NIHR | National Institute for Health Research

Journals Library

Check for updates

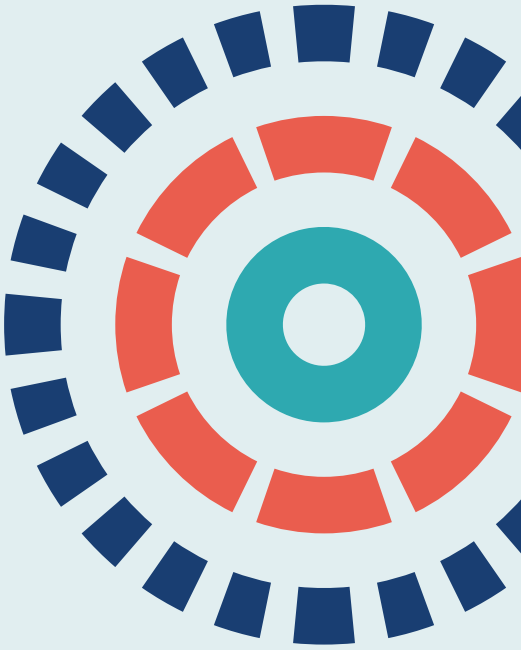
Efficacy and Mechanism Evaluation

Volume 8 • Issue 8 • July 2021

ISSN 2050-4365

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

Philip White, Barbara Gregson, Elaine McColl, Paul Brennan, Alison Steel, Philippa Watts, Ruth Wood, Clare Bowes, Mohsen Javadpour, Amanda Weston and Dipayan Mitra



DOI 10.3310/eme08080

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

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

[1]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[2]Wolfson Research Centre, Newcastle University, Newcastle upon Tyne, UK
[3]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[4]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[5]Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
[6]Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[7]National Neurosurgical Centre, Beaumont Hospital, Dublin, Republic of Ireland
[8]Independent layperson, Newcastle upon Tyne, UK
[9]Department of Neuroradiology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

*Corresponding author

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

This report should be referenced as follows:

White P, Gregson B, McColl E, Brennan P, Steel A, Watts P, *et al*. Emergent aneurysm treatment compared with treatment on neurological improvement in patients with ruptured poor-grade aneurysmal subarachnoid haemorrhage: the TOPSAT2 RCT. *Efficacy Mech Eval* 2021;**8**(8).

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.

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

NIHR Journals Library Editors

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

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

Abstract

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

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

[1]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[2]Wolfson Research Centre, Newcastle University, Newcastle upon Tyne, UK
[3]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[4]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[5]Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
[6]Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[7]National Neurosurgical Centre, Beaumont Hospital, Dublin, Republic of Ireland
[8]Independent layperson, Newcastle upon Tyne, UK
[9]Department of Neuroradiology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

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

Background: Aneurysmal subarachnoid haemorrhage is a major cause of haemorrhagic stroke. The incidence is ≈ 80 per million population per year; it peaks in the 40–60 years age range and often has a poor prognosis with the outcome linked to severity of the initial haemorrhage. Aneurysmal subarachnoid haemorrhage accounts for 5% of strokes, but 20% of quality-adjusted life-years are lost to stroke and much of that loss is concentrated in World Federation of Neurosurgical Societies grade 4–5 (or poor-grade) aneurysmal subarachnoid haemorrhage patients. Before endovascular coiling was available, the conventional management strategy for poor-grade aneurysmal subarachnoid haemorrhage patients was to treat the ruptured aneurysm on neurological improvement. That incurs a risk of aneurysm rebleeding, which is highest soon after the first bleed; if rebleed occurs prior to aneurysm treatment, prognosis is dismal. Reducing rebleeding with early treatment might improve outcome. Therefore, an early coiling strategy in grade 4–5 patients is appealing, but not robustly evidenced. Early treatment in all grade 4–5 patients might prevent death from rebleeding but possibly at the expense of creating severely disabled survivors, with attendant societal costs. Many neuroclinicians have expressed genuine uncertainty regarding whether or not to treat all grade 4–5 aneurysmal subarachnoid haemorrhage patients emergently (as soon as possible regardless of neurological status). A pilot trial, the treatment of poor-grade subarachnoid haemorrhage trial 1 (TOPSAT1), indicated that recruitment to a randomised trial to address this uncertainty was feasible.

Methods: We investigated a management policy in aneurysmal subarachnoid haemorrhage World Federation of Neurosurgical Societies grades 4 or 5 of securing the ruptured aneurysm emergently (within 24 hours of randomisation) compared with the strategy to treat the aneurysm on neurological improvement (to World Federation of Neurosurgical Societies grades 1–3), irrespective of when that improvement occurred. The treatment of poor-grade subarachnoid haemorrhage trial 2 (TOPSAT2) was a pragmatic, randomised, open-blinded, end-point design trial aiming to recruit 346 adult patients (aged 18–80 years) in 30 UK and European neuroscience centres. Randomisation was web based,

with minimisation criteria relating to age, grade, presence of hydrocephalus and UK location (vs. non-UK). Fifteen sites were opened to recruitment, 12 of which were in the UK. Standard institutional procedures for securing aneurysms were followed. An exploratory magnetic resonance biomarker substudy of 100 UK participants was planned but not opened. The primary end point was functional outcome at 12 months, determined by analysis of the modified Rankin Scale score. The secondary end points relating to safety were assessed.

Results: Of the 305 World Federation of Neurosurgical Societies grade 4–5 patients screened, 23 were randomised: 11 to the emergent treatment arm and 12 to the treatment on neurological improvement (control) arm. Trial recruitment was suspended when it was judged to have failed a feasibility assessment. The median time from ictus to treatment (where aneurysm was treated) was 26 hours in the emergent treatment arm and 163 hours in the treatment on neurological improvement arm. There were no statistically significant differences between arms in mortality ($p = 0.4$) or functional outcome at 365 days [modified Rankin Scale score 0–3 vs. 4–6 ($p = 0.32$)]. Sensitivity analysis was performed to examine the effect of missing data but differences remained non-significant.

Limitations: A limitation was the failure to recruit to time/target.

Conclusions: The randomised trial approach to investigating whether poor-grade aneurysmal subarachnoid haemorrhage patients should receive emergent treatment or be treated on neurological improvement proved unfeasible. No statistically significant differences were identified between the trial arms in mortality or functional outcome, but the small number of patients enrolled limits drawing firm conclusions.

Future work: No future work is currently planned.

Trial registration: Current Controlled Trials ISRCTN15960635.

Funding: This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 8. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
aSAH	aneurysmal subarachnoid haemorrhage
CI	confidence interval
CLRN	Comprehensive Local Research Network
CSF	cerebrospinal fluid
CT	computerised tomography
DMC	Data Monitoring Committee
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
EME	Efficacy and Mechanism Evaluation
ET	emergent treatment
EVD	external ventricular drain
GCS	Glasgow Coma Scale
ISAT	international subarachnoid aneurysm trial
ITU	intensive therapy unit
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NIHR	National Institute for Health Research
NNT	number needed to treat
NSC	neurosciences centre
OR	odds ratio
PI	principal investigator
PPI	patient and public involvement
PROBE	pragmatic randomised open-blinded end point
RCT	randomised controlled trial
SAE	serious adverse event
SAH	subarachnoid haemorrhage
SCIL	Subcutaneous Interleukin-1 Receptor Antagonist
SD	standard deviation
SRN	Stroke Research Network
SSNAP	Sentinel Stroke National Audit Programme
STICH	surgical trial in intracerebral haemorrhage
TMG	Trial Management Group
TONI	treatment on neurological improvement
TOPSAT1	treatment of poor-grade subarachnoid haemorrhage trial 1
TOPSAT2	treatment of poor-grade subarachnoid haemorrhage trial 2
TSC	Trial Steering Committee
WFNS	World Federation of Neurosurgical Societies

Plain English summary

Subarachnoid 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 consciousness 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).

Scientific summary

Background

Aneurysmal subarachnoid haemorrhage is a form of stroke that is associated with a high mortality rate, is characterised by a bleed in the brain, and is mostly caused by a ruptured aneurysm on one of the cranial arteries. During the latter part of the twentieth century it was recommended that the aneurysm be secured to prevent rebleed, deterioration and a poor outcome in cases of aneurysmal subarachnoid haemorrhage. In 2002, the randomised, controlled international subarachnoid aneurysm trial (ISAT) was published comparing two different methods of securing the aneurysm. The international subarachnoid aneurysm trial compared the usual neurosurgical technique of open surgery (placing a clip on the aneurysm neck) with a new endovascular technique of inserting detachable metal coils through a microcatheter placed (from the femoral artery in the groin) into the aneurysm itself to provide a dense scaffold to establish a clot that combined would occlude the aneurysm. This trial established that the endovascular procedure was more beneficial among the patients enrolled; however, it was mainly good-grade [World Federation of Neurosurgical Societies (WFNS) grades 1–3] aneurysmal subarachnoid haemorrhage patients who were recruited with a subset of aneurysm sizes and locations.

The WFNS grade relies primarily on the Glasgow Coma Scale score, with a score above 12 representing WFNS grades 1–3, a score of 3–6 (in profound coma) representing WFNS grade 5, and a score of 7–12 representing WFNS grade 4 [encompassing a range of impaired alertness from obtunded (Glasgow Coma Scale score 12) to markedly obtunded (Glasgow Coma Scale score 10) to moderate coma (Glasgow Coma Scale score 7 or 8)].

Since the 1980s, expert opinion has recommended expeditious treatment of a ruptured aneurysm in good-grade patients. For poor-grade patients (WFNS grades 4 or 5), because of the invasive nature of the operation and frequently unstable clinical status of these very ill patients, it was generally recommended that securing the aneurysm should be undertaken once the patient had improved neurologically. Although the international subarachnoid aneurysm trial demonstrated that the endovascular treatment (coiling) was preferable to clipping in good-grade patients (WFNS grades 1–3), there was no evidence as to whether or not this less invasive procedure should be preferentially undertaken in poor-grade patients, let alone on the optimum timing of such treatment. Seventy-two hours is very relevant because an important delayed complication of aneurysmal subarachnoid haemorrhage called delayed cerebral ischaemia (sometimes called symptomatic vasospasm) rarely develops before 72 hours, and it is widely recommended to avoid treatment within the 'vasospasm period' when possible. This applies more so for clipping than coiling but has applicability to both techniques, as the procedural risks are increased with both techniques if delayed cerebral ischaemia is present.

Objectives

To establish the efficacy of a strategy of early aneurysm treatment in a population of WFNS grade 4–5 (poor-grade) aneurysmal subarachnoid haemorrhage patients in comparison with the conventional strategy (developed when only clipping treatment was available) of treatment of the aneurysm after neurological improvement (to WFNS grades 1–3), whenever that occurred. Early treatment (or emergent treatment) meant securing the ruptured aneurysm by either coiling or clipping (as per local centre preference based on an individual case-by-case assessment) within 24 hours of randomisation at a neuroscience centre and within, at most, 72 hours of ictus. In the emergent arm, aneurysm treatment was to be undertaken regardless of any neurological response, provided that the patient met all the trial inclusion criteria (not including Glasgow Coma Scale score 3, as that is essentially an unresponsive patient with fixed, dilated pupils).

Methods

A prospective, randomised, open, parallel-group study with blinded outcome assessment (pragmatic, randomised, open-blinded, end-point design) was undertaken. The aim was to randomise 346 patients with aneurysmal subarachnoid haemorrhage and WFNS grades 4 or 5 to receive early treatment (within 72 hours of ictus) or to receive treatment for their aneurysm when they had improved neurologically (defined as improvement to WFNS grades 1–3). The treatment modality would be at the discretion of the local neurovascular team. Patients were to be recruited from 20 neuroscience centres in the UK that were able to undertake both management approaches, and 10 such centres in Europe. Web-based randomisation was used, randomising in the ratio 1 : 1 with minimisation criteria of WFNS grades 4 or 5, UK or non-UK centre, age band (18–50 years, 51–65 years and 66–80 years), and presence (or not) of clinically significant hydrocephalus requiring cerebrospinal fluid drainage. The primary outcome was measured at 12 months by a postal questionnaire sent to surviving patients (UK) or a similar follow-up by a local trial team (non-UK). Outcome was originally intended to be assessed using an ordinal analysis of the modified Rankin Scale (values 0 to 6), including death coded as a value of 6. Secondary outcomes included mortality, rebleed rate and dichotomisation cuts (at 0–2 vs. 3–6, and 0–3 vs. 4–6) of the modified Rankin Scale at 6 and 12 months.

