurse and neurologist for further evaluation and possible exclusion. Regardless of any decision to modify or discontinue the assigned intervention, the patient is retained in the trial whenever possible to enable follow-up data collection and prevent missing data. Patients are informed that they can retrieve their consent at any time without any consequences regarding their relationship with the staff or the content of their medical treatment. Patients are referred to municipality rehabilitation if the specialised treatment does not meet the patients' expectations.

**Usefulness of the trial**

Patients allocated to the intervention group will likely exercise more than usual. However, experience shows that many associate this with increased profits<sup>39</sup>. This study is done so that we in the future can organise the best possible rehabilitation for patients with glioma.

**Side effects, risks, complications and drawbacks**

We do not anticipate side-effects associated with the rehabilitation. On the contrary, we expect patients to experience similar positive effects on the treatment related side-effects as other cancer groups<sup>39-41</sup>.

**Outcome**

All outcome measures are gathered at baseline (FU-0) at the end of the 6th week of intervention (FU-1), at a 3-month follow up (FU-2) and at a 6-month follow-up (questionnaires only) (FU-3)(see figure 1). At baseline, descriptive variables for each subject in terms of gender, age, weight, height and cohabiting is assessed. Disease variables and treatments are obtained through review of medical records. Extend of resection is assessed through imaging definitions 72 hours postoperative. Data on tumor structures, residual tumor, infarct or hematoma in- or around the cavity and tumor localisation are extracted.

**Figure 1 Overview of the study design**

All physical assessment tools and questionnaires are set to be conducted within 90 minutes and occupational tests within 60 minutes. This is done to decrease the symptom burden and avoid risk of bias due to fatigue.

The tests battery includes two questionnaires: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30) and the EORTC brain cancer module (EORTC QLQ-BN20) on patients' perception on HRQoL and symptom burden. Five physiological tests measures physical function defined as: estimated maximum muscle strength (knee extension, knee flexion, arm flexion, arm extension and leg press) (1RM), maximal oxygen uptake (VO<sub>2peak</sub>), balance, gait velocity and steps frequency (10 meter walk test) and activity levels (AMPS and questions on physical activity<sup>42</sup>)(see Table 1).

The primary outcome is HRQoL and secondary outcomes are 1) symptom burden and side-effects from the medical treatment and 2) physical function defined as: estimated maximum muscle strength (knee extension, knee flexion, arm flexion and arm extension), VO<sub>2peak</sub>, balance, gait velocity and activity levels.

**Table 1 Outcome**

### Sample size

According to the scoring manual for EORTC QLQ-30 a change of 10 points or more is considered to be a moderate to large clinically significant change<sup>43</sup>. Based on this assumption and results of the feasibility study (n=24) a sample size is calculated. At an expected "effect size" of at least 10 points (SD  $\pm 24,6$ ) increase in the EORTC QLQ-30 General Health Scale/QoL (paragraphs 29 and 30) with a statistical power of  $\beta$  0.8 and  $\alpha$  of 0.05 the study requires 48 subjects in each arm. To meet an expected dropout-rate of approximately 15 % a total of 56 participants will be included in each group. Based on 90 new cases annually and an acceptance- and fulfilment of inclusion criteria based on the feasibility study of >80%, approximately 64 patients will be included per year. Enrollment is thus expected to extend for 22 months.

### Recruitment

On a daily basis the administration list from neurological- and neurosurgical departments is screened for potential subjects by the study nurse. Concurrently, a nurse from the neurosurgical department supplies information on planned cerebral tumor operations. The study leader/nurse approaches eligible patients at the neurosurgical department within 24 hours after returning from the intensive recovery room when the first contact with the therapist normally is scheduled. A KPS is estimated and permission to pass information on to a neurology specialist for histological assessment of inclusion/exclusion criteria is obtained. Before discharge (typically at the 4<sup>th</sup> postoperative day) the patient is approached a second time for oral information with the opportunity for relatives to be present. After 24 hours (or the nearest weekday) post-discharge the study leader/nurse contacts the patient by telephone and gets accept or refusal for study participation. If accepted, the patient will receive a formal invitation for baseline assessing through mail. For HGG this is simultaneously with the start of the radiation treatment approximately 4 weeks post discharge. For LGG patients not offered radiation treatment, the start of intervention is likewise 4 weeks post discharge. Informed consent is obtained at the baseline test.

### Randomisation

Participants are randomly assigned to a control or intervention group with a 1:1 allocation by block randomisation stratified by LGG versus HGG. The block size will not be disclosed to sustain concealment. Consecutively, closed, opaque, numbered envelopes containing assembly allocation are prepared by an assistant outside the study group. The envelopes are stored securely in a locked container. After baseline assessment tests the randomisation is performed by a secretary with no interest in the outcome of the study. The nurse will open the envelope and reveal the allocation for the patient.

### Blinding

Due to the nature of the intervention neither participants nor staff can be blinded to allocation but are instructed not to reveal the allocation status of the participant at the follow-up assessments. The testing personnel are blinded to which intervention the patients have received. An employee outside the research team will feed data into the computer in separate datasheets so that the researchers can analyse data without having access to information about the allocation.

### Data collection methods

HRQoL is assessed by means of the questionnaire EORTC-QLQ-30<sup>43</sup> with the addition of the questionnaire EORTC-BN20<sup>44</sup>. These are handed out at baseline tests to be completed at the hospital.

The EORTC QLQ-C30<sup>43</sup> consists of single and multi-item scales. There are 30 items of which 24 cumulate into nine multi-item scales representing various HRQoL dimensions: five functioning scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain and nausea and vomiting) and a global health status/QoL. Six single item scales assesses treatment-related symptoms: dyspnoea, loss of appetite,

sleep disturbance, constipation, diarrhoea and perceived financial consequences of the treatment. EORTC-BN20 demonstrates sufficient psychometric properties and is used in conjunction with the EORTC QLQ-C30 for assessing the HRQoL of brain tumor patients<sup>13</sup>. The EORTC-BN20 questionnaire contains 20 items of which 13 cumulates into four multi-item scales representing; future uncertainty, visual disorder, motor dysfunction, communication deficit and seven single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control)<sup>13</sup>. All raw scores of the EORTC QLQ-C30 and EORTC-BN20 are linearly changed to a 0–100 scale. High scores indicates a better perceived HRQoL for the global health status/QoL and functioning scales and worse score for the treatment-related symptom scale<sup>43 44</sup>.

**Physical function**

Muscle strength is assessed by indirect 1 repetition maximum (RM) test. The tests involve performance on TuffStuff variable resistance equipment and targets large muscle groups as follows: 1) leg press (knee extensors, hip extensors, hip adductors and ankle joint flexors), 2) arm flexion (m. biceps brachii, m. brachialis, m. brachioradialis), 3) arm extension (m. triceps brachii), 4) knee extension (m. quadriceps femoris) 5) knee flexion (m. satorius, m. gracilis, m. biceps femoris, m. semimembranosus, m. semi tendonis, m. gastrocnemius, m. plantaris).

The patients follow a familiarization protocol of performing a set of 12 submaximal repetitions with a load equivalent to an estimated 50% (educated guess) of a 1 RM followed by a two-minute break. The physiotherapist focuses on correction technique, breathing technique and execution of the habituation set. The patient then performs another habituation set of eight-submaximal repetitions with a load equal to 75% (educated guess) of 1RM. After a two minute break the actual RM test is commenced. The test is performed by the physiotherapist adding loads until the patient is expected to reach failure within 3-8 repetitions or the patient voluntarily stops. If the load can be carried nine times or more, the test is discontinued, and a break of two-minute is given before a heavier load is attempted. A load equivalent of 3RM-8RM has to be located within one to four trials (exclusive the habituation sets). Otherwise, the test is dismissed due to fatigue. The tester strictly observes each repetition and only trials completed with proper form through the full range of motion is counted. Subjects are encouraged to complete repetitions consecutively and verbal motivation is standardised using a protocol during all testing sessions. An equation proposed by Brzycki is used to estimate 1 RM<sup>45</sup>.

Measuring VO<sub>2peak</sub> directly is considered the gold standard but requires refined equipment, skilled technicians, time and money. It is also for a number of subjects associated with discomfort<sup>46</sup> and neurological specific impairments such as muscle weakness, fatigue, poor balance or spasticity can interfere with the patients' ability to reach maximum function using standard maximal exercise. There are no validated submaximal fitness tests for these patients, but the Åstrand-Rhyming one-point bicycle test is considered the best choice for safety reasons, when a maximum test is associated with risk. The Åstrand-Rhyming test estimates maximal oxygen uptake (fitness indicators) from workload and pulse rate as per protocol by Åstrand<sup>47</sup>. The participant cycles for 6 minutes at 50-60 rpm with a load that stabilises the pulse in the range of 110-170 beats/minute, at the last of the six minutes.

Balance is assessed by sway test. Laboratory-based assessment using measures of center of pressure (COP) recorded from a force platform is considered the gold standard measure of balance<sup>48</sup>. The Wii Balance Board (WBB) is a valid and low-cost system for assessing standing balance<sup>48</sup>. Good-to-excellent test-retest reproducibility has been demonstrated during a static bilateral stance in thirty young individuals by extracting raw vertical force data from the WBB<sup>48</sup>. The WBB makes it possible to obtain non-invasive data on subjects by four piezoelectric strain gauges built into the corners of the device. The outputs of these

gauges assess force distribution and the resultant movements in COP through a Bluetooth connection<sup>49</sup>. Sway measurements are assessed by a protocol previous used by Jørgensen et. al<sup>50</sup>.

Gait velocity and step frequency is assessed by 10 meter walk test (10MWT) as per protocol of Watson, a valid and reliable quantitative test to measure walking ability in patients with neurologic disorders<sup>51</sup>. The patient walks 10 meters from a standing position at a preferred speed. Patients are allowed to use a preferred aid if needed. Time is recorded using a stopwatch and the number of steps taken is counted. Mean time score and mean number of steps is calculated<sup>51</sup>.

