## Emergent aneurysm treatment compared with treatment on neurological improvement in patients with ruptured poor-grade aneurysmal subarachnoid haemorrhage: the TOPSAT2 RCT

Philip White,<sup>1\*</sup> Barbara Gregson,<sup>2</sup> Elaine McColl,<sup>3</sup> Paul Brennan,<sup>4</sup> Alison Steel,<sup>5</sup> Philippa Watts,<sup>5</sup> Ruth Wood,<sup>5</sup> Clare Bowes,<sup>6</sup> Mohsen Javadpour,<sup>7</sup> Amanda Weston<sup>8</sup> and Dipayan Mitra<sup>9</sup>

<sup>1</sup>Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

<sup>2</sup>Wolfson Research Centre, Newcastle University, Newcastle upon Tyne, UK
<sup>3</sup>Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
<sup>4</sup>Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
<sup>5</sup>Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
<sup>6</sup>Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
<sup>7</sup>National Neurosurgical Centre, Beaumont Hospital, Dublin, Republic of Ireland
<sup>8</sup>Independent layperson, Newcastle upon Tyne, UK

<sup>9</sup>Department of Neuroradiology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

\*Corresponding author phil.white@ncl.ac.uk

**Declared competing interests of authors:** Philip White has received grants from the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme, Medtronic (Fridley, MN, USA), Stryker (Kalamazoo, MI, USA) and Penumbra (Alameda, CA, USA), and has received personal fees from Microvention Terumo (Aliso Viejo, CA, USA). He is chairperson of the UK Neurointerventional Group, professional organisation of Neurointerventionists in the UK. Elaine McColl was a member of the NIHR Journals Library Editorial Group (2013–16). Mohsen Javadpour has received speaker fees from Brainlab (Munich, Germany) in relation to a lecture on image fusion for stereotactic radiosurgery.

Published July 2021 DOI: 10.3310/eme08080

# **Plain English summary**

### The TOPSAT2 RCT

Efficacy and Mechanism Evaluation 2021; Vol. 8: No. 8 DOI: 10.3310/eme08080

NIHR Journals Library www.journalslibrary.nihr.ac.uk

## **Plain English summary**

**S** ubarachnoid haemorrhage is a form of stroke where there is a bleed on the surface of the brain, usually caused by weaknesses in brain blood vessels called aneurysms. Unlike most strokes, it mainly affects younger people – typically those aged 40–60 years. Recovery largely depends on the severity of the brain injury caused by the bleed. The severity is assessed by the World Federation of Neurosurgical Societies grading system. This grading system largely relies on assessment of the level of consciousnessness using the clinically and universally used Glasgow Coma Scale. Patients with World Federation of Neurosurgical Societies grades 1–3 usually achieve good recovery (alive and independent), but patients with grades 4 or 5 often have a bad outcome (death or severe disability).

World Federation of Neurosurgical Societies grade 1–3 patients are treated quickly (as soon as is practicable after admission to a neurosciences centre) and mainly by aneurysm coiling when this is available and the aneurysm is suitable, based on evidence from trials. Coiling is a method where a very thin tube is fed inside blood vessels into the aneurysm in the brain and the aneurysm is blocked off by platinum wire coils placed through that tube. In the past, grade 4–5 subarachnoid haemorrhage patients tended to be treated only after their condition had improved, typically to a better grade (1–3). With the introduction of coiling, these patients are increasingly being treated sooner, but we do not know whether it is better to treat quickly or wait until the patient recovers (to a better level of consciousnessness).

In the treatment of poor-grade subarachnoid haemorrhage trial 2 (TOPSAT2), we randomly assigned patients with grade 4–5 subarachnoid haemorrhages to either early treatment, irrespective of condition, or treatment when their condition improved, irrespective of when that happened (so it was treat on improvement, not delayed treatment). Unfortunately, either many patients were not eligible for the trial or patients' doctors were uncertain of which approach was better, so were reluctant to enrol them in the trial, mostly choosing to treat them early. Therefore, the trial had to stop early because recruitment would have taken too long.

Twenty-three patients out of a target of 346 were randomised over a 25-month period. The average time from bleed to treatment was 26 hours in the early-treatment group and 163 hours in the treat on improvement group. The small number of patients enrolled limits the conclusions that can be drawn. No statistically significant differences were identified between the groups in rates of death or outcome (alive and independent). However, the data we obtained within the robust randomised controlled trial design used in TOPSAT2 have, as an offshoot, usefully demonstrated that timelines for both trial randomisation and treatment of aneurysmal subarachnoid haemorrhage patients within neuroscience centres have reduced (improved) in the UK since earlier subarachnoid haemorrhage trials (international subarachnoid aneurysm trial, 1994–2002).

## **Efficacy and Mechanism Evaluation**

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

#### Criteria for inclusion in the Efficacy and Mechanism Evaluation journal

Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

#### **EME** programme

The Efficacy and Mechanism Evaluation (EME) programme funds ambitious studies evaluating interventions that have the potential to make a step-change in the promotion of health, treatment of disease and improvement of rehabilitation or long-term care. Within these studies, EME supports research to improve the understanding of the mechanisms of both diseases and treatments.

The programme supports translational research into a wide range of new or repurposed interventions. These may include diagnostic or prognostic tests and decision-making tools, therapeutics or psychological treatments, medical devices, and public health initiatives delivered in the NHS.

The EME programme supports clinical trials and studies with other robust designs, which test the efficacy of interventions, and which may use clinical or well-validated surrogate outcomes. It only supports studies in man and where there is adequate proof of concept. The programme encourages hypothesis-driven mechanistic studies, integrated within the efficacy study, that explore the mechanisms of action of the intervention or the disease, the cause of differing responses, or improve the understanding of adverse effects. It funds similar mechanistic studies linked to studies funded by any NIHR programme.

The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

#### **This report**

The research reported in this issue of the journal was funded by the EME programme as project number 13/29/83. The contractual start date was in June 2016. The final report began editorial review in June 2020 and was accepted for publication in January 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health and Social Care.

Copyright © 2021 White *et al.* This work was produced by White *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaption in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

### NIHR Journals Library Editor-in-Chief

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

### NIHR Journals Library Editors

**Professor John Powell** Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Professor of Digital Health Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

**Professor Andrée Le May** Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

**Professor Matthias Beck** Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Emeritus Professor of Wellbeing Research, University of Winchester, UK

**Professor James Raftery** Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

**Professor Helen Snooks** Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

**Professor Jim Thornton** Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk