# Treatment of poor-grade subarachnoid haemorrhage trial 2

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

#### 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

Prof Philip White

#### Contact details

Institute of Neuroscience Newcastle University 3-4 Claremont Terrace Newcastle upon Tyne United Kingdom NE2 4AE

#### Type(s)

Public

#### Contact name

Ms Philippa Watts

#### Contact details

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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, Efficacy and Mechanism Evaluation (EME), 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 webbased 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		01/07/2021	05/04/2022	Yes	No
Protocol file	version 2	25/01/2019	11/08/2022	No	No
HRA research summary			28/06/2023	No	No