Changes in activity and performance status are assessed by an AMPS test which is a globally recognised assessment of everyday function. The AMPS is an observational, standardised performance-based assessment that obtains information on the quality of an individual's performance of activity of daily living (ADL) tasks<sup>52</sup>. According to AMPS, a higher score indicates an increased level of independence, increased safety in the community, and increased efficiency of performance<sup>52</sup>.

Physical activity levels at work and in leisure time are assessed through questions inspired by Saltin and Grimby<sup>42</sup>.

### Retention

Once a patient is randomised the study staff will make every effort to follow the patient for the entire study period. The staff is accountable for developing and implementing standard operating procedures to maximise level of follow-up and limiting participant burden related to visits and procedures. Before each follow-up the patient will receive a telephone call from the study leader or nurse and receive a formal invitation through mail. The nurse will give the study group an update on the patient's health status. If a patient has experienced a heavy disease progression or is not physically or mentally able to participate, s/he will be lost to follow-up in order to protect the safety. Participants may withdraw from the study for any reason at any time without it effects the primary treatment.

### Statistical method

The intervention group will be compared with controls for all primary analysis. We will use chi<sup>2</sup> test for binary outcomes and T-test or Mann Whitney for continuous outcomes. For subgroup analyses, we will use regression methods with appropriate interaction terms (respective subgroup × treatment group). Multivariable analyses will be based on logistic regression for binary outcomes and linear regression for continuous outcomes. All analyses are conducted using SPSS version 21 for Windows. For all tests 2-sided p-values with alpha = < 0.05 level of significance are used. A Bonferroni method is used to appropriately adjust the overall level of significance for multiple primary and secondary outcomes.

### Missing data

Linear Mixed Models & Generalised Estimating Equations are used for handling non-ignorable dropouts in the longitudinal study.

### Confidentiality

All study-related information will be stored securely at the study site in accordance with the Danish Data Protection Agency. All participant information will be stored in locked file cabinets in areas with limited access. All reports, data collection, process and administrative forms will be identified by a coded ID number to maintain participant confidentiality. All records containing names or other personal identifiers,

such as informed consent forms are stored separately from study records identified by code number. All local databases will be secured with password-protected access systems.

**Ethics and dissemination** The project was approved by the Regional Scientific Ethical Committees for Southern Denmark under Project-ID: (S-20140108) and by the Danish Data Protection Agency (J. no.2008-58-0035).

**Contributorship statement**  
Contributors AH, LRM, KS and JOJ were involved in the contribution and design of the study. All authors have read and approved the final manuscript.

**Competing interests**  
There are no competing interests.

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This research study received no specific grant from any funding agency in the public, commercial or non-profit sectors.

**Figure 1 Overview of the study design**

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Variable	Details	Unit
<b>Primary Outcome</b>		
HRQoL	EORTC-QLQ-C30	Score
<b>Secondary Outcomes</b>		
Symptom burden	EORTC-QLQ-30 with the addition of BN-20	score
Estimated maximum muscle strength of leg press	3-8 RM	Kg

TABLE 1 OUTCOME

Estimated maximum muscle strength of knee extension	3-8 RM	Kg
Estimated maximum muscle strength of knee flexion	3-8 RM	Kg
Estimated maximum muscle strength of arm flexion	3-8 RM	Kg
Estimated maximum muscle strength of arm extension	3-8 RM	Kg
Peak oxygen uptake (Vo2peak)	Åstrand-Rhyming cycle test	ml. O2/min/kg
Standing balance	Sway test	95% CI
Gait velocity	10 Meter Walk Test (10MWT)	sek.
Number of steps	10 Meter Walk Test (10MWT)	steps
Activity levels	The Assessment of Motor and Process Skills (AMPS)	score
Physical activity levels	Questionnaire	Score

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Title page

**The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among primary glioma patients – an RTC study protocol**

Corresponding author:

Anders Hansen Master of Health Science, Rehabilitation Unit, Odense University Hospital, Denmark.

[anders.hansen@rsyd.dk](mailto:anders.hansen@rsyd.dk) – [www.ouh.dk](http://www.ouh.dk)

Tlf: +45 2029 4467 / +45 6138 2536

Odense University Hospital

Sdr. Boulevard 29, entrance 108, 5000 Odense C

Denmark

Co-authors:

Lisbeth Kirstine Rosenbek Minet PT PhD, Rehabilitation Unit, Odense University Hospital, Denmark

Karen Sjøgaard Professor, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark

Jens Ole Jarden, M.D., D.MSci., Department of Neurology, Herlev University Hospital, University of Copenhagen, Denmark.

MeSH terms: Rehabilitation, Neurology, Oncology, Neurooncology, Interdisciplinary

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Abstract

**Introduction:** Gliomas are among the biggest challenges in neurological- and oncology rehabilitation and optimising treatment is of major clinical importance in this population. Though inpatient rehabilitation among glioma patients' results in improved functional measures, rehabilitation efforts are still not emphasized in this patient group and the literature lacks studies investigating the impact of outpatient rehabilitation.

