

Radiotherapy versus radiotherapy combined with temozolomide in high-risk low-grade gliomas after surgery: Study protocol for a randomized controlled clinical trial

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Abstract

Abstract Background It has been reported that radiation therapy followed by PCV chemotherapy (procarbazine, lomustine and vincristine) could improve progression-free survival (PFS) and overall survival (OS) in patients with high-risk WHO grade 2 gliomas after surgery. However, procarbazine is not available in China. In clinical practice, Chinese doctors often use radiotherapy combined with temozolomide to treat these patients, though large-scale prospective studies are lacking. This trial aims to confirm whether RT combined with temozolomide (TMZ) can improve PFS and OS in patients with high-risk low-grade gliomas (LGGs). **Methods/design** This is a two-group, randomized controlled trial (RCT) enrolling patients who have low-grade (WHO grade 2) gliomas aged 40 years or older without regard to the extent of resection or younger than 40 years old with subtotal resection or biopsy. Eligible participants will be randomly assigned to receive radiation therapy (RT) alone or RT plus temozolomide chemotherapy in a 1:1 ratio. The same RT will be given to all eligible participants regardless of whether they are randomly assigned to RT group or chemoradiotherapy (CRT) group. While in the CRT group, patients will receive adjuvant TMZ with or without concurrent radiochemotherapy. The primary outcome of this trial is progression-free survival and it will be analyzed by intention-to-treat (ITT). Secondary outcomes include OS, adverse events and cognitive function (CF). **Discussion** The objective of our research is to assess the effect of radiotherapy coupled with temozolomide in high-risk LGGs after surgery, compared with RT alone. Different histological types and molecular subtypes will be examined and subgroup analysis will be conducted based on them. Our data can provide evidence for postoperative adjuvant therapy in Chinese high-risk LGGs. **Trial Registration** Chinese Clinical Trial Registry, ChiCTR1800015199. Registered on 13th March, 2018. <http://www.chictr.org.cn>

Background

Grade 2 glioma accounts for about 15-20% of all brain tumors in adults [1]. According to the 2016 revision of the WHO classification of tumors of the central nervous system, the major pathological type of grade 2 LGGs includes diffuse astrocytomas (wild type IDH1, mutant IDH1 or not otherwise specified) and oligodendrogliomas (mutant IDH1 and 1p/19q co-deletion or not otherwise specified) [2]. The treatment modalities consist of surgery followed by observation, radiotherapy, chemotherapy or chemoradiation [3]. Although surgery can cure a proportion of patients, some patients still recur after surgery and even transform into high grade gliomas. Basing on longer survival data compared with high grade gliomas, postoperative treatment decisions about observation versus aggressive treatments must take into account possible clinical benefits and side effects which may affect quality of life. Nowadays, postoperative adjuvant treatment strategies depend on whether patient has high-risk factors. However, high risk factors have been changing in recent years. There used to be 6 factors considered to be high risk (astrocytoma, age>40years, Karnofsky performance score (KPS) <70, tumor dimension>6cm, tumor crossing midline, preoperative neurological function deficits of moderate to severe degree) [4]. From 2015, subtotal resection and >40 years old are regarded as main high-risk factors for LGGs [5]. Compared with low risk population, patients with high risk factors need aggressive treatments after surgery. EORTC 22845 is a prospective trial to compare early radiotherapy with deferred radiotherapy [6]. 314 LGGs with surgical resection or biopsy were randomized to receive either early RT or delayed RT delivered when progression took place. The results showed that immediate postoperative radiotherapy improved PFS and had better seizures control, but there was no impact on overall survival. Taken together, patients with high-risk WHO grade 2 glioma can benefit from postoperative adjuvant RT. In addition, comparison between adjuvant RT alone and

temozolomide (TMZ) alone was investigated in EORTC 22033-26033 [7]. No differences were observed between two arms in PFS. That is to say, TMZ has similar improved PFS, compared with RT group. Furthermore, can radiotherapy combined with chemotherapy improve clinical outcomes in these high risk LGG patients? RTOG 9802, a prospective clinical trial, indicated improvement in both PFS and OS with six cycles of adjuvant PCV chemotherapy following radiation, when compared with RT alone. Besides, the survival distribution continued to diverge over time [8-9]. However, procarbazine is not available in China. In clinical practice, Chinese doctors often use radiotherapy combined with TMZ to treat these patients, though large-scale prospective studies are lacking. TMZ is an alkylating agent with chemical property to cross the blood-brain barrier. It is one of standard treatments for high-grade glioma to take TMZ as concurrent and adjuvant chemotherapy [10-12]. However, in low-grade gliomas, further studies are indispensable to ascertain the role of TMZ in addition to RT. RTOG 0424, a single-arm phase II study, combined concurrent and adjuvant TMZ with RT to treat patients with LGG with at least 3 risk factors for relapse (age \geq 40 years, preoperative tumor diameter \geq 6 cm, astrocytoma histology, tumor crossing the midline, or a preoperative neurological deficit of more than mild extent) [13]. The 3-year OS rate was 73.1%, which not only significantly exceeded historical controls but also researched hypothesis. Despite RTOG 0424 unveiled that radiotherapy followed by TMZ chemotherapy for high-risk LGGs had survival benefits, it was a single-arm trial and Chinese data is still lacking. As a result, we decide to carry out a [randomized controlled trial](#) to confirm the advantage of TMZ chemotherapy added to RT for high-risk LGGs.

Methods/design

Study objective

The aim of this study is to compare the efficacy and safety of RT plus TMZ with RT alone for high-risk LGGs. Beyond that, we will focus on molecular features, in addition to histologic classification, to establish a more appropriate treatment modality for certain cohorts.

Study design

This is a multicentre, open-label, prospective RCT. The study has received ethical approval from China Registered Clinical Trial Ethics Committee. The protocol is written in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see [Additional file 1: SPIRIT Checklist](#)). Following informed consent, eligible patients will be allocated to a RT group (control group) or a CRT group (experimental group). The flow diagram of the main procedures is illustrated in [Fig.1](#).

Recruitment and informed consent

A total of two hundred and fifty participants will be recruited from 4 centres in China (see [Additional file 2](#)). Registration step can be done at any time after being diagnosed as WHO grade II glioma and it is expected to be completed within 5 years. Research staff is in charge of screening process to make sure each participant match the inclusion and exclusion criteria. An informed consent form (ICF) describing detailed study procedures and illustrating potential benefits and risks will be provided to all participants, so that they can decide whether or not to volunteer. Written informed consent must be acquired from all patients or their legal representatives prior to participating in this clinical trial.

Eligibility criteria

Inclusion criteria are as follows:

1. Newly diagnosed supratentorial WHO grade II gliomas;
2. Aged 18 to 39 years without total resection, or aged 40 to 70 years with any extent of resection or biopsy;
3. Karnofsky performance score (KPS) \geq 60;
4. No more than moderate neurologic symptoms and signs;
5. The interval between surgery and randomization is less than 12 weeks;
6. Have signed the consent form.

Exclusion criteria are as follows:

1. WHO grade 1 gliomas or high-grade gliomas according to WHO's grading system;
2. Have received prior radiation therapy to the head and neck region;
3. Have received prior chemotherapy;
4. Synchronous multiple primary malignant tumor excluding carcinoma of the cervix in situ or nonmelanomatous skin cancer;
5. Prior malignancy's disease-free survival less than 5 years;
6. Have active infection;
7. Patients are pregnant or breast-feeding.

Randomization

Qualified patients will be randomized in a 1:1 ratio using the method of block randomization. The blocked randomization sequence is generated by computer software SPSS, and the block size is determined by statisticians. After the patient has registered and signed the informed consent form, he or she will be allocated to RT group or CRT group by web-based central randomization. The allocation sequence is unavailable to researchers who will enroll participants or assign interventions.