Results

The trial was halted because of difficulties resulting in slow patient recruitment. Recruitment opened in December 2016 and the recruitment period was due to last for 44 months; however, by December 2018 only 23 patients had been recruited. Difficulties included an unexpectedly high rate of lack of clinical equipoise to enrol otherwise eligible patients [compared with findings in the treatment of poor-grade subarachnoid haemorrhage trial 1 (TOPSAT 1)]; competing studies in the most research-active centres; a slightly lower medical eligibility rate than predicted; and a change in approach by the UK trial sponsor (Newcastle upon Tyne Hospitals NHS Foundation Trust). The original sponsor changed policy mid-trial to no longer act as a sponsor for European Union-based sites. This resulted in substantial delays in agreeing new sponsorship arrangements for overseas sites, to contract finalisation between them and Newcastle University and to their eventual site set-up and initiation. This involved a change from direct sponsorship to a data-sharing agreement.

By the time the trial was halted, 15 sites had been initiated and 14 were screening (11 in the UK and three in Europe). A total of 1269 patients had been screened, of whom 305 were poor-grade patients. Of those, 111 were medically eligible and 23 had been randomised [11 to the emergent treatment arm and 12 to the treatment on neurological improvement (control) (whenever that occurred) arm]. Seventy-four out of 111 patients were not randomised because of a lack of equipoise. The baseline characteristics were similar in both groups with patients aged between 44 and 75 years (median age 63 years); 65% were female and 70% were from the UK. A total of 74% of patients were WFNS grade 5, and 26% were WFNS grade 4; 74% required drainage for hydrocephalus (or it was planned at time of enrolment). All patients were randomised within 48 hours of ictus with a median of 21 hours. Aneurysms tended to be located in the anterior communicating artery (43%) or posterior communicating artery (30%). The planned treatment as indicated at time of enrolment was endovascular (30%), neurosurgical (52%) or not stated (17%, applied to four patients in the treatment on neurological improvement arm). All patients in the emergent treatment arm had their aneurysm secured within 71 hours of ictus (median 26 hours), whereas for the four patients who went on to receive treatment on neurological improvement, the median time to treatment was 163 hours.

Primary outcome showed no difference between the two treatments ($p = 0.11$) but the mortality rate was, as expected with a population of mainly WFNS grade 5 subarachnoid haemorrhage patients, high, at 70% overall, with 55% of patients having died in the emergent treatment arm and 83% having died in the treatment on neurological improvement arm at 12 months ($p = 0.4$). Two patients did achieve a

modified Rankin Scale score of 0–2 at 12 months in the emergent treatment arm (18%) but none did in the treatment on neurological improvement arm ($p = 0.22$). A rebleed was reported for two patients in the treatment on neurological improvement arm (17%) but for none in the emergent treatment arm ($p = 0.48$).

Conclusions (implications for health care and recommendations for research)

The low recruitment limits the ability to draw firm conclusions from the data and make any recommendations in terms of treatment for poor-grade aneurysmal subarachnoid haemorrhage patients. The treatment of poor-grade subarachnoid haemorrhage trial 2 (TOPSAT 2) data indicate no evidence of a marked difference in outcome for the strategies of emergent treatment and treatment on neurological improvement, and is not able to provide evidence to indicate that the current heterogeneous approach to poor-grade management should change in one direction or another. Therefore, based on TOPSAT2, no service reconfiguration would be necessary.

The randomised controlled trial approach to investigating whether poor-grade aneurysmal subarachnoid haemorrhage patients should receive emergent treatment or be treated on neurological improvement proved unfeasible. The length of time between the feasibility study and the Phase III trial possibly resulted in a shift in practice by care staff at individual sites, which mitigated against the clinical equipoise required for a successful level of recruitment to TOPSAT2. A prospective observational study proposed to the funder, at their request, as an alternative method to collect systematic data during the final 2 years of the study about actual treatment received was not judged as providing adequate value for money.

Magnetic resonance imaging remains very challenging in aneurysmal subarachnoid haemorrhage patients, particularly in poor-grade patients, and therefore the use of magnetic resonance imaging-based biomarkers to stratify an approach to their treatment does not seem to provide a promising area for investigation at present.

Trial registration

This trial is registered as ISRCTN15960635.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 8. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is one of the major causes of haemorrhagic stroke. In the UK and developed world its incidence is ≈ 80 per million population per year,[1] and it often affects young, previously fit people, with peak occurrence in the 40–60 years age range. It often has a poor prognosis and so it carries a disproportionate socioeconomic burden. aSAH accounts for just 5% of strokes, but 20% of the quality-adjusted life-years lost to stroke in the UK and developed world, with much of that loss being concentrated in poor-grade aSAH patients.[1] The outcome of aSAH patients is often linked to the severity of the initial haemorrhage and the degree of neurological disability at the time of presentation. The total socioeconomic burden of stroke is approximately £26B per annum in the UK.[2]

Existing research

To assess patients systematically on the basis of their initial neurological status, various grading systems have been introduced, with the World Federation of Neurosurgical Societies (WFNS) grading system being the most widely used.[3] Patients with WFNS grades 1–3 are considered 'good grade'. These patients mostly make a reasonable physical recovery and are usually managed aggressively with early coiling or clipping of their aneurysms. Patients with WFNS grades 4 or 5 are considered 'poor grade' and generally have considerably worse outcomes than those with grades 1–3. Traditionally, neurosurgical clipping of aneurysms in these patients has been deferred until their neurological status improves. This is because surgery at an early stage in this group of patients is thought to be associated with an unacceptably high risk of stroke.[4]

In more recent years, intracranial aneurysms have been treated primarily by endovascular coiling [85% coiling rate in the 2013 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report].[1] Packing the aneurysm with platinum coils through a minimally invasive endovascular route avoids the need for craniotomy and retraction/manipulation of an already oedematous brain. There is high-quality evidence favouring coiling in grade 1–3 patients.[5–7] However, there is no good-quality evidence to indicate whether coiling should be undertaken early or only after neurological improvement in grade 4–5 patients. Grade 4–5 aSAH patients are not usually considered for clipping unless they make substantial clinical improvement. The landmark, UK-led, international subarachnoid aneurysm trial (ISAT)[6] compared coiling with clipping but included predominantly grade 1–3 patients. Just 5% of patients recruited into ISAT were grades 4 or 5 (most were grade 4). The small number of poor-grade patients enrolled, and probably the differential centre enrolment bias around grade, meant that no conclusions on poor-grade management could be drawn. Overall, 37% (46/123) of grade 4–5 patients enrolled in ISAT had a good outcome at 1 year (alive and independent), compared with 75% of grade 1–3 patients.[6] In the only other substantial trial of aneurysm coiling versus clipping of which we are aware, a more representative 19% (91/471) of patients were grades 4 or 5, but outcome data by individual clinical grade (on randomisation) were not presented; however, the odds ratio (OR) for poor outcome was 3.51 [95% confidence interval (CI) 2.21 to 5.68] for grade 3–5 patients combined, compared with grade 1–2 patients, on multivariable analysis.[7]

The conventional management strategy for grade 4–5 patients [treatment on neurological improvement (TONI) (control) arm] incurs a risk of aneurysm rebleed. The patient outcome if a rebleed occurs prior to aneurysm treatment is dismal, as > 80% of patients have a poor outcome.[6,7] Grade 4–5 patients are also thought to have a higher aneurysm rebleed rate than grade 1–3 patients, and this risk is highest quite soon after the first bleed.[4]

Therefore, reducing the chance of rebleeding by early aneurysm treatment may improve patient outcome. Based on this assumption, an early coiling strategy in grade 4–5 patients is being practised in many centres and some of the results are encouraging.[8–15] One larger (459 patients) heterogeneous population-based non-randomised prospective study found evidence that treatment of ruptured intracranial aneurysms within 24 hours of aSAH improves medium- and long-term clinical outcome.[16] The benefit of such ultra-early treatment was even more apparent for patients treated with endovascular coiling.

Review of prior literature on early coiling in poor-grade patients published from 2002 (when coiling became a proven aneurysm therapy) until 2015 identified eight relevant studies.[8–15] Unfortunately, none of these studies had a control group and most were small, retrospective studies carried out in a single centre, therefore suffering from inherent selection, review and recall bias. Overall, this was a very heterogeneous group of studies in terms of methodology, inclusion criteria, treatment timing and outcome measures used (and their timing).

Summary analysis of the eight studies identified a combined mortality rate of 36%, with good outcome in 52% (258/495). That represents an absolute 15% improvement over ISAT results, despite studies in the summary analysis including proportionately more WFNS grade 5 patients than were enrolled in ISAT. The primary and over-riding difference between ISAT and the subsequent acute aneurysm treatment literature is the timing of the aneurysm treatment.

A Chinese registry of poor-grade aSAH patients was published in early 2014.[17] This was an observational rather than a randomised study, examining outcomes rather than management strategy. A randomised poor-grade trial protocol for a single Chinese centre has also been published recently.[18] However, this proposed a trial of 99 patients examining timing of clipping in three groups of 33 (at < 3 days, 3–7 days and > 7 days), none of which is truly early aggressive aneurysm treatment. On both grounds (treatment modality and timelines), it is not comparable with the treatment of poor-grade subarachnoid haemorrhage trial 2 (TOPSAT2).

Newcastle feasibility study: TOPSAT1[19]

The treatment of poor-grade subarachnoid haemorrhage trial 1 (TOPSAT1) was carried out in a single UK neuroscience centre (Newcastle upon Tyne Hospitals NHS Foundation Trust). Adult patients with WFNS grade 4–5 aSAHs were randomised within 24 hours of admission to neurocritical care to either the emergent treatment (ET) arm or the TONI arm with analysis on an intention-to-treat basis. If randomised to ET, the aneurysm was treated endovascularly (coiled) within 24 hours of randomisation. Feasibility of randomisation, recruitment rate, safety profile and functional outcome at the time of discharge and at 6 months were assessed. If the patient was initially admitted to a different hospital, confirmation of the Glasgow Coma Scale (GCS) (and thus derivation of WFNS grading) prior to intubation/ventilation was sought from the hospital transfer/referral letter.

The exclusion criteria were as follows:

- age > 75 years
- signs of brainstem death not promptly reversed by anti-cerebral oedema treatment
- pure intra-ventricular haemorrhage
- large intracerebral haematoma requiring immediate surgical clot evacuation
- pregnancy
- cardiorespiratory instability
- lack of clinical equipoise.

An appropriate clinician [e.g. an intensive therapy unit (ITU) consultant/registrar, neurological consultant/registrar or interventional neuroradiology consultant/registrar] discussed the trial and provided written information to the next of kin. The clinician returned after a maximum of 4 hours to

allow adequate time for reflection and obtained informed assent for the trial from the next of kin. If assent was not obtained from the next of kin, the reason for this was documented.

Fifty patients who were admitted to neurocritical care with grade 4–5 aSAHs were screened from August 2008 to January 2011. Fourteen patients were eligible for TOPSAT1 (28%). Eight out of fourteen patients were randomised (57%): four male and four female, with a mean age of 53 years. In six patients, relatives were not available to give assent (four cases) or assent was refused (two cases). Five patients were randomised to the ET arm and three patients were randomised to the TONI arm. Of the patients in the ET arm, three patients had a WFNS grade of 5 and two had a WFNS grade of 4. Of patients in the TONI arm, two patients had a WFNS grade of 5 and one had a WFNS grade of 4. There were no treatment-related adverse events (AEs) related to endovascular aneurysm treatment in either arm. No patients were lost to follow-up or crossed over arms in TOPSAT1.