**Method:** This protocol describes a randomised 6 week parallel group rehabilitation study investigating an outpatient interdisciplinary rehabilitation program. The intervention consists of 6 weeks intensive physiotherapy as groups exercise in conjunction with 0-6 weeks of individual occupational therapy if a need is present. The aim of this paper is to describe the design of the upcoming RCT. The results of the RCT will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer.

**Ethics and dissemination:** The project is approved by the Regional Scientific Ethical Committees for Southern Denmark under Project-ID: (S-20140108) and by the Danish Data Protection Agency (J. no.2008-58-0035). Dissemination will occur through presentation and findings will be published in peer-reviewed journals.

A key strength of this study is the randomised design and it is the first study to investigate a standardised outpatient interdisciplinary rehabilitation program among glioma patients. A potential limitation is the uncertainty and risk of side-effects to the concomitant treatment which enhances the risk of dropout. ClinicalTrials.gov Identifier: NCT02221986

Background

Primary brain tumor is a complicated condition due to complex diagnostic and treatment regimes. It has a progressive nature and a poor prognosis causing 2% of all cancer-related deaths<sup>1 2</sup>. Gliomas are the most frequent primary neoplasm in the CNS<sup>3</sup> and according to World Health Organization histologically categorized into low-grade glioma (LGG) (WHO grades I/II) or high-grade glioma (HGG) (WHO grades III/IV)<sup>4</sup>. Gliomas are among the biggest challenges in neurological- and oncology rehabilitation<sup>5 6</sup> and optimising treatment is of major clinical importance in this population. Patients often have neurological deficits such as sensory and motor, cognitive, functional deficits (hemiparesis, dysphasia, ataxia) and psychosocial (personality changes, loss of insight or empathy) factors due to tumor localisation or remote effects<sup>7 8</sup>. Not only does the damage to the brain tissue from tumor growth result in neurological impairment, the treatments can produce significant side-effects including severe muscle weakness, fatigue, headache, vomiting and insomnia<sup>9 10</sup>. The majority of patients have multiple impairments often resulting in great suffering and low health-related quality of life (HRQoL)<sup>7 9-11</sup>. Since the vast majority of patients cannot be cured outcome measures in clinical cancer research have traditionally focused on prolonging the overall survival, progression-free survival or response to the medical treatment<sup>12-15</sup>. Today there is a general agreement that HRQoL measures are increasingly important and The American Society of Clinical Oncology has suggested, that QoL measurements are an important primary endpoint in any Phase III study<sup>16</sup>. HRQoL plays a role in predicting survival or survival duration<sup>17</sup> among standard prognostic indicators such as histology and clinical stage. However, research on glioma patients' perception on HRQoL is sparse compared to other patient categories with neoplasms<sup>13 18</sup>. Advances in the neurosurgical techniques and medical treatment have resulted in an increased survival time<sup>19-23</sup>. This has led to a pronounced proportion of patients having a rehabilitation need<sup>24</sup>. Several studies indicate that glioma patients receiving inpatient rehabilitation acquire significant HRQoL, cognitive and functional gains similar with those seen in patients with non-neoplastic neurological conditions<sup>2 6 8 9 25-33</sup>. Despite of this, rehabilitation efforts are still not emphasised in this patient group<sup>24 29 30 34 35</sup> and a Cochrane

review recently concluded, that no well-designed clinical trials have investigated the effect of multidisciplinary rehabilitation in brain tumor patients<sup>9</sup>. Available data are often limited by small sample size studies<sup>27 30</sup>, heterogeneous diagnostic groups with histologically mixed tumor types<sup>29 32</sup> and missing details concerning resection and characteristics of the tumor including size and location or information regarding neurological deficits or treatment to date<sup>2 32</sup>. In the present study, interdisciplinary rehabilitation is defined as the coordinated distribution of interdimensional rehabilitation (such as physiotherapy, occupational therapy, nursing, psychology and other allied health interventions) to improve symptoms, maximising functional independence and participation by using a holistic bio psychosocial model (covering physical and psychosocial aspects) of care, as defined by The International Classification of Functioning, Disability and Health (ICF)<sup>36</sup>.

Little is known of the functional path of glioma patients in the outpatient rehabilitation phase and it has been suggested that prospective studies should test the effect of properly selected training interventions to avert and/or relieve dysfunction<sup>5 33</sup>. To our knowledge no randomised studies have investigated if a standardised outpatient interdisciplinary rehabilitation program among glioma patients has effect on HRQoL, symptom burden or physical function. The results of the present RCT study will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer.

### Research hypothesis

We hypothesise that patients attending an interdisciplinary rehabilitation program of intensive specialised physiotherapy and occupational therapy will improve their perception of HRQoL, reduce symptom burden and maintain or delay regression in physical function (defined as muscle strength, VO<sub>2peak</sub>, balance, gait function and activity levels).

