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Treatment of poor-grade subarachnoid haemorrhage trial 2

Submission date 01/09/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 05/09/2016	**Overall study status** Completed	
Last Edited 11/08/2022	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
A spontaneous subarachnoid haemorrhage (SAH) is a type of stroke caused by sudden bleeding over the surface of the brain. It is usually caused when a bulge in a blood vessel wall (brain aneurysm) bursts (ruptures) because the vessel wall has become weakened over time. Following the rupture, blood pools inside the skull (which cannot expand due to its rigid structure) leading to increased pressure on the brain and oxygen starvation (cerebral ischaemia), leading to brain damage. Recovery largely depends on the extent of this damage, and is assessed using the WFNS (World Federation of Neurosurgical Societies) grading system. Patients with WFNS grade 1-3 usually recover well, but patients with high WFNS grade (4-5) often end up with a bad outcome such as death or severe disability. Grade 1-3 patients are treated early, based on high quality evidence from studies. However, there is no good evidence base for determining the best way of treating those with grade 4-5 SAH. There are currently two strategies for treating these patients: early treatment or treatment after neurological (brain and nervous system) recovery. The aim of this study is to compare these two approaches to find out which is the better treatment option. A sample of patients also take part in a sub-study, in which they undergo MRI scanning, in order to find out the relationship between brain markers and outcome, and whether they might be used to identify patients who would benefit from each treatment strategy.

Who can participate?
Adults who have had an SAH graded WFNS 4 or 5.

What does the study involve?
Patients are randomly allocated to one of two groups. Those in the first group are kept under close observation, and have aneurysm treatment after they recover consciousness. Those in the second group receive treatment for their aneurysm within 24 hours. Participants in both groups have their recovery monitored over the next 12 months using questionnaires. The questionnaire takes about 20 minutes to complete, and is sent out by post, along with a pre-paid reply envelope. Participants are asked to complete and return the questionnaire, with the help of a friend or relative, or with a member of the research team by telephone to go through the

questions if necessary, or online via the trial website. Around one third of the participants also take part in a related study, in which they attend a hospital appointment at the start of the study and after six months to have their brain scanned using an MRI machine.

What are the possible benefits and risks of participating?
There are no direct benefits or risks involved for those participating in the main study. The total effective dose from patients participating in the MRI sub study can therefore be taken as approximately 6 mSv which is equivalent to approximately 2.5 years of exposure to average UK natural background radiation, placing the study into the 'intermediate' risk category.

Where is the study run from?
Royal Victoria Infirmary (lead centre) and eight other NHS hospitals in England (UK)

When is the study starting and how long is it expected to run for?
December 2015 to December 2018 (updated 04/03/2021, previously: March 2021)

Who is funding the study?
National Institute for Health Research Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact?
1. Professor Philip White (scientific)
2. Ms Philippa Watts (public)
TOPSAT2@ncl.ac.uk

Study website
https://www.topsat2.co.uk/

Contact information

Type(s)
Public

Contact name
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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
7842

Study information

Scientific Title
Randomised Controlled Study for patients with high grade Subarachnoid haemorrhage to determine whether or not early (within 24 hours) treatment or treatment after neurological recovery has a better outcome than the other

Acronym
TOPSAT2

Study objectives
The aim of this study is to establish the efficacy of a strategy of early aneurysm treatment (within 72h of ictus) in a population of World Federation of Neurosurgical Societies grade 4-5 (high grade) aneurysmal subarachnoid haemorrhage (aSAH) patients in comparison with the conventional strategy of treatment of aneurysm after neurological improvement (to WFNS grade 1-3).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire & The Humber - Leeds East Research Ethics Committee, 20/06/2016, ref: 16/YH/0234

Study design
Multi-centre prospective randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Subarachnoid haemorrhage

Interventions
Participants are randomised to undergo either endovascular (coiling) or neurosurgical (clipping) treatment for their aneurysm within 24 hours of ictus or upon neurological improvement. Both are standard procedures and are performed whether or not they are in the study. At the time of enrolment all patients will be unconscious and therefore unable to consent, and so REC/HRA approval for assent has been sought. There are no further treatments and no study bloods are being taken.

Participants will be followed up for a total period of 12 months within the trial site that patients were admitted to until day 30 or discharge (whichever is the sooner), and then at 6 and 12 months later by way of postal or online mRS and EQ5D questionnaires completed by the participants.

Intervention Type
Procedure/Surgery

Primary outcome measure
Functional outcome is measured by ordinal analysis of modified Rankin Score (mRS) at 12 months.

Secondary outcome measures
1. mRS is measured by dichotomisation of scores 0-3 (no or significant symptoms) vs 4-6 (severe symptoms and mortality) and 0-2 (no or few symptoms) v 3-6 (significant symptoms and mortality) at 12 months
2. Mortality rate is measured by -survival analysis at 30 days, six months and 12 months
3. Re-bleeding rate is measured by the number of re-bleeds that have occurred at 12 months
4. Treatment related complication rate & SAE report rates are measured by the number of treatment related complications and SAEs that have occurred at 12 months
5. Time to hospital discharge is measured by length of time in hospital from randomisation at discharge date
6. Length of ITU/HDU stay is measured by length of time in ITU/HDU from randomisation at discharge date
7. Functional outcome is measured by ordinal analysis of modified Rankin Score (mRS) at 6 months

Overall study start date
01/12/2015

Completion date
18/12/2018

Eligibility

Key inclusion criteria
1. Aged 18-80 years
2. WFNS grade 4 or 5 SAH (grade for trial eligibility purposes is the WFNS grade recorded at first medical assessment following: hospital attendance AND confirmation of the diagnosis of SAH – by CT (or MRI) and/or lumbar puncture)
3. Assent obtained from next of kin, professional consultee or welfare attorney/nearest relative

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
346

Total final enrolment
305

Key exclusion criteria
1.WFNS grade 1-3, or uncertain WFNS grade (where patient recovers quickly and proves not to be of true high grade):
1.1. Patients of uncertain grade on transfer to a neuroscience unit where a formal sedation hold is undertaken at the neurosciences centre and the patient is established to be truly grade 4 or 5 will be eligible for trial
1.2. This will also apply to patients of uncertain grade undergoing sedation hold after insertion of external ventricular drain (EVD) or other early intervention for hydrocephalus
2. Signs of coning or brain death not promptly reversed by anti-cerebral oedema treatment
3. Pure intraventricular haemorrhage (no SAH)
4. Large intracerebral haematoma which requires immediate clot evacuation
5. Significant aneurysmal SAH-related haemodynamic instability
6. Lack of clinical equipoise
7. Lack of assent/consent

8. Pregnancy
9. Pre SAH modified Rankin score >2
10. Pre-existing severe co-morbidity such that clinical follow up at 12 months is judged unlikely
11. Non-saccular, Mycotic, giant or other atypical aneurysm

For MRI sub study only
Known absolute contra indication to MRI

Date of first enrolment
12/09/2016

Date of final enrolment
10/09/2019

Locations

Countries of recruitment
Czech Republic

England

Estonia

Hungary

Latvia

Lithuania

Poland

United Kingdom

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
TS4 3BW

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Queen's Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Hurstwood Park Neurological Centre
Lewes Road
Haywards Heath
United Kingdom
RH16 4EX

Study participating centre
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
Royal Hallamshire Hospital
Glossop Road

Sheffield
United Kingdom
S10 2JF

Study participating centre
The Walton Centre
Lower Lane
Liverpool
United Kingdom
L9 7LJ

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Newcastle Joint Research Office
Level 1, Regent Point
Regent Farm Road
Gosforth
Newcastle upon Tyne
England
United Kingdom
NE3 3HD

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Progress and final outcomes will be disseminated at relevant neurosurgical, stroke, neuroradiology, MRI and critical care conferences by platform and poster presentations. Five to six research publications based on the findings are expected to be published in international peer reviewed journals. Results will also be reported to the Sponsor and Funder, and will be available on their websites. Manuscripts, abstracts and other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identifiable in any study report.
A procedural safety paper will be submitted within weeks of the end of randomisation. There will also be multiple outputs around MR imaging techniques in high grade SAH. More detailed subgroup analysis and modelling of care are additional papers, identified as likely outputs of the TOPSAT2 study. The Stroke Research component embedded within NIHR Research Division 2, Newcastle University, professional societies (British Society Neurological Surgeons, British Society Neuroradiologists, UK Neurointerventional Group, British Neurovascular Group), Royal Colleges and contacts with the Clinical Senates, UK Stroke Forum and the Stroke Association will be utilised to disseminate the findings more widely to the public. This will include use of web-based information, newsletters and press releases.
The study team will feed back to centres via newsletters, the website and trial close down meetings and publications, and to participants via website, newsletter and the publicity generated. More direct personal or small group feedback will be given to the PPI groups involved in developing, contributing to and supporting TOPSAT 2. Feedback in the form of a lay summary will be provided to participants via the general section of the trial website, participant-specific newsletter at the end of trial (if they indicated they wished to receive it) and by wider publicity generated.

Intention to publish date
31/03/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Results article	version 2	01/07/2021	05/04/2022	Yes	No
Protocol file		25/01/2019	11/08/2022	No	No
HRA research summary			28/06/2023	No	No