Functional outcomes were assessed at the time of discharge and at 6 months following ictus using the standard modified Rankin Scale (mRS) questionnaire. There was no statistically significant difference between the arms (but the number of patients in this feasibility study was very small and it was not powered for formal analysis of efficacy).

It was demonstrated in TOPSAT1 that recruitment into a randomised controlled trial (RCT) of management policy for grade 4–5 aSAH patients was feasible. The recruitment rate among patients eligible for the study was encouraging, at 57%. However, TOPSAT1 did not have Stroke Research Network (SRN)/Comprehensive Local Research Network (CLRN) support, which limited recruitment to 5 days per week rather than 7 days; no specific trial funding was secured and TOPSAT1 had narrower eligibility criteria than were proposed for TOPSAT2. In addition, since TOPSAT1 ended, the use of an appropriate consultee to gain assent in urgent acute trials involving incapacitated patients has become widely accepted in the NHS. Therefore, applying all these improvements in resource/practice to the TOPSAT1 screening log, we estimated that at least 12 additional patients would have been eligible for TOPSAT2 (52% overall eligibility): 10% by eliminating delays to randomisation by SRN/CLRN support, 6% by including patients aged up to 80 years and 8% by utilisation of an appropriate consultee for assent. Therefore, it was felt that there was good evidence to support an appreciably higher participation rate being achieved from the aSAH population in TOPSAT2 than in TOPSAT1.

Manchester audit of high-grade subarachnoid haemorrhage

Additional data on grade 4–5 patients were sought from the earlier Manchester audit of high-grade subarachnoid haemorrhage (SAH) (Mr Hiren Patel, Consultant Neurosurgeon, Salford Royal NHS Foundation Trust, 20 November 2013, personal communication). Eighty patients were admitted to Salford neurocritical care over a 2-year period, 21 of whom improved in neurological status quickly (26%); 44 out of the 59 remaining 'true grade 4–5' patients had the ruptured aneurysm treated early, with 23 good outcomes (39%). Most of those 44 patients would have been eligible for TOPSAT2, so again an approximately 50% eligibility rate.

National Confidential Enquiry into Patient Outcome and Death report

The 2013 NCEPOD report[1] revealed many grade 4–5 aSAH patients were simply not admitted to NSCs; 124 out of 404 (31%) SAH patients referred to NSCs were not transferred, with poor clinical grade being the overwhelming reason for this. In the absence of evidence for benefit with early grade 4–5 aneurysm treatment this can be medically justified, but the practice is undoubtedly associated with poor outcome in terms of death and disability.

The NCEPOD report[1] also highlighted the heterogeneity of UK management of grade 4–5 aSAH patients in terms of both admission rates and subsequent management. Grade 4–5 patients accounted for between 8% and 50% of admissions and some units never admitted grade 5 patients. Overall, 22% of patients in the NCEPOD report[1] were WFNS grades 4 or 5 on admission to a neurosciences centre (NSC), with approximately equal numbers in each grade. Twenty-eight per cent of grade 4 patients and 14% of grade 5

patients had a reasonable functional outcome on discharge from the NSC (a formal mRS assessment was not available) but no longer-term follow-up was obtained. This indicates that the 'real-world' current good outcome rate even in grade 4–5 aSAH patients admitted to NSCs in the NHS averages only around 20%, compared with case series literature indicating > 50% good outcomes with early aneurysm treatment.[1]

Biomarkers of aneurysmal subarachnoid haemorrhage outcome

One of the challenges in managing patients with grade 4–5 aSAHs is that the only accepted tool in predicting a patient's outcome is the admission clinical grading. However, all indications are that patients with high-grade aSAHs are not a homogeneous group, and some patients' true clinical grading is unknown because they have been previously ventilated and intubated for brain imaging and/or transfer. There could be other more accurate early predictors of outcome that would help select patients for the most appropriate management strategies, including whether or not to transfer to neurocritical care and whether or not to treat the ruptured aneurysm early and aggressively.

Neurological damage following aSAH is a complex and evolving process. The initial phase starts with the ictus and is a response to the initial haemorrhage. A further variable phase is a consequence of vasospastic ischaemia. This is substantially absent for approximately 3 days following ictus and then evolves to a variable degree of neurological damage up to around 4 weeks post haemorrhage, with a peak typically at days 4–12. Another phase may occur related to hydrocephalus. This may arise at any point up to some months post ictus but is concentrated in the first 2–3 weeks. The proposed exploratory magnetic resonance imaging (MRI) mechanistic study had two rationales. The first was to establish whether or not MRI could be used to guide the decision on early versus deferred treatment. The second was to measure the risks posed to nervous tissue by aneurysm repair and to relate this to timing.

Imaging biomarkers

We identified a number of specific MRI-based biomarkers[20–22] that may be hypothesised to have potential predictive power in this setting. These included changes in overall cerebral perfusion, the presence of increased intracerebral pressure with associated changes in cerebral tissue compliance, the presence of dysfunctional autoregulatory hydrodynamics and the presence of early inflammatory change. Diffusion-weighted imaging (DWI) is well established as an imaging marker of acute ischaemia and highly relevant to correlate risks posed by early treatment. It has been demonstrated that DWI on early MRI in SAH patients shows substantially more changes in grade 4–5 patients than in grade 1–2 patients.[20] Furthermore, studies suggest that the more extensive the changes on DWI in grade 4–5 aSAH patients, the worse the prognosis.[21] Another promising technique is diffusion tensor imaging (DTI), which provides information on the integrity of fibre tracts in the brain. Studies have shown DTI changes in the corticospinal tract in patients with SAH who have focal limb weakness.[22] Comparison of DTI studies in grade 4–5 aSAH patients can potentially give us insight into the mechanism of cerebral damage and help predict outcome. Dynamic contrast magnetic resonance has been demonstrated to reveal breakdown in the blood–brain barrier (quantification of contrast leakage in ischaemic and inflammatory diseases) and the integrity of this post SAH is hypothesised to be a biomarker for complications such as vasospasm, and possibly even as an independent predictor of outcome.

Rationale

There is genuine uncertainty about the optimal management strategy for grade 4–5 aSAH patients and a lack of high-quality research evidence in this area, confirmed by the NCEPOD report.[1]

Although there is reasonable evidence that fewer rebleeds occur in patients with good clinical grades treated by coiling ultra-early, there are additional procedural risks in poor-grade patients.[23] Therefore, the management of poor-grade aSAH is based on individual or team experience, although there is a

clear trend for these poor-grade patients being treated more aggressively, mostly with early coiling. This is mainly because, with the availability of coiling as a less invasive alternative to clipping, most clinicians are not comfortable with leaving a ruptured aneurysm unprotected at a stage when the risk of rebleed is greatest. However, this is not an evidence-based approach and potentially exposes health-care systems to the following considerable extra costs:

- A substantial additional demand on already stretched neurocritical care bed and staff resources.
- Long-term care costs if early coiling results in survival with major disability rather than improving the proportion of patients with a truly good outcome (alive and independent or with minor disability in the medium to long term at follow-up).
- Costs of possibly unnecessary aneurysm coiling (staff, infrastructure and consumables).
- Drive to deliver weekend coiling services locally rather than by potentially cheaper networking (networking between centres may be a good option for grade 1–3 aSAH patients but not so for grade 4–5 patients for whom extra transfer between centres may be risky, is very staff/equipment resource intensive, risks ITU overload at a centre and is costly).

Conversely, if an early-treatment strategy (primarily with coiling) of grade 4–5 aSAH patients was proven to be superior in a RCT, there is a compelling argument that it should be provided to all patients. Endovascular coiling services would need to be extended to cover 7 days, as it would not be logical to admit a critically ill patient to an intensive care bed from a peripheral hospital and then delay coiling treatment because of lack of endovascular service. In 2013, approximately one-quarter of UK NSCs offered a robust weekend coiling service [NCEPOD[1] + UK Neurointerventional Group (UKNG) survey 2013, undertaken on behalf of the UKNG by Professor Phillip White (Newcastle University, 2013, personal communication)].

Crucially, there is a need for better understanding of the mechanisms involved in determining outcome in these patients. The current practice, which is reliant on crude clinical grading and to some extent the initial computerised tomography (CT) scan for risk stratification, needs to be refined. There is an urgent need for biomarkers for better understanding of the disease and, therefore, better selection of patients for aggressive management, as well as potentially stratifying long-term care and rehabilitation needs. This would help to ensure that appropriate individualised medicine is practised in an area where treatment/care costs for each patient are relatively high, but societal socioeconomic impact is also disproportionately high.

Patient and public involvement (PPI) was central to developing TOPSAT2. Feedback following presentations to the Newcastle SAH survivors' group fed into the development of the process of obtaining assent from relatives and the way that follow-up would be conducted. The Trial Steering Committee (TSC) also included two PPI members, an aSAH survivor and a relative, who were involved at every stage of the study, including contributing to the *Plain English summary* and the final report.

For many neurosurgeons/interventional neuroradiologists in UK NSCs, surveys confirmed that there was genuine uncertainty (clinical equipoise) regarding whether or not to treat all grade 4–5 aSAH patients as soon as possible; this also has service provision implications. The main risk in TOPSAT2 was that more patients would undergo aneurysm treatment, mostly by coiling, with some attendant risks that would otherwise not be the case. Some of these patients would die after coiling but before neurological improvement. In relation to the early-treatment procedure, this was estimated to occur in no more than 10–15 out of 170 patients enrolled on the ET arm.

The risk of modern aneurysm coiling-related long-term morbidity/mortality is around 3–5%, although it may be slightly higher in grade 4–5 patients (unclear from existing RCT data).[13,24] However, we know that rebleeding from an aneurysm has an awful prognosis (82% poor outcome in ISAT across patients of all grades) and that the rebleed rate is also higher in grade 4–5 patients.[4,6]

By contrast, the potential benefits of determining the optimum management strategy for aSAH were considerable. If early treatment was proved, service reconfiguration would be necessary but the outcome for grade 4–5 aSAH patients in the UK could be transformed. Studies on early treatment for grade 4–5 patients indicate good outcome rates around 50%, yet the NCEPOD report[1] found that many grade 4–5 patients were not admitted to a NSC in the UK. Even when patients are admitted, very few NSCs provide treatment 7 days per week. Furthermore, delays to treatment are correlated with poor outcome. There are almost 1300 grade 4–5 aSAH patients per annum in the UK and NCEPOD data show that ≈ 20% currently have a good outcome, yet almost 50% might have a good outcome with consistent early aggressive (emergent) treatment (with substantial associated societal health benefit). Although an early intervention strategy for all grade 4–5 patients would be very expensive initially, it would carry substantial long-term care and social benefits savings. However, that expense provides a strong case for the care of poor-grade aSAH to be truly individualised, which the use of imaging biomarkers can potentially help to deliver.

If TONI was at least as good as ET, fewer patients would need NSC admission and some might avoid ITU admission; there would be savings on coils and other consumables that could be made immediately, and simpler options would be viable for coiling services out of hours.

Objectives

Primary objective

To establish the efficacy of a strategy of early aneurysm treatment (within 72 hours of ictus) in a population of WFNS grade 4–5 aSAH patients in comparison with the conventional strategy of treatment of aneurysm only after neurological improvement (defined for the trial as improvement to WFNS grades 1–3) by comparing functional outcome at 12 months between the two arms – by ordinal analysis of mRS outcomes.

Secondary objectives

- Dichotomised mRS: cut-off points 0–3 versus 4–6; 0–2 versus 3–6.
- Mortality rate (30 days and 12 months).
- Rebleeding rate from randomisation.
- Treatment-related complication rate and serious adverse event (SAE) report rates. SAEs followed until resolution.
- Time in hospital to discharge (from NSC) and length of neurocritical care stay.
- mRS at discharge (or 30 days).
- Functional outcome at 6 months determined by ordinal analysis of mRS.