Interventions

Eligible patients will be assigned 1:1 to an experimental group or a control group. In experimental group, patients will be treated with RT combined with adjuvant TMZ with or without concurrent TMZ. And in control group, patients will only have RT treatment. Both groups will receive the same intensity modulated radiation therapy (IMRT). The radiation dose is 50-54 Gy given in 25-30 fractions (1.8-2.0 Gy once daily, 5 days per week). RT treatment volumes will be defined using pre- and postoperative T2 or fluid-attenuated inversion recovery (FLAIR) on MRI. Drug dose adjustments are allowed according to blood counts and adverse reactions. Concurrent chemotherapy is to receive oral TMZ, 75 mg/m² per day, during radiation therapy. Concurrent TMZ can be used for 42 days continuously if an absolute neutrophil count (ANC) is not less than 1.5x10⁹ cells per L and platelet

count not less than 100×10^9 cells per L and non-haematological toxicity of grade 0 or 1 (except alopecia, nausea, and vomiting) according to version 4.03 of the National Cancer Institute Common Toxicity Criteria (NCI-CTC). In the case of ANC less than 1.5×10^9 cells per L but more than 0.5×10^9 cells per L, platelet count less than 100×10^9 cells per L but more than 10×10^9 cells per L, or non-haematological toxicity of grade 2, concurrent TMZ treatment should suspend until recovery to toxicity of grade 0 or 1. Temozolomide chemotherapy will be terminated when one of the following conditions occurs: ANC < 0.5×10^9 cells per L, platelet count < 10×10^9 cells per L, non-haematological toxicity of grade 3 or 4.

Patients who are assigned to adopt adjuvant chemotherapy will be treated with six cycles of TMZ, 150 to 200 mg/m² per day for five consecutive days, repeated every 4 weeks. There is a 28-day break during RT and adjuvant TMZ. The first cycle dose of adjuvant chemotherapy is 150 mg/m². A higher dose of 200 mg/m² is recommended in the subsequent cycles if ANC not less than 1.5×10^9 /L and platelet count not less than 100×10^9 /L and non-haematological toxicity of grade 0 or 1 (except alopecia, nausea, and vomiting) during the first cycle. The dose will reduce by 50mg/m² if ANC is less than 1×10^9 cells per L or platelet count less than 50×10^9 cells per L or non-haematological toxicity of grade 3 during any period of adjuvant chemotherapy. Patients have to discontinue adjuvant TMZ if grade 4 non-haematological is recorded or the dose of TMZ has reduced to less than 100 mg/m² or grade 3 non-haematological reoccurs after dose reduction.

Outcomes

Our primary outcome is progression-free survival which is calculated from the date of randomization to the date of first reported disease progression or the date of death caused by any cause. Secondary outcomes are overall survival, adverse events and cognitive function. OS is calculated from the date of randomization until death caused by any cause. Cognitive function will be assessed by Mini-Mental State Examination (MMSE).

Adverse events (AE)

Investigators should explain to participants in detail that they are required to faithfully reflect changes in their condition during and after treatment. Researchers are supposed to pay close attention to adverse events while observing the curative effect. The following information should be recorded in the case report form (CRF): symptom, occurrence time, severity, duration, treatment measures and outcomes. Researchers should evaluate the association between AE and treatment and record them timely and truly with signature and date. The grading of adverse events will accord with CTC-AE v4.03.

Baseline and follow-up visits

After obtaining written informed consent, baseline assessment including physical examination, KPS, complete blood count (CBC), serum biochemistry will be completed within 7 days before interventions. Postoperative head MRI and cognitive function test are allowed to complete within 28 days prior to treatment. During treatment, complete blood count and serum biochemistry (including renal and liver function, electrolyte and lactate dehydrogenase) will be conducted weekly. The first follow-up visit (KPS, head MRI, cognitive function) will be done one month after radiotherapy. Then every 3 months in the first 2 years, every half year from 3 to 5 years and at least annually thereafter. Participants will be followed up to 10 years after the end of treatment for the last patient. The schedule of assessments before, during and after treatment are displayed in Table 1.

Table 1. Study schedule of enrollment, intervention, and assessments.