### Objectives

The primary objective is to investigate if a structured rehabilitation program of intensive specialised physiotherapy and occupational therapy versus standard care has effect on HRQoL. Secondary objective is to investigate if the rehabilitation program can reduce the symptom burden and maintain or delay regression in physical function.

### Trial design

This trial is designed as a randomised, controlled, outcome assessor blinded, interdisciplinary exploratory trial with parallel groups.

### Study setting

The intervention is set to begin in September 2014 at Odense University Hospital (OUH) in the Region of Southern Denmark and end in early spring 2017. With a regional population of 1.2 million approximately 90 patients are annually diagnosed with glioma (WHO grades I-IV) at OUH.

### Eligibility criteria

Patient eligibility for randomisation and inclusion must comply with: (i) diagnosis of primary glioma (WHO grades I-IV), (ii) age  $\geq 18$ , reference with diagnosis or treatment at Odense University Hospital, (iii) Karnofsky performance score (KPS)  $\geq 70$  and (iiii) ability to understand Danish. Exclusion criteria are (i) pregnancy, (ii) known psychiatric diagnosis or substance abuse, (iii) heart problems excluding intense exercise (NYHA group III and IV) and (IV) pronounced impressive or expressive aphasia. The reason for

excluding KPS <70 is to ensure inclusion of patients able to conduct the physical training at an active and independent level, having cognitive ability to complete questionnaires and socially be able to interact with others.

**Intervention**

The intervention consists of 6 weeks intensive outpatient physiotherapy in conjunction with 0-6 weeks of occupational therapy if need is indicated. The physical intervention contains supervised group exercise of 90 minutes three times a week in groups up to four patients included continuously. Exercise includes individually tailored strength training of main muscle groups with increasing load ranging from 15 to 10 repetition maximum (RM) (leg press, arm flexion, arm extension, knee flexion and knee extension), cardio training (20 minutes of cycling or treadmill with intensities ranging from 65% to 85% of the heart rate reserve), body awareness training or relaxation (training of proprioception, postural control or stability of the core muscles tailored to personal needs). Every session starts with 5 to 10 minutes of warm-up. The strength training workload is calculated based on baseline tests and patients follow a training diary with instructions to progression. The cardiovascular training is monitored by pulse through means of a wireless heart rate transmitter worn by the patients.

The occupational therapy intervention consists of individual training 60 minutes twice a week for patients having deficits in activity or participation levels measured by the Assessment of Motor and Process Skills (AMPS). The training focuses on bettering the patients functional capacity, body, activity and participation level by adapting activities, regaining or developing activity abilities and/or rebuilding and developing patient skills<sup>37</sup>. The occupational therapy is terminated before the 6th week if the patient has reached the appointed functional goals and follow-up assessments are conducted.

The control group receives usual standard of care (e.g. no training, individual training or group training in the municipality). The amount of training in this group is based on a questionnaire at the follow-up trials.

**Safety**

Prior to each physical training session the study nurse assesses each individual patient for the following conditions: diastolic blood pressure <45 or >100, pulse >100, temperature above 38°C, respiration frequency at rest >20, infection requiring treatment with antibiotics, ongoing bleeding; fresh petechiae, bruises<sup>38</sup>, blood-leukocytes <5×10<sup>9</sup>/L and blood-thrombocytes <5 x 10<sup>3</sup>/μL. If a condition is found, the patients will be excluded from the physical workout on that specific day and a physician will be informed. All patients are instructed to interrupt or stop training at any time if they feel faint or unwell.

**Feasibility study**

Before initiating the RCT-study a feasibility study on 24 patients has been conducted to (i) test the feasibility and safety of a twelve week interdisciplinary rehabilitation program of individually activity based training and physical exercise as a group intervention for patients with primary glioma, (ii) to assess the preliminary effects on HRQoL, symptom burden and physical function and (iii) to determine the effect sizes and sample needed for the RCT-study. The feasibility study also informed the intensity and progression in the final program and secured that the training was well tolerated by this specific group of patients.

**Criteria for discontinuing allocated intervention for a given trial participant**

It is to be expected that some patients will experience side effects to their concomitant treatment with radiation, chemotherapy or cortisone. For a given patient, the assigned study intervention will be discontinued at the discretion of the trial investigators if the healthcare-staff notices a change behaviour

occurring in the patient or the symptom burden is too high. The Physical and emotional status of the patients are evaluated before every training session. If patients exceed the set of specified requirements, s/he is referred to the study nurse and neurologist for further evaluation and possible exclusion. Regardless of any decision to modify or discontinue the assigned intervention, the patient is retained in the trial whenever possible to enable follow-up data collection and prevent missing data. Patients are informed that they can retrieve their consent at any time without any consequences regarding their relationship with the staff or the content of their medical treatment. Patients are referred to municipality rehabilitation if the specialised treatment does not meet the patients' expectations.