Magnetic resonance imaging substudy objective

To explore whether or not brain MRI markers in patients with poor-grade aSAH are related to outcome and whether or not they might be used to identify patients who would benefit from each treatment strategy, that is to stratify the management of grade 4–5 aSAH patients.

Chapter 2 Methods

Design

The TOPSAT2 trial was a pragmatic, randomised, open-blinded, end-point (PROBE), controlled, parallel-group study conducted in the UK and Eastern Europe. Extending recruitment beyond the UK was necessary to obtain the desired sample size within a reasonable time frame. Eastern Europe was chosen because of established links from surgical trials in intracerebral haemorrhage (STICHs).[25–27] It was planned to open 20 centres in the UK and 10 outside the UK, recruiting 246 UK and 100 non-UK participants. The proposed MRI substudy was to recruit a total of 100 consecutive participants from the UK only, in a subset of sites able to participate in it.

Participants were randomised to one of two groups in a 1 : 1 ratio to receive the standard local treatment for aneurysm either (a) as soon as possible within 72 hours of ictus (ET arm) or (b) after neurological improvement to WFNS grades 1–3 (TONI arm).

Eligibility

Eligible participants were adults aged 18–80 years and had been diagnosed with aSAH grades 4 or 5 on the WFNS scale. For trial eligibility purposes, the grade was that recorded at their first medical assessment following hospital attendance and confirmation of the diagnosis of SAH by CT (or MRI) and/or lumbar puncture. The protocol stressed that before including a participant in the trial it must also be confirmed that it would be possible to treat them within 72 hours of ictus, should they be randomised to the ET arm.

The exclusion criteria were as follows:

- Age > 80 years (the prognosis of poor-grade aSAH patients in this subgroup is extremely poor and they are a very small percentage of NSC aSAH admissions).
- WFNS grades 1–3, or uncertain WFNS grade. However, patients with aneurysms of uncertain grade on transfer to a NSC where a formal sedation hold was undertaken and the patient was subsequently established to be truly grades 4 or 5 were eligible for the trial. This also applied to patients with aneurysms of uncertain grade undergoing sedation hold after insertion of an external ventricular drain (EVD) or other early intervention for hydrocephalus.
- Signs of coning or brain death on arrival at the NSC.
- Pure aneurysmal intraventricular haemorrhage (no SAH).
- Large intracerebral haematoma from an aneurysm requiring immediate surgical clot evacuation.
- Significant aSAH-related haemodynamic instability.
- Lack of clinical equipoise.
- Lack of assent/consent.
- Pregnancy.
- Pre-SAH mRS > 2.
- Pre-existing severe comorbidity such that clinical follow-up at 12 months was judged unlikely.
- Non-saccular, mycotic, giant or other atypical aneurysm (as these are conditions for which early simple coiling/clipping would not be appropriate).

Recruitment

Locations

It was anticipated that up to 20 NSCs in the UK would participate. All UK NSCs ($n = 26$) with a functional interventional neuroradiology service were contacted with a feasibility form and asked for expressions of interest.

Feasibility was also initially carried out at seven non-UK centres in Czechia, Hungary, Latvia, Macedonia, Poland and two sites in Lithuania, using established contacts from the STICH. Two expressions of interest to participate were returned. Further forms were sent out to potential non-UK principal investigators (PIs) during the course of the study as more sites were sought (Romania and additional contacts in Czechia, Latvia, Poland and Hungary). Non-European centres (in Asia, Oceania and North America) did approach the TOPSAT2 team about joining but sponsorship arrangements were not in place to include non-European sites at the time suspension of trial recruitment was agreed by the TSC.

Overall, out of the 26 UK NSCs with functional interventional neuroradiology services, 25 were approached to participate [Edinburgh was not eligible as a site as the Data Monitoring Committee (DMC) chairperson was based in ITU there; the Efficacy and Mechanism Evaluation (EME) programme would not accept this unit as a trial site]. Fifteen centres were opened to recruitment between September 2016 and August 2018: 12 in the UK (Newcastle, Leeds, Sheffield, Middlesbrough, University College London, King's College London, Oxford, Royal London Hospital, Birmingham, Stoke-on-Trent, Nottingham and Cambridge) and three not in the UK (Riga, Latvia; Łódź, Poland; and Timişoara, Romania). A further two centres (Liverpool Walton Centre, UK, and Prague, Czechia) signed contracts but, unfortunately, did not open to recruitment before recruitment was suspended.

Process

Once a poor-grade SAH patient was admitted to neurocritical care at a trial centre, the patient was stabilised from neurological and cardiorespiratory points of view as per local protocol. If the patient was initially admitted to a different hospital, confirmation of the WFNS grade prior to transfer was sought from the referral letter or by directly contacting the referring team. If the WFNS grade before transfer could not be established (e.g. the patient was immediately intubated/ventilated), the patient was considered to be of uncertain grade (WFNS U) and was ineligible for the trial unless subsequent formal sedation hold and reassessment confirmed poor grade, as described in *Eligibility*. However, there was no requirement at the trial centre to confirm the patient's WFNS grade by reversing sedation in the ITU. Once aSAH was confirmed and the patient was stable, the admitting neurosurgical/anaesthetic team assessed the patient with regard to eligibility for the trial.

An appropriate clinician (e.g. an ITU consultant/registrar, neurological consultant/registrar or interventional neuroradiology consultant/registrar) with documented responsibility on the delegation log discussed the trial with the patient's next of kin and provided them with the participant information sheet. A delegated individual then returned after an appropriate interval (maximum 4 hours) to allow adequate time for reflection, and obtained assent for the trial from the appropriate consultee. The PI was responsible for ensuring that informed assent for trial participation was given by each patient's next of kin or relative, or by a nominated consultee, for patients fulfilling the TOPSAT2 eligibility criteria.

An important part of the design of the consent process was PPI. Through contact with the Newcastle SAH survivors' group, former SAH patients and their relatives were able to advise on this and provided insight into how best to approach a potential participant's next of kin, as the incapacitating nature of the condition precluded obtaining prospective informed consent from participants themselves. Wherever possible, an attempt was made to establish the views of the patient with regard to involvement in research from a personal consultee. If no personal consultee or next of kin could be identified, the researcher approached a person with no connection to the study who was pre-identified as willing to

be consulted about the participation of a person lacking capacity, to act as a consultee. The nominated professional/personal consultee completed a consultee declaration form that was countersigned by the PI or delegated personnel. Professional consultees were (medical) consultants who could not be otherwise actively involved in the trial.

If a participant regained mental capacity, they were fully informed about the trial and their consent was sought to continue. If at that point they did not wish to remain in the trial, then they were withdrawn. This is in accordance with the Mental Capacity Act 2005[28] (England and Wales).

Interventions

Standard procedures at the centre for coiling (or clipping) the aneurysm were followed. If the patient had more than one aneurysm, the neurovascular team treated the aneurysm that, in their judgement, was most likely to have caused the SAH. Standard care for grade 4–5 aSAH patients was provided to all trial participants; no additional clinical intervention and no new treatment method was undertaken as part of the trial.

Outcomes

Primary end point/outcome

The primary end point was functional outcome at 12 months determined by ordinal analysis of the mRS. The mRS is a widely used outcome measure in stroke (including aSAH) and is based on the ability to carry out usual day-to-day activities.

The mRS at 12 months was established using a questionnaire for the participant (or their carer) to complete (see *Appendix 1*). After hospital discharge in the UK, a member of the research team at Newcastle University contacted the general practitioner to establish whether or not the participant was still alive and to obtain information about the participant's clinical condition. If the participant was known to be alive, the study questionnaire was sent by post to the address given at recruitment, with a reply postage-paid envelope. Alternatively, patients could, if they wished, complete the questionnaire online through the trial website (www.topsat2.co.uk). For participants outside the UK, follow-up, including establishing the participant's vital status, was to be carried out by staff at the recruiting centre. This difference was because of sponsorship arrangements that had to be changed during the trial (see *Scientific summary* for detailed discussion of this).

Secondary end points/outcomes

- Dichotomised mRS: 0–3 versus 4–6; 0–2 versus 3–6.
- Mortality rate (at 30 days and 12 months).
- Rebleeding rate from randomisation.
- Treatment-related complication rate and number of reported SAEs. SAEs followed until resolution.
- Time in hospital to discharge (from NSC) and length of stay in neurocritical care.
- mRS at discharge.
- Functional outcome at 6 months determined by ordinal analysis of mRS – by questionnaire, as above.

Magnetic resonance imaging substudy outcomes

- Lesion load on DWI.
- Fractional anisotropy values on DTI.
- Brain perfusion and cerebrospinal fluid (CSF) parameters.
- Endothelial permeability.
- Blood–brain barrier integrity on MRI.

Sample size

The outcome measure in TOPSAT2 was based on the mRS, a 7-point scale, with values 0–5 representing increasing disability and a value of 6 representing death. In the past it was common to dichotomise such a scale for outcome analysis, resulting in a loss of information as not all patients contribute to the detection of a treatment effect. The Optimising Analysis of Stroke Trials Collaboration and other authors have shown the benefit of ordinal analysis in the field of stroke.[29] Using an ordinal analysis achieves substantially greater statistical power to detect a treatment effect with equal sample size. The sample size calculation was therefore based on a proportional odds regression ordinal analysis of the mRS.

The best available literature was used to provide the expected distribution of mRS after grade 4–5 aSAH patients, although it was a non-randomised study.[30] Detecting a difference in clinical outcome (i.e. favouring one treatment strategy over the other) by an OR of > 1.5 would be compelling evidence to rapidly change to a uniform practice, as would a number needed to treat (NNT) of < 10. Expected mRS distribution data (0, no symptoms 17%; 1, minor symptoms 10%; 2, some restriction in lifestyle 6%; 3, significant restriction in lifestyle 19%; 4, partially dependent 11%; 5, fully dependent 10%; and 6, dead 27%)[30] was entered into the 'sample size for ordered categories' routine of the Compare2 program in WinPepi version 11.43 during July 2014 and using two-sided significance of 5%, power of 80%, and 1 : 1 ratio of sample size, the sample sizes needed for different ORs (where the OR is assumed to be the same at all cutting points) were examined.

With 167 participants in each arm, a proportional odds model ordinal analysis of mRS gave a cumulative OR in favour of better mRS in one treatment arm of 1.7 at a 5% significance level and 80% power. A margin was built in to allow for losses to follow-up and crossovers, giving a total sample size of 346 (173 per arm). Loss to follow-up of $< 2\%$ was based on data from multiple UK-based aneurysm coiling trials.[6,31,32]

Using the expected distribution from the best available evidence[30] as the control event rate and calculating the expected number of patients to fall in each outcome for the treatment group given an OR of 1.7, the NNT was calculated as the inverse of the proportion of pairwise comparisons, with a better result in the treatment group minus the proportion with a worse result. This gave a NNT of 5.7.

A sample size of 346 was sufficient that some secondary outcome analyses, including a dichotomised mRS, could also reach statistical significance. For instance, for a mRS 0–2 (alive and independent) versus 3–6 (dead or dependent) comparison, a 15% absolute difference in treatment effect would be statistically detectable.

If equal numbers of grades 4 and 5 patients had been recruited (and they are approximately equal in proportion of aSAH patients), with 346 patients overall, the trial was powered to detect a statistically significant OR of 2.2 for improved clinical outcome, favouring one treatment strategy over the other by individual grade, particularly for grade 5. This is clinically relevant given the appreciable differences between grades 4 and 5 patients; the optimum management strategy may differ between grades.

Randomisation

Randomisation was carried out by the research team at sites through the use of an online system accessed through the trial website (www.topsat2.co.uk), and hosted by the Centre for Healthcare

Randomised Trials, University of Aberdeen. Randomisation utilised a minimisation algorithm with an 80% chance of being allocated to the minimisation group to reduce differences in the two arms with respect to the following:

- WFNS grades 4 or 5 (so distributed equally between the two arms)
- participant age at the time of randomisation (age bands 18–50 years, 51–65 years and 66–80 years)
- presence of clinically significant hydrocephalus requiring CSF drainage procedure (yes/no)
- UK/non-UK site.

