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Does giving an anti-epileptic drug before surgery help prevent seizures in patients with glioma (a type of brain tumour) who have not previously had a seizure?

Submission date
10/07/2018

Recruitment status
No longer recruiting

Registration date
02/07/2019

Overall study status
Completed

Last Edited
12/05/2026

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Gliomas are the most common type of primary brain tumour, with about 6000 new cases each year in the UK. 1 in 5 patients (20%) with a suspected glioma will present with an epileptic seizure and be treated with an anti-epileptic drug (AED). 4 in 5 patients (80%) do not present with seizures. Up to half of these patients will develop epilepsy requiring AED over their lifetime. Seizures can cause anxiety, loss of independence, affect quality of life & sometimes threaten life. AEDs prevent seizures in 50% of patients with epilepsy and reduce the frequency and severity of seizures in a further 20-30%. Currently, some doctors prescribe AEDs to patients before neurosurgery for tumours, whilst others do not. Researchers need to find out whether AEDs are effective and worthwhile to give the best advice to surgeons and patients in future. Previous studies of AEDs to prevent seizures in patients with a brain tumour have not shown clear results. However, these studies have included tumour types where the risk of seizures is low and they used older AEDs that may interfere with chemotherapy used in brain tumours and have a high risk of side effects. The newer AED, levetiracetam, has fewer side effects and does not interfere with chemotherapy drugs. There is a balance of potential advantages and disadvantages for prescribing levetiracetam. The aim of this study is to find out whether giving patients with a suspected primary brain tumour (cerebral glioma), who have never had a seizure, levetiracetam before surgery to see if it will help prevent them from developing seizures. This will help to give neurosurgeons in the UK the best advice about how to treat patients with a cerebral glioma.

Who can participate?
Patients due to have surgery who have recently been diagnosed with a possible brain tumour, and who have never had an epileptic seizure

What does the study involve?
Participants have a series of tests and examinations to confirm that they are eligible. They are then randomly allocated into two groups. The first group receive levetiracetam daily for 1 year.

The second group receive no anti-epileptic drug; this is currently normal practice. Participants are contacted by the trials research nurse monthly by phone to check about any seizures or side effects. If there is a seizure, participants are asked to contact their usual treating team. A neurologist reviews the participant to confirm whether a seizure has occurred. Participants who have a seizure are asked to complete a seizure diary card and questionnaire about the severity of their seizure. All participants are asked to complete questionnaires about their symptoms and possible side effects at entry into the study and every 3 months for a minimum of 1 year. There is no need for any additional blood tests or additional hospital visits. Participants are able to continue on levetiracetam at the end of the study or come off it if they wish.

What are the possible benefits and risks of participating?
It is not known whether there will be a direct benefit to the participants. The researchers hope to be able to find out if taking levetiracetam before surgery will have any effect on delaying, stopping or altering the severity of any seizure that happens after the surgery. Participants taking levetiracetam might expect a lower risk of developing seizures, although the size of this effect is as yet unknown. The results of the trial will hopefully allow the researchers to provide the best advice on preventing seizures in patients with suspected cerebral glioma. A disadvantage of taking part in the study is that participants could experience side effects of levetiracetam. The levetiracetam is given at a lower dose for the first two weeks before increasing to the required dose to help reduce the side effects.

Where is the study run from?
Scottish Clinical Trials Unit, Edinburgh (SCTRU) (UK)

When is the study starting and how long is it expected to run for?
February 2019 to November 2023

Who is funding the study?
The study is funded by the National Institute for Health Research (NIHR). UCB Pharma, the manufacturer of levetiracetam, have provided this drug free of charge for patients taking part in this study that are allocated to the levetiracetam group

Who is the main contact?
Mrs Tracy McEleney, Service Manager, Public Health Scotland (PHS) Research Office, Edinburgh (UK), phs.researchoffice@phs.scot

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-001312-30

Protocol serial number
HTA 16/31/136

Study information

Scientific Title
Seizure PRophylaxis IN Glioma (SPRING): a Phase III randomised trial comparing prophylactic levetiracetam versus no prophylactic antiepileptic drug in patients with newly diagnosed presumed supratentorial glioma

Acronym
SPRING

Study objectives
There is no consensus regarding the need for prophylactic AEDs in newly-diagnosed suspected glioma patients who have not experienced seizures. Unfortunately, data regarding prophylactic AED use is scant and inconclusive. Most of the available evidence comes from older, small studies that enrolled patients with brain metastases and benign tumours in addition to gliomas. Furthermore, these studies universally evaluated prophylaxis with first-generation AEDs such as phenytoin, phenobarbital, carbamazepine, and valproic acid. These drugs have higher rates of early adverse effects (such as rash, haematological or liver upset) compared to levetiracetam, and they have important interactions with other drugs including corticosteroids and chemotherapeutics. Levetiracetam is an effective, safe, and well-tolerated medication. It has no known drug interactions and does not require serum level monitoring. It is however frequently associated with fatigue (15%), behavioural problems (13-38%) and problems with aggression. A definitive clinical trial is needed to determine whether the policy of prophylactic levetiracetam therapy reduces the risk of first seizures in this patient population. In addition, evaluation of the impact of levetiracetam on fatigue, behaviour and aggression is needed in this vulnerable population with already high rates of fatigue, cognitive and behavioural problems. There is some evidence that levetiracetam may worsen these symptoms. There is a need to study this area in a well-designed randomised controlled trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/02/2019, East of England – Essex REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; Tel: +44 (0)207 104 8115; Email: nrescommittee.eastofengland-essex@nhs.net); REC ref: 18/EE/0389