	Study Period							
	Enrollment	Allocation	Post-allocation	Week 10	Week 11-34	Within 2 years	3-5 years	5-10 years
Time point	-4 weeks	0	Week 0-6	Week 10	Week 11-34	Within 2 years	3-5 years	5-10 years
Enrollment:								
Eligibility screen	X							
Informed consent	X							
Randomization	X							
Allocation		X						
Interventions:								
RT			X					
Concurrent TMZ			X					
Adjuvant TMZ				X	X			
Assessments:								
Physical examination		X				every 3 months	every 6 months	annually
KPS		X		X		every 3 months	every 6 months	annually
CBC		X	weekly	X	weekly			
Serum biochemistry		X	weekly	X	weekly			
Postoperative head MRI	X			X		every 3 months	every 6 months	annually
Cognitive function	X			X		every 3 months	every 6 months	annually
Adverse events			X	X	X	every 3 months	every 6 months	annually

Abbreviations :RT, radiation therapy; TMZ, temozolomide; KPS, Karnofsky performance score; CBC, complete blood count.

Sample size

This RCT is designed as a superiority trial. Based on literature reports and clinical experience, the median OS of the RT group is 7.8 years and that of chemoradiotherapy group (RT plus TMZ) is 13.3 years. One-sided log-rank test with a significance level of 0.05, a test power of 80%, withdrawal and loss of follow-up rate of 10% is applied in this trial. The sample size estimated by software PASS 11 is 125 subjects per group.

Data collection and management

All relevant information of each subject should be recorded in CRF and inputted in ResMan, an Internet-based electronic data capture, timely and truly by trained research staff. Personal information of each subject is confidential. In order to promote participant retention, researchers will instruct subjects to take the medicine as prescribed. Besides, patients will be informed of the follow-up visit by telephone in advance, and all items will be measured in strict accordance with assessments schedule shown in Table 1. Two data entry staffs are needed to input the data independently. After reviewing and confirming that the database is correct, electronic data will be conserved and backup. As original material, CRF should not be changed easily. Researcher has to sign and date when it is necessary to modify. The locked electronic data files are not allowed to make any changes. The database will be statistically analyzed by statistical analysts as required by the statistical plan. Principal investigator has the access to the final dataset, while other investigators are prohibited from entering.. Except for the name-related data, the disclosure of the information to third parties is prohibited. After the completion of the trial, the responsible unit of the study has the right to publish contents related to the experiment in the form of a paper.

Data analysis

Professional statisticians undertake statistical analysis tasks and participate in the whole process from trial design, implementation to analysis and summary. Kaplan-Meier will be used to estimate median PFS and OS, and log-rank test will be used to compare differences between two arms. Furthermore, a COX's proportional hazards analysis will be done to estimate the hazard ratio (HR) and 95% confidence interval (CI). Regarding prognostic factors, uni-and multi variate analysis including age, histology, treatment method, IDH mutation, 1p19q status, and MGMT promoter status will be used to analyze their impact on PFS and OS. Safety analysis, mainly for adverse events, will be done in safety set (SS) population. All effectiveness analysis (PFS, OS, cognitive function) will be done on an intention-to-treat set. ITT analysis will be put to use to handle non-compliance and missing data.

Data monitoring

To ensure the safety and validity of the trial, the data will be overseen by an independent Data Safety Monitoring Board (DSMB) during study period. The board consists of clinicians and statisticians and will monitor all implementation activities including but not limited to the enrollment of each centre, starting time of procedures and drop out. All adverse events and issues concerning interventions will be reported to DSMB in line with requirements. All data entered into the database will be checked by DSMB before being locked, and no changes will be permitted. To ensure data security, data must be backed up in time and irrelevant personnel cannot access and modify data.

Discussion

Optimal adjuvant management of adult low-grade gliomas is controversial. RTOG 9802 has shown striking survival improvements for LGGs treated with adjuvant RT followed by PCV chemotherapy, and there is a significant average MMSE score increase in both arms [14]. But obviously, the incidence of adverse events in chemoradiotherapy group is higher than RT group. So it is crucial to weigh the efficacy and safety of these treatments and further clarify how to combine them. Pathological molecular typing is an essential component of diagnosis and treatment of glioma at present. This clinical trial is the first large-scale prospective study to compare the effect of RT alone with RT plus TMZ involving molecular subtypes in high-risk LGGs. The outcomes of this trial are expected to evaluate predictive effects of diverse molecular markers (IDH1/IDH2 mutations, 1p/19q co-deletion, MGMT promoter methylation status) and to find appropriate treatment pattern based on them.

Cognitive function has aroused extensive concern in patients with brain tumours. EORTC 22033-26033, a prospective study of patients with LGGs, revealed no significant difference between RT group and TMZ group [15]. Therefore, it didn't back the treatment of TMZ alone over RT alone. In our study, MMSE, a widely used screening test for dementia and cognitive dysfunction and a practical approach for ranking the cognitive state [16-19], will be applied to assess the CF in both randomly assigned arms. It may affect the choice of individual therapeutic strategy for patients with LGGs if RT plus concomitant and adjuvant TMZ improves survival outcomes without additional CF damage than RT alone.

Trial Status

The final protocol version is 1.0 and dated 11th February, 2018. Patient recruitment began on 10th April, 2018 after we acquired ethic approval, and is ongoing. We anticipate the recruitment phase to be complete by April 2023.

List Of Abbreviations

PFS: progression-free survival **OS:** overall survival **TMZ:** temozolomide

CF: cognitive function **IDH:** isocitrate dehydrogenase

PCV: procarbazine, lomustine, and vincristine

LGG(s): low-grade glioma (s) **RCT:** randomized controlled trial

RT: radiation therapy, radiotherapy **CRT:** chemoradiotherapy

MT: mutant **WT:** wild-type **ITT:** intention-to-treat

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

ICF: informed consent form **KPS:** Karnofsky performance score

IMRT: intensity modulated radiation therapy

FLAIR: fluid-attenuated inversion recovery **ANC:** absolute neutrophil count

NCI-CTC: National Cancer Institute Common Toxicity Criteria

CBC: complete blood count **AE:** adverse events **CRF:** case report form

HR: hazard ratio **CI:** confidence interval **SS:** safety set

MMSE: Mini-Mental State Examination

DSMB: Data Safety Monitoring Board

Declarations

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Ethics approval and consent to participate

The trial protocol was registered on 13 March, 2018 by Chinese Clinical Trial Registry (ChiCTR1800015199). Central ethical approval has been confirmed from Chinese Ethics Committee of Registering Clinical Trials (approval no. ChiECRCT-20180033) on 4th April, 2018, and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained. All participants have to provide written informed consent form before enrolment.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XCP is the project designer and is responsible for the research. All authors participated in drafting the manuscript, XCP and YW revise it. XCP and YH take charge of target volume delineation and the quality control of radiation. XCP, YW, YH, HG, JJW participate in recruiting participants, obtaining informed consent, assessing patients' cognitive function as well as filling out the MMSE form. JJW, YH and HG are involved in data collection. LH and XLM contributed to perform randomized sequence generation and will conduct the statistical analysis. XCP, JJW, YW, YH and HG will monitor adverse events and must report them in time. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Figures