The remaining 20% followed a totally random allocation.

If the participant was randomised to the ET arm, the result of randomisation was communicated to the neurovascular team treating the aneurysm. They decided on the most appropriate treatment strategy but, as per the RCT evidence base, if the aneurysm was technically amenable to coiling, coiling was the initial therapeutic option. Not all Eastern European centres provided an endovascular service, so only neurosurgical treatment (clipping) was available at those centres. The usual institutional surgical consent form for the procedure was completed, and the aneurysm was treated within 24 hours of randomisation and 72 hours of the ictal bleed that led to hospital admission.

If the participant was randomised to the TONI arm, the result was communicated to the ITU and neurovascular team, who continued to manage the patient as per the established local protocol. Once the patient's neurological status improved to WFNS grade 3 or better, the aneurysm was treated expeditiously. There was no specific time delay criterion for aneurysm treatment in this arm, but it was anticipated that treatment beyond 1 month post randomisation would be exceptional owing to both the lower risk of rebleeding after that time and the very guarded prognosis if a participant had not recovered sufficiently neurologically for treatment within 1 month.

Statistical methods

Analysis of the primary outcome measure

Trial analysis was on a modified intention-to-treat basis. Where patients were lost to follow-up, they were removed from the primary outcome analysis; however, a sensitivity analysis was performed to assess the effect of missing data. The primary outcome is a comparison of the mRS, treated as an ordinal scale, at 12 months (including death coded as 6) under the two treatment strategy arms using a Wilcoxon rank-sum test. Various planned analyses were not undertaken because of the small sample size. These include a proportional odds model of the primary outcome, a sensitivity analysis of the proportional odds model (of primary outcome), adjusting for the minimisation criteria (WFNS grade, age band, hydrocephalus requiring drainage, and whether or not the patient was randomised within the UK) and a per-protocol analysis.

Analysis of secondary outcome measures

Secondary outcomes of dichotomised mRS (0–3 vs. 4–6; 0–2 vs. 3–6) at discharge, 6 and 12 months, mortality rate at 30 days, 6 and 12 months, rebleeding rate and treatment-related complication rate between the arms were to be compared using a chi-squared test or a Fisher's exact test as appropriate. mRS at discharge and 6 months were to be compared using the Wilcoxon rank-sum test. Survival time, time to discharge and length of ITU/high dependency unit stay were to be compared between arms using survival plots, and the log-rank test has been reported. Owing to early termination of the trial and the small sample size, the ordered outcomes were not compared using the proportional odds models.

Subgroup analyses

Analyses were planned for the following subgroups: WFNS grade at randomisation (4–5), age band (18–50 years, 51–65 years, 66–80 years), if there was clinically significant hydrocephalus requiring

CSF drainage (yes/no), location of the site (UK/non-UK) and treatment actually received (coil vs. clip). Had the trial not been terminated early, ORs and CIs would have been reported and interaction tests undertaken.

Safety

Monitoring for safety was undertaken in accordance with good clinical practice. Full details and definitions were provided in the trial protocol. The local investigator responsible for the care of the participant was asked to assign causality and expectedness of SAEs, in accordance with the trial protocol.

It was anticipated that most AEs that would occur during the trial, whether serious or not, would be expected because of the clinical indication and the standard treatment that the patient was receiving. A full list of expected SAEs related to acute SAH and aneurysm treatment is provided in *Appendix 2*.

All AEs related to the trial intervention (randomisation to either the ET arm or the TONI arm) were recorded in the case report form/electronic case report form. Those classified by the trial centre as SAEs were reported to the chief investigator, Clinical Trials Unit and sponsor on a SAE form, which was sent using either secure fax-to-e-mail transmission or secure e-mail. Details of the events were entered into the trial database. SAEs were followed up until resolution.

Chapter 3 Results

Participant flow

Figure 1 shows the participant flow through the study from screening to 12-month follow-up.

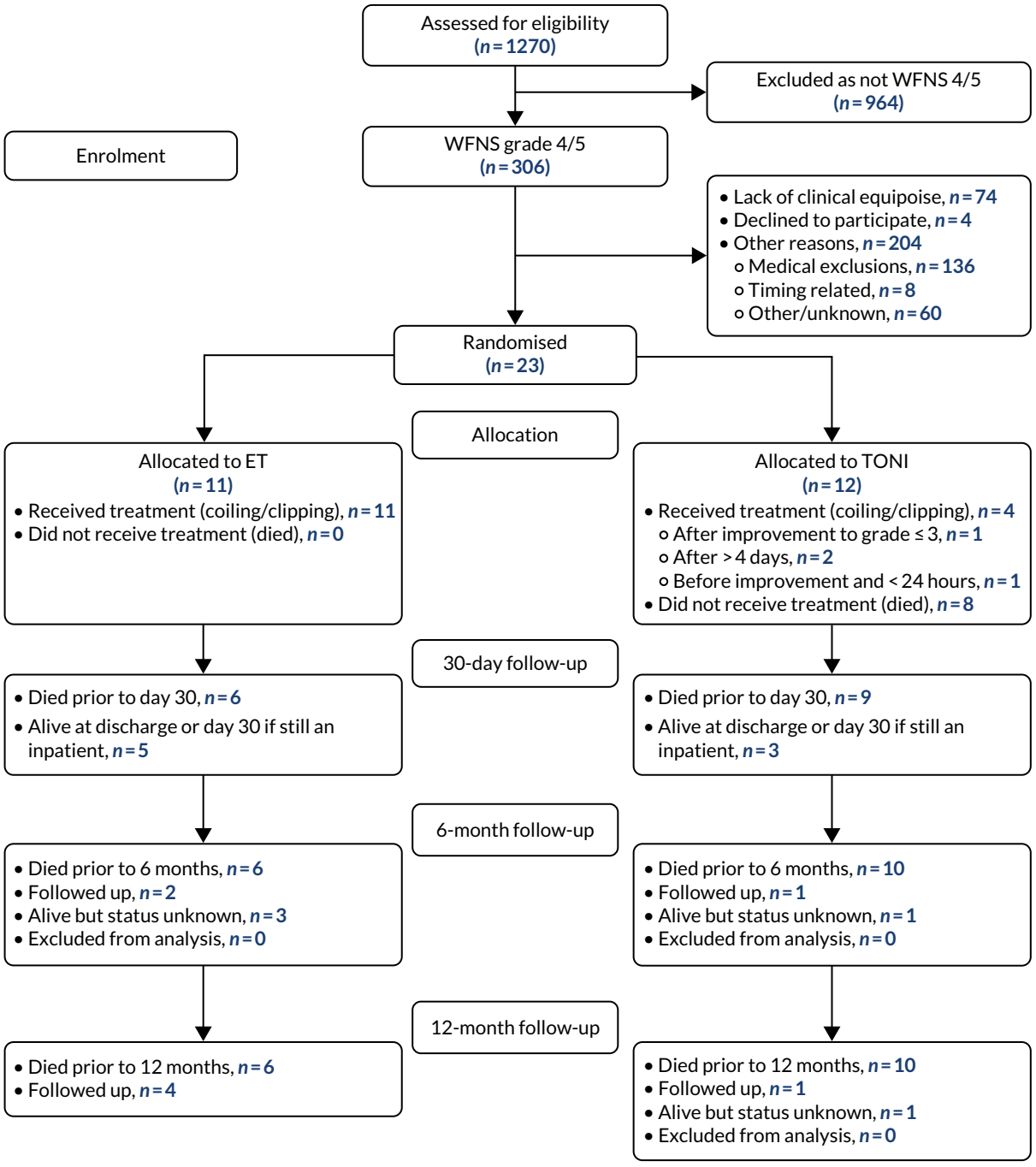


FIGURE 1 The TOPSAT2 CONSORT flow diagram.

Screening

A total of 1269 grade 1–5 aSAH patients were screened (1189 from UK sites, 80 from non-UK sites), of whom 964 (936 UK, 28 non-UK) were immediately excluded because their aneurysm was not classified as poor grade (WFNS grades 4 or 5). Of the 305 poor-grade patients screened (286 UK, 19 non-UK), 23 were randomised; 16 were from UK sites and seven were from a single, non-UK site. *Table 1* shows the number of patients screened at each site with the proportion of those recruited. See *Tables 2* and *3* for more details of screened patients.

Recruitment

Recruitment opened on 20 September 2016 in Newcastle upon Tyne and a further 14 sites were opened over the subsequent 22 months, including three non-UK sites (Łódź, Poland; Riga, Latvia; and Timişoara, Romania).

TABLE 1 Screening and recruitment by site for TOPSAT2

Site name	Number screened	Number grade 4/5 screened	Number medically eligible	% grade 4/5 medically eligible[a]	% eligible of those screened	Number recruited	% recruited of those screened
Newcastle	134	25	0	0	19	0	0
Sheffield	166	25	17	68	15	0	0
Stoke-on-Trent	124	42	21	50	30	4	3
Leeds	182	48	11	23	26	2	1
King's College London	146	34	33	97	23	1	1
Oxford	118	34	23	68	29	3	3
Nottingham	150	34	9	26	23	0	0
University College London	77	12	4	36	16	2	3
Middlesbrough[b]	0	0	0	0	0	0	0
Łódź	34	6	0	0	18	0	0
Royal London	16	2	2	100	13	2	13
Birmingham	59	25	10	40	42	1	2
Cambridge	17	6	1	17	35	1	6
Riga	8	3	0	0	38	0	0
Timişoara	38	10	8	80	26	7	18
Overall	1269	306 (24%)	139	48	24	23	2

a Excluding unknown reason (as some might not have been medical exclusion, e.g. lack of equipoise or assent), proportion of grade 4–5 patients eligible of those screened is 47%.
b Middlesbrough lacked a neurointerventional service during most of the trial recruitment period so diverted most aSAH patients to Newcastle.

TABLE 2 Poor-grade patients screened but not recruited to TOPSAT2 by reason given in screening log

Reason not recruited	Number of patients
Not aged 18–80 years	6
Lack of clinical equipoise	74
Lack of assent	4
Patient died/fixed GCS score of 3/deteriorated (before enrolment feasible)	16
WFNS grades 1–3, or uncertain WFNS grade (where patient recovers quickly and proves not to be of true poor grade)	18
Signs of coning or brain death not promptly reversed by anti-cerebral oedema treatment	28
Pure intraventricular haemorrhage (no SAH)	3
Large intracerebral haematoma that requires immediate clot evacuation	24
Significant aSAH-related haemodynamic instability	6
Pre-SAH mRS score > 2	11
Pre-existing severe comorbidity such that clinical follow-up at 12 months is judged unlikely	21
Non-saccular, mycotic, giant or other atypical aneurysm	3
Cannot be treated within 72 hours of ictus if allocated to ET arm	8
Other	18
Unknown reason	42

TABLE 3 Breakdown of 'other' reasons clinically eligible patients not recruited

Reason not recruited	Number of patients
Combination of reasons	3
Not appropriate for study	5
Withdrawal of treatment	1
Administrative issues	1
Out of time (to meet protocol requirement on random and/or Rx)	3
Elected for early coiling	5
Total	18

The first participant was randomised on 2 March 2017, 6 months after screening started. A chart of actual cumulative recruitment by month (up until recruitment was paused in December 2018) against target recruitment over the same period is shown in *Figure 2*.

Baseline characteristics

Twenty-three participants were recruited to TOPSAT2. Eleven were randomised to the ET arm and 12 to the TONI arm. The baseline characteristics of each of the two randomisation arms are shown in *Table 4*. Participants ranged in age from 44 to 75 years with a median age of 63 years. They were more likely to be female (65%) than male, and more were recruited in the UK (70%) than outside the UK. Most participants had an aneurysm of WFNS grade of 5 (74%) and Fisher grade 4 (87%), confirming their poor-grade status, although nearly all participants had a pre-stroke mRS of 0 (70%) or 1 (26%).

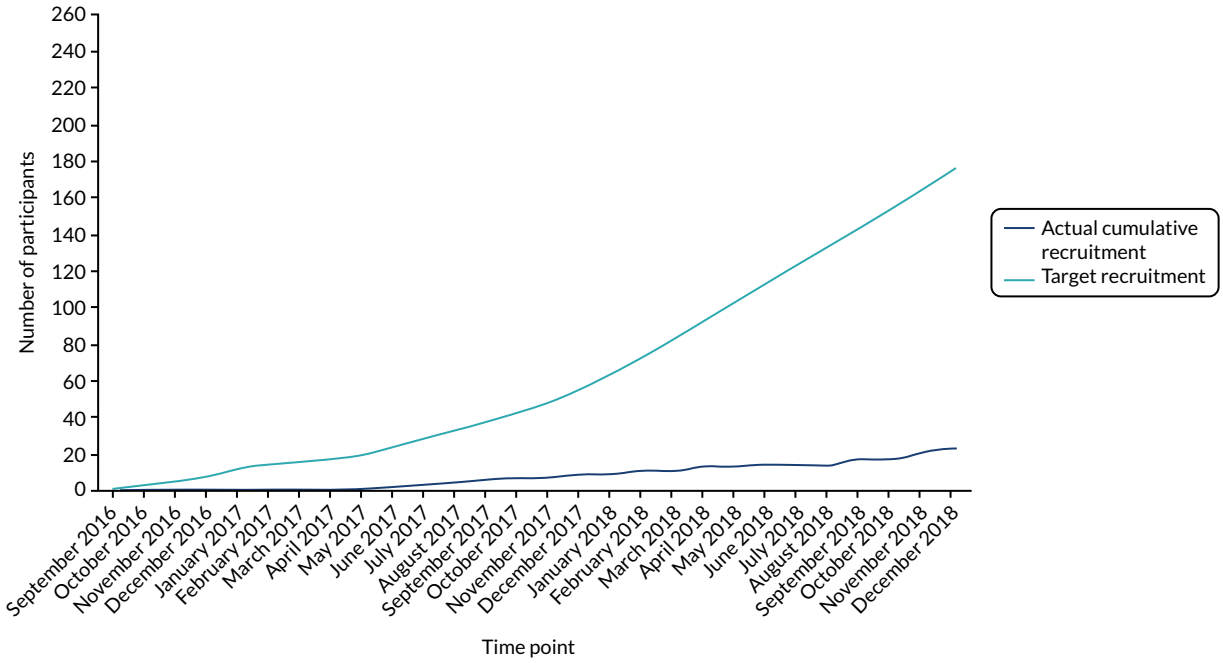


FIGURE 2 Planned and actual recruitment for TOPSAT2.

TABLE 4 Baseline characteristics of TOPSAT2 participants by arm

Randomised	ET (*N* = 11)	TONI (*N* = 12)	Total (*N* = 23)
Age (years)			
Mean	62.2	60.6	61.3
SD	11.4	9.8	10.1
Median	65	59	63
Q1, Q3	52, 73	52, 70	52, 70
Minimum, maximum	44, 75	47, 75	44, 75
Age band (years), *n* (%)			
18–50	2 (18)	2 (17)	4 (17)
51–65	4 (36)	5 (42)	9 (39)
66–80	5 (45)	5 (42)	10 (43)
Sex, *n* (%)			
Male	4 (36)	4 (33)	8 (35)
Female	7 (64)	8 (67)	15 (65)
Site location, *n* (%)			
UK	8 (73)	8 (67)	16 (70)
Non-UK	3 (27)	4 (33)	7 (30)
Pre-stroke residence, *n* (%)			
At home alone	3 (27)	3 (25)	6 (26)
Home with family/friends	7 (64)	9 (75)	16 (70)
Sheltered housing	0	0	0
Other	1 (9)	0	1 (4)

TABLE 4 Baseline characteristics of TOPSAT2 participants by arm (*continued*)

Randomised	ET (*N* = 11)	TONI (*N* = 12)	Total (*N* = 23)
Previous SAH, *n* (%)			
No	11 (100)	12 (100)	23 (100)
Yes	0	0	0
Previous medical history, *n* (%)			
High blood pressure[a]	5 (45)	5 (42)	10 (43)
Known diabetic	0	1 (8)	1 (4)
Severe dementia	0	0	0
Severe renal failure	0	1 (8)	1 (4)
Severe cardiac failure	0	0	0
Metastatic cancer (not controlled)	0	0	0
Smoker	4 (36)	5 (42)	9 (39)
GCS – eye prior to intubation, *n* (%)			
E1	7 (64)	9 (75)	16 (70)
E2	0	1 (8)	1 (4)
E3	1 (9)	1 (8)	2 (9)
E4	2 (18)	1 (8)	3 (13)
Not recorded	1 (9)	0	1 (4)
GCS – motor prior to intubation, *n* (%)			
M1	3 (27)	3 (25)	6 (26)
M2	1 (9)	1 (8)	2 (9)
M3	3 (27)	2 (17)	5 (22)
M4	0	3 (25)	4 (17)
M5	3 (27)	2 (17)	5 (22)
M6	0	1 (8)	1 (4)
Not recorded	1 (9)	0	1 (4)
GCS – verbal prior to intubation, *n* (%)			
V1	6 (55)	9 (75)	15 (65)
V2	2 (18)	3 (25)	5 (22)
V3	0	0	0
V4	1 (9)	0	1 (4)
V5	0	0	0
Not recorded	2 (18)	0	2 (9)
WFNS, *n* (%)			
Grade 4	2 (18)	4 (33)	6 (26)
Grade 5	9 (82)	8 (67)	17 (74)
Fisher grade, *n* (%)			
1	0	0	0
2	0	0	0
3	3 (27)	0	3 (13)
4	8 (73)	12 (100)	20 (87)

continued

TABLE 4 Baseline characteristics of TOPSAT2 participants by arm (*continued*)

Randomised	ET (*N* = 11)	TONI (*N* = 12)	Total (*N* = 23)
Hydrocephalus requiring drainage, *n* (%)			
No	3 (27)	3 (25)	6 (26)
Done or planned	8 (73)	9 (75)	17 (74)
Pre-stroke mRS, *n* (%)			
0	6 (55)	10 (83)	16 (70)
1	4 (36)	2 (17)	6 (26)
2	1 (9)	0	1 (4)
3	0	0	0
4	0	0	0
5	0	0	0
Time from ictus to randomisation			
Median (hours)	17.9	21.3	20.9
Minimum, maximum	2.1, 47.8	2.8, 47.4	2.1, 47.8
Q1, Q3	8.1, 39.6	14.5, 35.7	8.8, 39.2
Abnormal blood readings (clinically significant), *n* (%)			
APTT	0	0	0
Prothrombin time	0	0	0
International normalised ratio if on warfarin	0	0	0
Platelets	0	0	0
Haemoglobin	2 (18)	1 (8)	3 (13)
eGFR	0	0	
Glucose	0	1 (8)	1 (4)
Sodium	0	1 (8)	1 (4)
Potassium	1 (9)	0	1 (4)
Urea	0	0	0
Creatinine	1 (9)	0	1 (4)
Number of aneurysms, *n* (%)			
1	8 (73)	9 (75)	17 (74)
2	2 (18)	2 (17)	4 (17)
3	1 (9)	0	1 (4)
4	0	0	0
5	0	1 (8)	1 (4)

APTT, activated partial thromboplastin time; eGFR, estimated glomerular filtration rate; SD, standard deviation.
a Patients have known hypertension or are on hypertensive medication.

The average time from ictus to randomisation was 20.9 hours. Randomisation resulted in two well-matched treatment arms.

A table of baseline characteristics by WFNS grade is provided in *Appendix 3*, and a table of baseline characteristics by location of site (UK vs. non-UK) is provided in *Appendix 4*.

Aneurysm treatment details

The aneurysm characteristics are shown in *Table 5*. The majority of aneurysms were located in the anterior communicating artery (43%) or posterior communicating artery (30%). The planned treatment of the aneurysm was endovascular (coiling) in 30% of patients and neurosurgical (clipping) in 52% of patients but was not stated for 17% of patients who were in the TONI arm. Although there did appear to be a difference in planned treatment between the two treatment arms, with 55% planned coiling in the ET arm and 8% in the TONI arm, it is likely that coiling would have been the eventual preferred treatment in the 'not yet planned' participants, as these were all UK patients where coiling was more prevalent. The time from ictus to securing the aneurysm in the ET arm varied between 3 and 71 hours, with a median of 26 hours, whereas for the TONI arm it varied between 15 and 434 hours, with a median of 163 hours (over 6 days) for the four patients treated.

TABLE 5 Aneurysm characteristics and proposed treatment

Randomised	ET (*N* = 11)	TONI (*N* = 12)	Randomised (*N* = 23)
Location of aneurysm (primary outcome)*, n *(%)			
Anterior cerebral artery			
Anterior communicating	5 (45)	5 (42)	10 (43)
Proximal to anterior	0	0	0
Communicating	1 (9)	0	1 (4)
Pericallosal	0	0	0
Internal carotid artery			
Proximal or ophthalmic region	0	0	0
Posterior communicating	3 (27)	4 (33)	7 (30)
Bifurcation	0	1 (8)	1 (4)
Other internal carotid artery	1 (9)	0	1 (4)
Middle cerebral artery			
Proximal to bifurcation	0	0	0
Bifurcation	1 (9)	1 (8)	2 (9)
Distal to bifurcation	0	0	0
Posterior circulation			
Basilar bifurcation	0	0	0
Basilar trunk	0	0	0
Superior cerebellar	0	0	0
Posterior cerebral	0	1 (8)	1 (4)
Posterior inferior cerebellar	0	0	0
Planned treatment*, n *(%)			
Endovascular	6 (55)	1 (8)	7 (30)
Neurosurgical	5 (45)	7 (58)	12 (52)
Other (not yet planned)		4 (33)	4 (17)
Time from ictus to treatment for those treated*, n *(%)			
Median (hours)	26	163	27
Minimum, maximum	3, 71	15, 434	3, 434
Q1, Q3	20, 45	39, 270	20, 71
Not treated	0	8	8

Emergent treatment arm

All 11 patients in this arm each had only one aneurysm treated because it was either the only aneurysm or considered to be the cause of the bleed. At the time of treatment the WFNS grade was the same as at randomisation for all patients, confirming that the aneurysm was secured prior to neurological improvement of the participant. Seven patients had coiling and four had clipping.

Treatment on neurological improvement arm

A total of 4 out of 12 patients randomised to this arm went on to receive treatment: three patients had one aneurysm treated and one patient had two aneurysms treated. At the time of treatment, two of these aneurysms were grade 5, one was grade 4 and one was grade 2, demonstrating that only one TONI participant had actually shown the required degree of neurological improvement prior to the aneurysm being secured. One grade 5 patient had treatment within 24 hours and was therefore a crossover. The other two did not have their aneurysm secured for > 4 days. One patient had coiling and three had clipping.

Coiling

Of the eight patients who had coiling, a balloon was used for four of the ET patients and for the single TONI patient; a stent was used for one ET patient. The rest had unassisted coiling (no balloon). No patients had a flow diverter, web or other permanently implanted neck bridge device.

All patients had intravenous heparin, which was administered during the procedure in all patients except one ET patient, in whom it was administered post procedure. Two ET patients received aspirin, one of whom also received oral aspirin. Two other ET patients and the TONI patient received oral aspirin alone. No patients received clopidogrel or equivalent.

No patients suffered from aneurysm rupture or parent artery occlusion, but one ET patient had a coil migration or significant protrusion, and two ET patients had a dissection or vessel perforation. No patients had a groin haemorrhage, thromboembolic complication or required an additional procedure.

Clipping

The procedure was completed for all seven patients across both arms with no aneurysm rupture, parent artery occlusion or vasospasm.

Complications

Only one treated participant reported delayed ischaemic deficit (a TONI patient who had clipping). This was the only participant for whom a haematoma was reported and who also suffered a rebleed at this time point. The rebleed occurred after treatment and was confirmed by CT but did not require treatment.

Other neurosurgical procedures

Of the ET patients, two coiled patients had an EVD and one clipped patient had a ventriculoperitoneal shunt.

Of the TONI patients, two untreated participants had an EVD and one clipped participant had a ventriculoperitoneal shunt.

Four ET patients (one coiled, three clipped) had triple-H therapy and one untreated patient also had triple-H therapy. No balloon angioplasty procedures were reported.

There were no responses provided to these questions for four untreated participants.

Outcomes

The primary objective for TOPSAT2 was functional outcome at 12 months using the mRS. Outcomes for each arm at 6 and 12 months after randomisation are shown in *Table 6*.

TABLE 6 Outcomes at 6 and 12 months: mRS and residence

Randomised	ET (*N* = 11)	TONI (*N* = 12)	Randomised (*N* = 23)
mRS at 12 months (primary outcome), *n*			
0	1	0	1
1	0	0	0
2	1	0	1
3	0	0	0
4	0	1	1
5	2	0	2
6	6	10	16
Lost to follow-up	1 (at home)	1 (at home)	2
mRS at 6 months, *n*			
0	1	0	1
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	1	1	2
6	6	10	16
Lost to follow-up	3	1	4
Place of residence at 6 months, *n*			
Home	1	0	1
Residential home	0	0	2
Nursing home	0	0	16
Hospital	1	1	4
Rehabilitation unit	0	0	
Other	0	0	
Not applicable – deceased	6	10	
Lost to follow-up	3	1	
Place of residence at 12 months, *n*			
Home	2	1	3
Residential home	0	0	0
Nursing home	1	1	2
Hospital	1	0	1
Rehabilitation unit	1	0	1
Other	0	0	0
Not applicable – deceased	6	10	16

Primary outcome

Using a Wilcoxon rank-sum test (Mann–Whitney *U*-test) there was no evidence of a difference in 12-month mRS between patients receiving ET and patients receiving TONI ($p = 0.11$). However, there were two patients who did not respond but who were known (from general practitioner or hospital records) to be living at home. Patients living at home are most likely to have a mRS of between 0 and 3. To carry out a sensitivity analysis to include the patients with missing data, two possible scenarios were examined: first, assuming the missing case in the ET arm has the best outcome (mRS = 0) and in the TONI arm has the worst outcome (mRS = 3), and, second, vice versa. These two analyses give rank-sum test results of $p = 0.13$ and $p = 0.19$, respectively. The two TONI patients alive at 12 months had their aneurysms secured after more than 4 days.

Secondary outcomes

At 6 months, the Wilcoxon rank-sum test gives a value of $p = 0.33$ for the patients with known mRS. However, at 6 months there were four patients alive but for whom mRS was unknown (three ET patients and one TONI patient), and at this time their place of residence was also not known. Their best possible mRS was 0 and their worst possible mRS was 5. Assuming that the patients in the ET arm whose mRS were unknown had a value of 0 and the patient in the TONI arm whose mRS was unknown had a value of 5, and then assuming the opposite scores for those in each arm, the Wilcoxon rank-sum test produced *p*-values of 0.08 and 0.18, respectively.

Table 7 shows the outcomes for mortality and for dichotomised mRS, with the break between mRS 3 and mRS 4 and between mRS 2 and mRS 3, respectively. There is no evidence of a difference between the two treatment arms. Only one patient died after 30 days. *Figure 3* shows the results of the survival analysis (Log-rank $p = 0.32$).

TABLE 7 Secondary outcomes: mortality and dichotomised mRS

Secondary outcomes	ET (*N* = 11), *n* (%)	TONI (*N* = 12), *n* (%)	Fisher's exact test
Dead at 30 days	6 (55)	9 (75)	$p = 0.40$
Dead at 6 or 12 months	6 (55)	10 (83)	$p = 0.19$
12-month mRS 0–3 vs. 4–6[a]	3 (27)	1 (8)	$p = 0.32$
12-month mRS 0–2 vs. 3–6[a]	2 (18)	0	$p = 0.22$

a At 12 months, two patients were lost to follow-up (one in each group) but both were known to be living at home at that point, so for these analyses they were assumed to both have a mRS of 3.

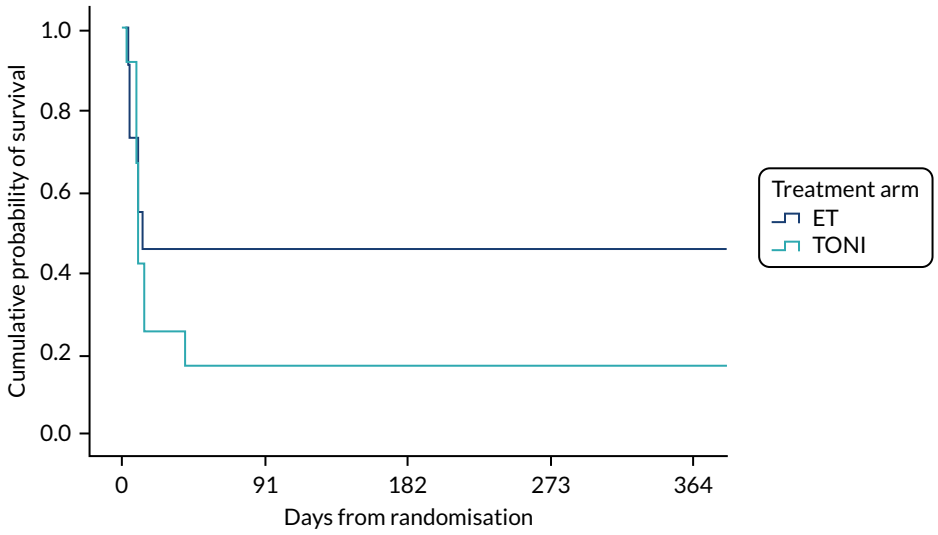


FIGURE 3 Kaplan–Meier plot.

Table 8 shows cause of death for all patients who died in the trial and demonstrates that the main cause of death in both arms for these poor-grade patients is subarachnoid haemorrhage.

Table 9 shows outcomes at 30 days. By day 30, six ET patients and 10 TONI patients had died. Of the survivors, two ET patients had been discharged: one to be home alone (mRS = 2) and the other into rehabilitation (mRS = 3). The remaining three ET patients (all mRS 5) and two TONI patients (mRS 4 and 5) were still in hospital. There was no evidence of a difference in mRS at 30 days

TABLE 8 Cause of death

Cause	ET (*N* = 6), *n* (%)	TONI (*N* = 10), *n* (%)	Total (*N* = 16), *n* (%)
Subarachnoid haemorrhage	3 (50)	6 (60)	9 (56)
Cardiac arrest	1 (17)	2 (20)	3 (19)
Pneumonia	1 (17)		1 (6)
Cerebral infarction	1 (17)	2 (20)	3 (19)

TABLE 9 Outcomes at 30 days

Randomised	ET (*N* = 11)	TONI (*N* = 12)	Randomised (*N* = 23)
Status by day 30, *n* (%)			
Died before discharge	6 (55)	9 (75)	15 (65)
Discharged	2 (18)	0	2 (9)
Still in hospital	3 (27)	3 (25)	6 (26)
Discharged to, *n* (%)			
Home alone	1	0	1 (50)
Home not alone	0	0	1 (50)
Residential home	0	0	21
Nursing home	0	0	
Referring hospital	0	0	
Rehabilitation unit	1	0	
Other	0	0	
Not applicable	9	12	
Number of days in ITU by 30 days			
Mean	11.8	14.8	13.4
SD	7.7	9.2	8.3
Median	13	10	10
Q1, Q3	5, 15	9.2, 24.8	8, 15
Minimum, maximum	3, 30	4, 30	3, 30
mRS score at 30 days, *n* (%)			
0	0	0	0
1	0	0	0
2	1 (9)	0	1 (4)
3	1 (9)	0	1 (4)
4	0	1 (8)	1 (4)
5	3 (27)	1 (8)	4 (17)
6	6 (55)	10 (83)	16 (70)

SD, standard deviation.

(Wilcoxon rank-sum test $p = 0.33$). Length of time in ITU by day 30 varied between 3 and 30 days with a median in the ET group of 13 days [mean 11.8 days; standard deviation (SD) 7.7 days] and a median in the TONI group of 10 days (mean 14.8 days; SD 9.2 days) (Wilcoxon rank-sum test $p = 0.68$).

Adverse events

There were 41 AEs recorded: 19 in the ET arm (mean 1.7 per participant) and 22 in the TONI arm (mean 1.8 per participant). The number of AEs for an individual participant ranged from 0 to 5, as shown in *Figure 4*.

The nature of AEs is shown in *Table 10*. There are no statistically significant differences between the arms, although infections were more likely to be reported in patients allocated to the ET arm (Fisher's exact $p = 0.08$), whereas brain oedema ($p = 0.35$) and cardiorespiratory ($p = 0.17$) events were more

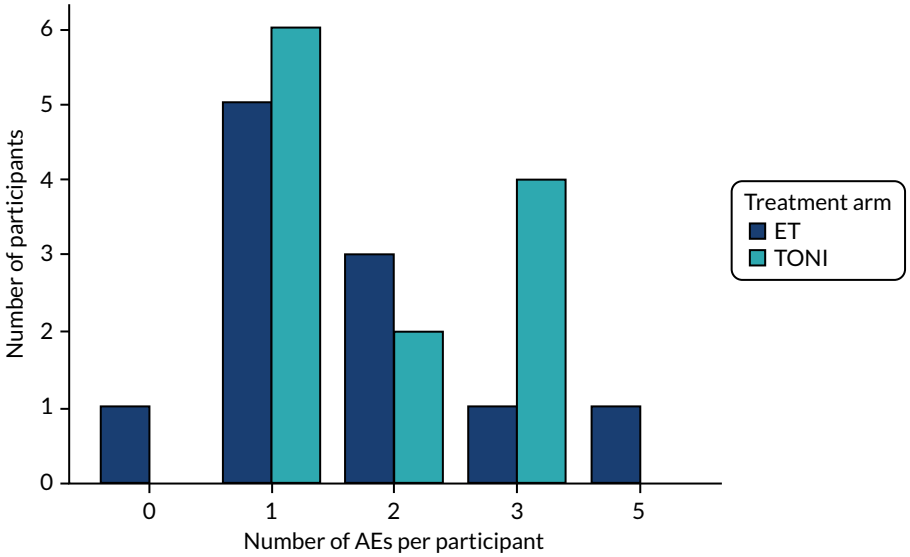


FIGURE 4 Number of AEs per participant.

TABLE 10 Adverse events in TOPSAT2

Type of AE	ET ($n = 11$)	TONI ($n = 12$)	Total
Neurological			
Impaired CSF drainage	3	3	6
Vasospasm related	2	0	2
Rebleed	0	2	2
Brain swelling/oedema	1	4	5
Stroke	1	0	1
Systemic			
Cardiorespiratory	3	8	11
Renal	2	1	3
Infections	5	1	6
Other	2	3	5
Total	19	22	41

likely to be reported in patients allocated to the TONI arm. Most of the 'other' events (four out of the five) were death (in the fifth a new infarction was reported).

Serious adverse events

Seventeen SAEs were reported, all resulting in the death of the patients: six in the ET arm and 10 in the TONI arm (one TONI patient was reported as having two separate SAEs: a rebleed followed by a stroke 6 days later). All SAEs in the ET arm resulted in the death of the patients but were judged to be unrelated to the intervention by both site and chief investigator. Eight of the SAEs in the TONI arm were unrelated; of the others, one was probably related (a rebleed) and two were judged probably unrelated (a myocardial infarction and a new cerebral infarction). All of these were expected outcomes of the disease.

Other analysis

Appendix 4 reports the baseline characteristics of UK and non-UK participants. Non-UK participants tended to be older and were more likely to be male and to have high blood pressure. The planned treatment to secure all aneurysms for non-UK participants was neurosurgical clipping. The mortality rate differed between UK (56%) and non-UK (100%) participants (Fisher's exact $p = 0.06$).