Study design
Two-arm multicentre Phase III randomised trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Glioma

Interventions
After a patient has consented to participate in the study and after ensuring that the patient meets all eligibility criteria, sites will randomise the patient using a web-based randomisation system. This will not be a blinded study and will not have placebo control and as such will be a "real world" study of prophylactic anti-epileptic drug (AED) vs no AED. Patients will be randomised into one of two arms:
Group 1: Levetiracetam 500 mg twice daily for 2 weeks then increasing to 750 mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500 mg prior to surgery. (In those with moderate chronic kidney disease stage 3 (estimated Glomerular Filtration Rate eGFR 30-59 mL/min/1.73m2) a starting dose of 250 mg twice a day for 2 weeks, then increasing to 500 mg twice a day thereafter).
Group 2: no AED treatment (standard care)

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Levetiracetam

Primary outcome(s)
Number of patients developing seizures measured using two-sided type I error level of 5% at 1 year

Key secondary outcome(s))
1. Time to first seizure measured using accelerated failure time model at 1 year
2. Time to first tonic clonic seizure measured using accelerated failure time model at 1 year
3. Mood, personality, fatigue and memory measured using Mann-Whitney U test (exact method) at 1 year
4. Severity of first seizure should it occur, measured using the LAEP questionnaire at pre surgery (baseline) and 3 monthly to coincide with clinic visits
5. Quality of life, measured using the relative changes in health-related quality of life (HRQoL) resulting from the physical and psychological benefit together with any harms associated with each treatment strategy . This will be administered at pre-surgery (baseline), 3 months, 6 months, 9 months and 12 months post randomisation
6. Progression-free survival determined clinically based upon interpretation of MRI scans, clinical state of the patient and steroid dose at 1 year of randomisation
7. Overall survival measured by using by the median overall survival time for each study arm, tabulated together with the corresponding 80% confidence interval. This will be measured at 1

year of randomisation
8. Costs to the NHS and personal social services (PSS) measured using a within-trial economic analysis which will estimate the incremental cost per quality-adjusted life year (QALY) gained over a 12-month time horizon. The perspective of the analysis (i.e. whose costs and benefits are considered) will be the NHS and personal social services, but the researchers will also take a wider perspective by including costs borne by trial participants, for example out of pocket expenses on health care and the time and travel costs of accessing care. This will be measured over the 12 months trial follow-up
9. Cost-effectiveness of prophylactic levetiracetam measured as incremental cost per QALY at 12 months and modelled over estimated survival

Completion date
02/11/2023

Eligibility

Key inclusion criteria
Patients:
1. Patients with suspected cerebral glioma on MRI or CT
2. Capable of giving informed consent
3. Patients must be ≥16 years old
4. Patients must have a Karnofsky performance status of >60
5. Patients must be able to safely swallow pills
6. Planned surgery for presumed glioma (biopsy or resection)

Carers:
Capable of giving informed consent

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Upper age limit
100 years

Sex
All

Total final enrolment
107

Key exclusion criteria

Patients:
1. Pregnant
2. History of any type of seizure for at least 10 years prior to randomisation
3. Known Severe Chronic Kidney Disease (CKD4 - eGRR <30 ml/min)
4. Concomitant methotrexate
5. Concomitant Anti-Epileptic Drug (including use for other reasons (e.g. pain))
6. Concomitant Benzodiazepines
7. Hypersensitivity to Levetiracetam

Date of first enrolment
15/07/2019

Date of final enrolment
31/08/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
Scotland
EH4 2XU

Study participating centre
The Walton Centre
Department of Neurosurgery
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Lower Lane
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
Hull Royal Infirmary
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Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
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ST4 6QG

Study participating centre
University Hospital Southampton
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Tremona Road
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Study participating centre
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M6 8HD

Study participating centre
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Oxford
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OX3 9DU

Study participating centre

Royal Preston Hospital
Sharoe Green Lane
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PR2 9HT

Sponsor information

Organisation
Public Health Scotland

ROR
https://ror.org/023wh8b50

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All presentations and publications relating to the trial must be authorised by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by the Trial

Management Group, representatives from SCTRU and high accruing clinicians. The trials offices and all participating centres and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning their patients, which is directly relevant to the questions posed in the trial, until the main results have been published.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		05/11/2025	12/05/2026	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version V5.1	04/02/2019	11/07/2019	No	No
Study website		11/11/2025	11/11/2025	No	Yes