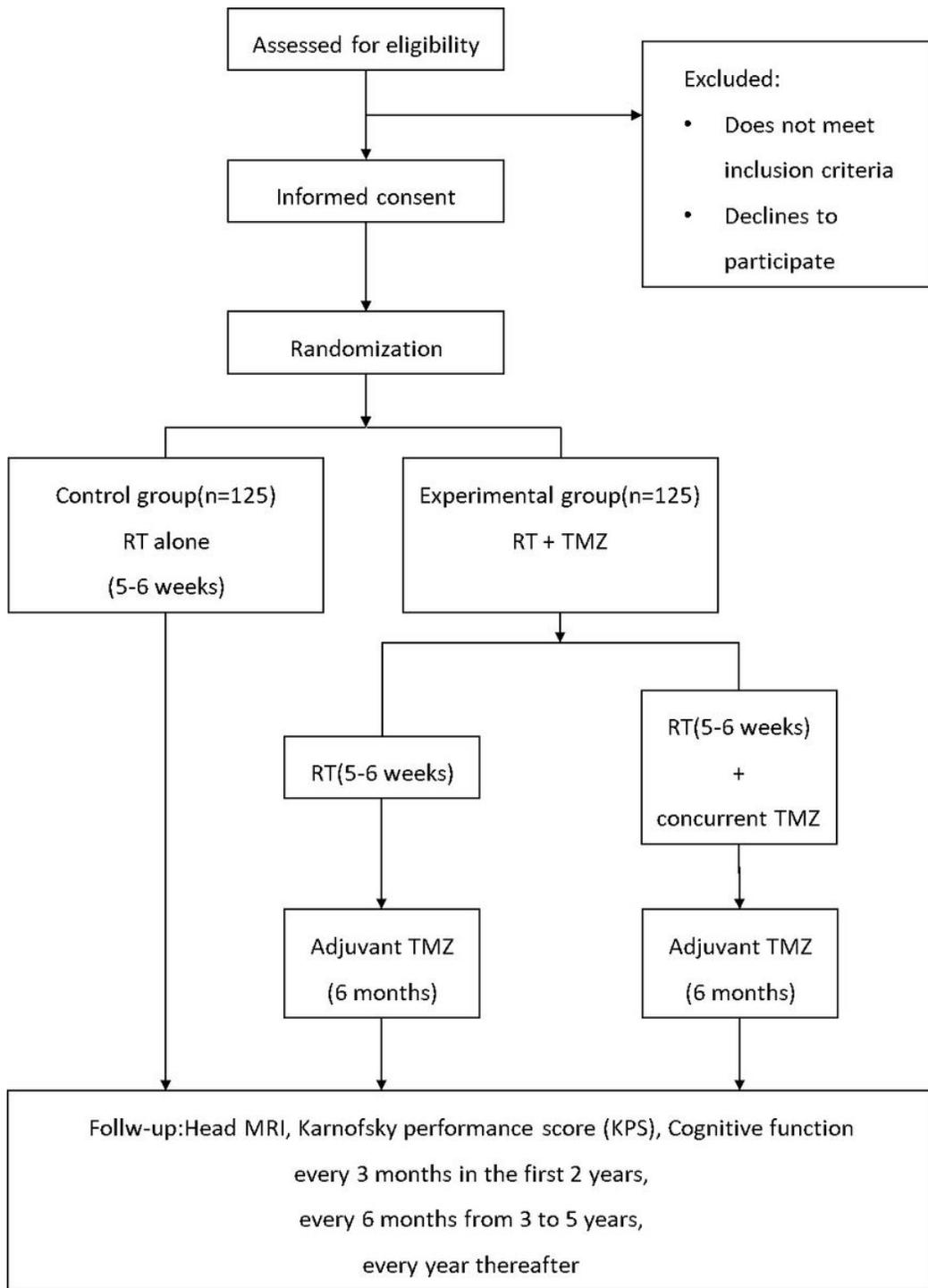


Figure 1

Study flowchart. Abbreviations :RT, radiation therapy; TMZ, temozolomide.

	Study Period							
	Enrollment	Allocation	Post-allocation					
	-4 weeks	0	Week 0-6	Week 10	Week 11-34	Within 2 years	3-5 years	5-10 years
Enrollment:								
Eligibility screen	X							
Informed consent	X							
Randomization	X							
Allocation		X						
Interventions:								
RT			X					
Concurrent TMZ			X					
Adjuvant TMZ				X	X			
Assessments:								
Physical examination		X				every 3 months	every 6 months	annually
KPS		X		X		every 3 months	every 6 months	annually
CBC		X	weekly	X	weekly			
Serum biochemistry		X	weekly	X	weekly			
Postoperative head MRI	X			X		every 3 months	every 6 months	annually
Cognitive function	X			X		every 3 months	every 6 months	annually
Adverse events			X	X	X	every 3 months	every 6 months	annually

Figure 2

SPIRIT Figure

Supplementary Files

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