### Usefulness of the trial

Patients allocated to the intervention group will likely exercise more than usual. However, experience shows that many associate this with increased profits<sup>39</sup>. This study is done so that we in the future can organise the best possible rehabilitation for patients with glioma.

### Side effects, risks, complications and drawbacks

We do not anticipate side-effects associated with the rehabilitation. On the contrary, we expect patients to experience similar positive effects on the treatment related side-effects as other cancer groups<sup>39-41</sup>.

### Outcome

All outcome measures are gathered at baseline (FU-0) at the end of the 6th week of intervention (FU-1), at a 3-month follow up (FU-2) and at a 6-month follow-up (questionnaires only) (FU-3) (see Figure 1). At baseline, descriptive variables for each subject in terms of gender, age, weight, height and cohabiting is assessed. Disease variables and treatments are obtained through review of medical records. Extend of resection is assessed through imaging definitions 72 hours postoperative. Data on tumor structures, residual tumor, infarct or hematoma in- or around the cavity and tumor localisation are extracted.

### Figure 1 Overview of the study design

All physical assessment tools and questionnaires are set to be conducted within 90 minutes and occupational tests within 60 minutes. This is done to decrease the symptom burden and avoid risk of bias due to fatigue.

The tests battery includes two questionnaires: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30) and the EORTC brain cancer module (EORTC QLQ-BN20) on patients' perception on HRQoL and symptom burden. Five physiological tests measures physical function defined as: estimated maximum muscle strength (knee extension, knee flexion, arm flexion, arm extension and leg press) (1RM), maximal oxygen uptake ( $VO_{2peak}$ ), balance, gait velocity and steps frequency (10 meter walk test) and activity levels (AMPS and questions on physical activity<sup>42</sup>) (see Table 1).

The primary outcome is HRQoL and secondary outcomes are 1) symptom burden and side-effects from the medical treatment and 2) physical function defined as: estimated maximum muscle strength (knee extension, knee flexion, arm flexion and arm extension),  $VO_{2peak}$ , balance, gait velocity and activity levels.

### Paste Table 1 Outcome

#### Sample size

According to the scoring manual for EORTC QLQ-30 a change of 10 points or more is considered to be a moderate to large clinically significant change<sup>43</sup>. Based on this assumption and results of the feasibility

study (n=24) a sample size is calculated. At an expected "effect size" of at least 10 points (SD  $\pm 24,6$ ) increase in the EORTC QLQ-30 General Health Scale/QoL (paragraphs 29 and 30) with a statistical power of  $\beta$  0.8 and  $\alpha$  of 0.05 the study requires 48 subjects in each arm. To meet an expected dropout-rate of approximately 15 % a total of 56 participants will be included in each group. Based on 90 new cases annually and an acceptance- and fulfilment of inclusion criteria based on the feasibility study of >80%, approximately 64 patients will be included per year. Enrollment is thus expected to extend for 22 months.

**Recruitment**

On a daily basis the administration list from neurological- and neurosurgical departments is screened for potential subjects by the study nurse. Concurrently, a nurse from the neurosurgical department supplies information on planned cerebral tumor operations. The study leader/nurse approaches eligible patients at the neurosurgical department within 24 hours after returning from the intensive recovery room when the first contact with the therapist normally is scheduled. A KPS is estimated and permission to pass information on to a neurology specialist for histological assessment of inclusion/exclusion criteria is obtained. Before discharge (typically at the 4<sup>th</sup> postoperative day) the patient is approached a second time for oral information with the opportunity for relatives to be present. After 24 hours (or the nearest weekday) post-discharge the study leader/nurse contacts the patient by telephone and gets accept or refusal for study participation. If accepted, the patient will receive a formal invitation for baseline assessing through mail. For HGG this is simultaneously with the start of the radiation treatment approximately 4 weeks post discharge. For LGG patients not offered radiation treatment, the start of intervention is likewise 4 weeks post discharge. Informed consent is obtained at the baseline test.

**Randomisation**

Participants are randomly assigned to a control or intervention group with a 1:1 allocation by block randomisation stratified by LGG versus HGG. The block size will not be disclosed to sustain concealment. Consecutively, closed, opaque, numbered envelopes containing assembly allocation are prepared by an assistant outside the study group. The envelopes are stored securely in a locked container. After baseline assessment tests the randomisation is performed by a secretary with no interest in the outcome of the study. The nurse will open the envelope and reveal the allocation for the patient.

**Blinding**

Due to the nature of the intervention neither participants nor staff can be blinded to allocation but are instructed not to reveal the allocation status of the participant at the follow-up assessments. The testing personnel are blinded to which intervention the patients have received. An employee outside the research team will feed data into the computer in separate datasheets so that the researchers can analyse data without having access to information about the allocation.

**Data collection methods**

HRQoL is assessed by means of the questionnaire EORTC-QLQ-30<sup>43</sup> with the addition of the questionnaire EORTC-BN20<sup>44</sup>. These are handed out at baseline tests to be completed at the hospital.

The EORTC QLQ-C30<sup>43</sup> consists of single and multi-item scales. There are 30 items of which 24 cumulate into nine multi-item scales representing various HRQoL dimensions: five functioning scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain and nausea and vomiting) and a global health status/QoL. Six single item scales assesses treatment-related symptoms: dyspnoea, loss of appetite, sleep disturbance, constipation, diarrhoea and perceived financial consequences of the treatment. EORTC-BN20 demonstrates sufficient psychometric properties and is used in conjunction with the EORTC QLQ-C30 for assessing the HRQoL of brain tumor patients<sup>13</sup>. The EORTC-BN20 questionnaire contains 20 items of

which 13 cumulates into four multi-item scales representing; future uncertainty, visual disorder, motor dysfunction, communication deficit and seven single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control)<sup>13</sup>. All raw scores of the EORCT QLQ-C30 and EORTC-BN20 are linearly changed to a 0–100 scale. High scores indicates a better perceived HRQoL for the global health status/QoL and functioning scales and worse score for the treatment-related symptom scale<sup>43 44</sup>.

### Physical function

Muscle strength is assessed by indirect 1 repetition maximum (RM) test. The tests involve performance on TuffStuff variable resistance equipment and targets large muscle groups as follows: 1) leg press (knee extensors, hip extensors, hip adductors and ankle joint flexors), 2) arm flexion (m. biceps brachii, m. brachialis, m. brachioradialis), 3) arm extension (m. triceps brachii), 4) knee extension (m. quadriceps femoris) 5) knee flexion (m. satorius, m. gracilis, m. biceps femoris, m. semimembranosus, m. semitendinosus, m. gastrocnemius, m. plantaris).

The patients follow a familiarization protocol of performing a set of 12 submaximal repetitions with a load equivalent to an estimated 50% (educated guess) of a 1 RM followed by a two-minute break. The physiotherapist focuses on correction technique, breathing technique and execution of the habituation set. The patient then performs another habituation set of eight-submaximal repetitions with a load equal to 75% (educated guess) of 1RM. After a two minute break the actual RM test is commenced. The test is performed by the physiotherapist adding loads until the patient is expected to reach failure within 3-8 repetitions or the patient voluntarily stops. If the load can be carried nine times or more, the test is discontinued, and a break of two-minute is given before a heavier load is attempted. A load equivalent of 3RM-8RM has to be located within one to four trials (exclusive the habituation sets). Otherwise, the test is dismissed due to fatigue. The tester strictly observes each repetition and only trials completed with proper form through the full range of motion is counted. Subjects are encouraged to complete repetitions consecutively and verbal motivation is standardised using a protocol during all testing sessions. An equation proposed by Brzycki is used to estimate 1 RM<sup>45</sup>.

Measuring  $VO_{2peak}$  directly is considered the gold standard but requires refined equipment, skilled technicians, time and money. It is also for a number of subjects associated with discomfort<sup>46</sup> and neurological specific impairments such as muscle weakness, fatigue, poor balance or spasticity can interfere with the patients' ability to reach maximum function using standard maximal exercise. There are no validated submaximal fitness tests for these patients, but the Åstrand-Rhyming one-point bicycle test is considered the best choice for safety reasons, when a maximum test is associated with risk. The Åstrand-Rhyming test estimates maximal oxygen uptake (fitness indicators) from workload and pulse rate as per protocol by Åstrand<sup>47</sup>. The participant cycles for 6 minutes at 50-60 rpm with a load that stabilises the pulse in the range of 110-170 beats/minute, at the last of the six minutes.

Balance is assessed by sway test. Laboratory-based assessment using measures of center of pressure (COP) recorded from a force platform is considered the gold standard measure of balance<sup>48</sup>. The Wii Balance Board (WBB) is a valid and low-cost system for assessing standing balance<sup>48</sup>. Good-to-excellent test-retest reproducibility has been demonstrated during a static bilateral stance in thirty young individuals by extracting raw vertical force data from the WBB<sup>48</sup>. The WBB makes it possible to obtain non-invasive data on subjects by four piezoelectric strain gauges built into the corners of the device. The outputs of these gauges assess force distribution and the resultant movements in COP through a Bluetooth connection<sup>49</sup>. Sway measurements are assessed by a protocol previous used by Jørgensen et. al<sup>50</sup>.

Gait velocity and step frequency is assessed by 10 meter walk test (10MWT) as per protocol of Watson, a valid and reliable quantitative test to measure walking ability in patients with neurologic disorders<sup>51</sup>. The patient walks 10 meters from a standing position at a preferred speed. Patients are allowed to use a preferred aid if needed. Time is recorded using a stopwatch and the number of steps taken is counted. Mean time score and mean number of steps is calculated<sup>51</sup>.

Changes in activity and performance status are assessed by an AMPS test which is a globally recognised assessment of everyday function. The AMPS is an observational, standardised performance-based assessment that obtains information on the quality of an individual's performance of activity of daily living (ADL) tasks<sup>52</sup>. According to AMPS, a higher score indicates an increased level of independence, increased safety in the community, and increased efficiency of performance<sup>52</sup>.

Physical activity levels at work and in leisure time are assessed through questions inspired by Saltin and Grimby<sup>42</sup>.

**Retention**

Once a patient is randomised the study staff will make every effort to follow the patient for the entire study period. The staff is accountable for developing and implementing standard operating procedures to maximise level of follow-up and limiting participant burden related to visits and procedures. Before each follow-up the patient will receive a telephone call from the study leader or nurse and receive a formal invitation through mail. The nurse will give the study group an update on the patient's health status. If a patient has experienced a heavy disease progression or is not physically or mentally able to participate, s/he will be lost to follow-up in order to protect the safety. Participants may withdraw from the study for any reason at any time without it effects the primary treatment.

**Statistical method**

The intervention group will be compared with controls for all primary analysis. We will use chi<sup>2</sup> test for binary outcomes and T-test or Mann Whitney for continuous outcomes. For subgroup analyses, we will use regression methods with appropriate interaction terms (respective subgroup × treatment group). Multivariable analyses will be based on logistic regression for binary outcomes and linear regression for continuous outcomes. All analyses are conducted using SPSS version 21 for Windows. For all tests 2-sided p-values with alpha = < 0.05 level of significance are used. A Bonferroni method is used to appropriately adjust the overall level of significance for multiple primary and secondary outcomes.

**Missing data**

Linear Mixed Models & Generalised Estimating Equations are used for handling non-ignorable dropouts in the longitudinal study.

**Confidentiality**

All study-related information will be stored securely at the study site in accordance with the Danish Data Protection Agency. All participant information will be stored in locked file cabinets in areas with limited access. All reports, data collection, process and administrative forms will be identified by a coded ID number to maintain participant confidentiality. All records containing names or other personal identifiers, such as informed consent forms are stored separately from study records identified by code number. All local databases will be secured with password-protected access systems.

**Ethics and dissemination** The project was approved by the Regional Scientific Ethical Committees for Southern Denmark under Project-ID: (S-20140108) and by the Danish Data Protection Agency (J. no.2008-58-0035).

#### Contributorship statement

Contributors AH, LRM, KS and JOJ were involved in the contribution and design of the study. All authors have read and approved the final manuscript.

#### Competing interests

There are no competing interests.

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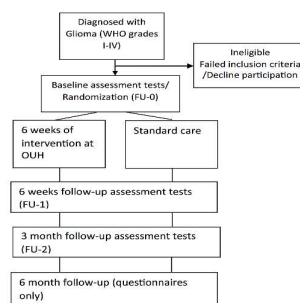
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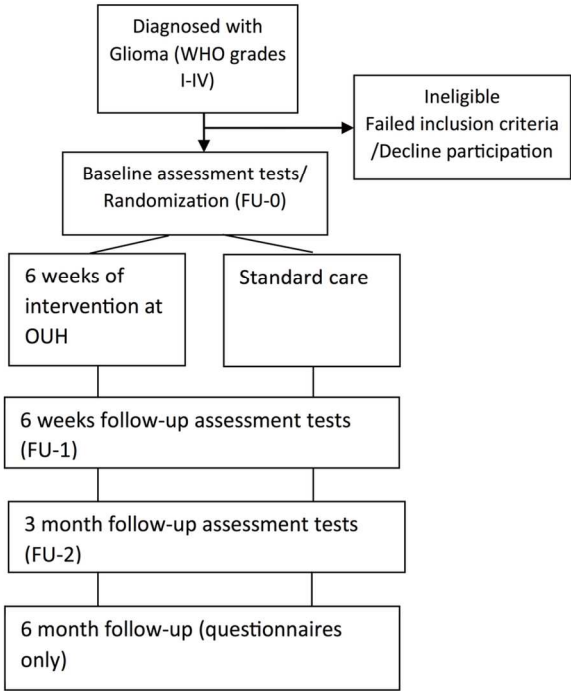
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Figure 1



Variable	Details	Unit
<b>Primary Outcome</b>	<b>EORTC-QLQ-C30</b>	<b>Score</b>
<b>Secondary Outcomes</b>		
Symptoms burden	EORTC-QLQ-30 with the addition of BN-20	score
Estimated maximum muscle strength of leg press	3-B RM	Kg
Estimated maximum muscle strength of knee extension	3-B RM	Kg
Estimated maximum muscle strength of knee flexion	3-B RM	Kg
Estimated maximum muscle strength of arm flexion	3-B RM	Kg
Estimated maximum muscle strength of arm extension	3-B RM	Kg
Peak oxygen uptake (Vo2peak)	Astrand-Rhyming cycle test	ml, O2/min/kg
Standing balance	Sway test	95% CI
Gait velocity	10 Meter Walk Test (10MWT)	sek.
Number of steps	10 Meter Walk Test (10MWT)	steps
Activity levels	The Assessment of Motor and Process Skills (AMPS)	score
Physical activity levels	Questionnaire	Score

Table 1



124x90mm (300 x 300 DPI)