Appendix 3 reports the baseline characteristics by WFNS grade. Participants with WFNS grade 4 tended to be older, but the other baseline variables showed little difference, and there was no evidence of a difference in mortality rate, with rates of 83% in grade 4 patients and of 65% in grade 5 (Fisher's exact $p = 0.62$).

Summary of results

Of the 1269 aSAH patients screened, 305 were identified as poor grade. From this group, 23 patients were recruited and randomised to the ET group (11 patients) or TONI group (12 patients). Patients had a median age of 63 years, 65% were female and 74% were WFNS grade 5. All patients randomised to the ET group had their aneurysm clipped or coiled within 3 days and prior to any change in their WFNS grade. Only four patients randomised to the TONI group went on to have their aneurysm secured: three before neurological improvement and one after improvement to grade 2. As expected, the mortality rate was high among poor-grade patients: 55% for the ET group and 83% for the TONI group. There was no evidence of a statistically significant difference in the mRS between the two groups at 12 months, as per the Wilcoxon rank-sum test ($p = 0.11$).

Chapter 4 Discussion

Overview of recruitment and comparison of clinical results with other key studies

Recruitment to TOPSAT2 proved to be very challenging in both the UK and Eastern Europe, and the reasons are explored in detail in *Reasons for early termination*.

Comparison with previous studies

Perhaps the most relevant comparison is with the NCEPOD report[1] into SAH in the UK (excluding Scotland) in November 2013. The median age in the NCEPOD sample overall was 57 years compared with 63 years in TOPSAT2, but no breakdown of age by grade was performed on the NCEPOD sample. However, as approximately 19% of patients in the NCEPOD sample were managed conservatively and not admitted to a NSC, with poor grade as a reason for conservative management in many cases, it is reasonable to suppose that the more elderly and comorbid patients were actually under-represented in the NCEPOD NSC admissions. Therefore, it is likely that the underlying age differential between TOPSAT2 and NCEPOD poor-grade patients would probably have been somewhat greater than 6 years. It is also important to note that the clinical outcome from aSAH is strongly linked to age with a fairly linear effect; for instance, in the ISAT trial those patients < 60 years had a poor outcome rate of 24%, whereas for those 60 years and over it was 37%, a 54% relative risk increase.[6]

The sex profiles of the NCEPOD sample and TOPSAT2 RCT are similar at nearly 70% and 65% female, respectively. The high rates of smoking (39%) and hypertension (43%) seen in the TOPSAT2 trial are typical of the aSAH population; 70% of the TOPSAT2 population was recruited in the UK where in 2017–18 overall smoking prevalence was < 15% and overall hypertension prevalence was < 30% for adults. No participants had a prior history of SAH, but this may well be a small-sample phenomenon. Interestingly, hypertension rates were much higher but smoking rates were lower in non-UK participants than in UK participants, although these might be confounded by the higher average age and 57% male profile of non-UK participants (smoking generally being more common in men). The sex mix in non-UK recruitment is most likely to be another small-numbers effect, as across Europe aSAH is universally more common in females than in males.

The time from ictus to randomisation in the TOPSAT2 trial was a median of just 21 hours and, as randomisation could be performed only after admission to a NSC, this indicates a fairly rapid care pathway. That is both reassuring and indicates a real improvement since the ISAT trial,[33] in which time from ictus to randomisation was a median of 2 days. There was also an acknowledged appreciably lower time to randomisation in ISAT for the 22% of international participants than for UK participants.[33,34] That differential national timeline (ictus to randomisation) effect was seen to a much lesser extent in TOPSAT2 with only a 4-hour lower median time in non-UK compared with UK centres. With regard to aneurysm treatment undertaken/planned, the Eastern European recruiting centre did not provide an endovascular service, so only neurosurgical treatment was available and that does have an impact on the overall clipping versus coiling rates in the trial.

Predominantly good-grade patients were recruited by ISAT, with < 5% being WFNS grade 4–5 patients and with no detailed results being presented for poor-grade patients, therefore it tells us relatively little about poor-grade aSAH. In NCEPOD, which was a population-based sample, ≈ 22% of the patients admitted with aSAH to NSCs were WFNS grades 4 or 5, with only slightly more grade 5 than grade 4 patients. In contrast, recruitment into the TOPSAT2 trial did not reflect those earlier population-based data; again, only NSC-admitted patients could be included in TOPSAT2, but 74% were grade 5 and not the 50–55% range expected if randomisation reflected admissions in the

NCEPOD national sample. Therefore, there was a clear selection bias in TOPSAT2 towards enrolling grade 5 and older poor-grade patients, and this probably reflects equipoise towards grade 5 patients but not grade 4 patients (see below for detailed discussion of clinical equipoise in relation to TOPSAT2). The balance (%) of grade (4 vs. 5) recruitment in the non-UK centre was more as expected from the UK-based NCEPOD sample, indicating that in actively recruiting centres, the (lack of) clinical equipoise issue seemed to be a UK phenomenon, with predominantly grade 5 and older grade 4 patients recruited in the UK. Two-thirds of grade 4 patients were in the 66–80 years age band compared with only 35% of grade 5 patients.

In the NCEPOD report,[1] 62% of aSAH patients admitted to NSCs required some intervention for hydrocephalus, but this includes patients with aneurysms of all grades, and the rate of hydrocephalus is correlated with the extent of blood load on CT (the Fisher grade). That, in turn, correlates with the clinical (WFNS) grade; simply put, the more blood on the CT scan the greater the chance of being in a poorer clinical grade. Given that all TOPSAT2 patients were poor grade, it is unsurprising that the actual or planned intervention rate for hydrocephalus was rather greater in TOPSAT2 than in the NCEOPD report[1] at 74%.

Regarding clinical outcomes, in NCEPOD at discharge, 16% of grade 5 patients were mRS 0–2 and 65% died prior to discharge, whereas 40% of grade 4 patients attained mRS of 0–2 and only 24% died. The timeline for NSC discharge used in NCEPOD roughly equates to the 30-day clinical outcomes in TOPSAT2, especially as few poor-grade patients are discharged before 30 days. In TOPSAT2 overall, 70% died, reflecting both the preponderance of grade 5 patients and the higher average age of the TOPSAT2 cohort. Again, in TOPSAT2 data there are clear differences in outcomes between WFNS grade 4 and grade 5 patients, albeit very few WFNS grade 4 patients were enrolled in TOPSAT2 (only six), so that formal statistical testing for differences is not appropriate. Given that there have been no major management changes in the 3–5 years since the NCEPOD report[1] and the period of TOPSAT2 recruitment (December 2016–December 2018), except a drive in the UK to admit and treat aSAH within 48 hours, this similarity in outcomes is as expected.

The outcomes for those patients who experience rebleeding are universally acknowledged as being very poor: 82% bad outcome in ISAT and 75% in NCEPOD. In TOPSAT2, as the trial numbers are very small and the frequency of rebleeding is fairly low, these events were rare, with only two cases of rebleeding reported.

In the limited data provided in a trial with 23 patients enrolled, TOPSAT2 does not support the concept that a TONI approach is inevitably associated with a much higher rate of rebleeding events than treating all emergently regardless of neurological status. The Kaplan–Meier survival analysis (see *Figure 3*) does not indicate any statistically significant difference in survival between the ET and TONI arms ($p = 0.32$). Comparison of mortality rates at 30, 180 and 365 days found no statistically significant difference between groups at any time point.

In terms of overall clinical outcome, not only mortality, there was again no statistically significant difference identified between the arms within the limitations of such a modest sample size. Sensitivity analysis was performed to allow for missing Rankin Scale outcome data, but this also did not indicate any outcome differences.

The mortality rate differed between UK (56%) and non-UK (100%) centres but did not quite reach statistically significant difference. This trend could reflect a number of factors, including that the Romanian centre did not have access to coiling as a treatment option; it recruited older patients with more comorbidities and had different critical care provision (to UK). Of course, it could also be a small-numbers effect.

All SAEs were expected events related to poor-grade aSAH, with no statistically significant difference between the arms. Only one event in the TONI arm, a rebleed before aneurysm treatment, could be adjudicated as probably related to the intervention. Likewise, regarding AEs, there were no statistically

significant differences between the arms. As expected, the occurrence of any AE was very common in the enrolled population, predominantly grade 5 and of older average age than in most aSAH trials.

Reasons for early termination

The trial recruited only 23 patients over 25 months; therefore, feasibility could not be confirmed and recruitment had to be terminated early. Furthermore, although by then centres had been opened in four European countries, participants were actually recruited only in the UK and Romania, and only 9 out of 15 open centres recruited participants. It was clear that this patchy enrolment pattern applied across both UK and Eastern European centres so that opening additional European centres did not seem likely to overcome the very slow recruitment. Various measures were taken to attempt to stimulate recruitment: we conducted local training with ITUs/neurosurgery departments and we offered feedback calls for units, as required, following on from site initiation visits/issues arising. We presented TOPSAT2 at multiple relevant conferences including the UK Neurointerventional Group, the European Association of Neurological Societies, the European Society of Minimally Invasive Neurological Therapy, the Society of British Neurological Surgeons, the British Neurovascular Group and the British Society of Neuroradiologists. We ran stands at multiple national/international conferences to raise awareness/profile. We held trial webinars for after 'conference season' as an ongoing awareness raiser and to specifically address/discuss equipoise issues as well as to assist with site/PI training. We addressed any issues arising and focused on recruitment in the trial monthly newsletter.

In addition, through one of the co-applicants, Mr Paul Brennan, we engaged further with the British Neurosurgical Trainees Research Collaborative to assist with TOPSAT2 screening and enrolment. We developed training materials/a slide-set for ITU staff and neurosurgeons. We also agreed on a policy of preferential enrolment with the EME-funded Subcutaneous Interleukin-1 Receptor Antagonist (SCIL) trial run from Manchester (this recruited patients of all SAH grades), so that neither trial interfered with recruitment of the other. Both trials actively encouraged their centres to recruit any SAH case eligible into either TOPSAT2 or SCIL, as appropriate (see *Appendix 5*).

A total of 1269 patients were assessed by centre using screening logs. These findings are summarised in *Table 2*.

Data from screening logs indicate that the proportion of poor-grade SAH patients was within the anticipated range (expected 22% and actual 24%) and that the medically eligible proportion of poor-grade patients was also very close to expected, at 48% (50% expected). The reasons for screened poor-grade SAH patients not being eligible were summarised in *Tables 2* and *3*.

The reason for non-eligibility was known for 240 out of 305 patients. Definite (known) contraindications (to trial enrolment) account for a majority of reasons for non-eligibility (147/240). Of non-medical reasons for non-eligibility, the lack of clinical equipoise (74/240) is by far the largest factor and accounts for 28% of all poor-grade patients overall (where the reason for non-eligibility was recorded). Of the 42 grade 4–5 patients screened as non-eligible but with no reason given for non-eligibility, it is possible, indeed probable, that a fair proportion of these were also medically eligible but lack of equipoise was not declared and recorded. It was the unexpectedly high 'lack of clinical equipoise' rate in otherwise medically eligible poor-grade patients that undermined recruitment, not timelines (15 patients) or lack of assent (four patients). Centres had to confirm such clinical equipoise regarding the question of treat all early regardless of improvement versus TONI (irrespective of whether that improvement was early or late) to participate in the trial and, indeed, several large UK centres that declared they lacked equipoise declined to participate on those grounds. 'Other' (18/240) comprises a large number of reasons but can be aggregated into three main groupings (more than one reason applying in some cases): timeline related (delayed presentation or admission to NSC, etc.) for 15 patients, query over grade for five patients, and a combination of reasons for non-eligibility for three patients.

There was a good conversion rate, of 23 out of 45 for patients screened as eligible, in TOPSAT2 (51% of eligible enrolled vs. 20% expected). Therefore, had the lack of clinical equipoise rate been remotely similar to that seen in the TOPSAT1 pilot (4%), recruitment would have been increased by ≈ 35 patients. In other words, there would have been a $< 150\%$ increase in recruitment during the trial recruitment period, rendering it feasible to have completed the trial with more centres opened.

It is uncertain what part the UK national drive towards treating aSAH within 48 hours may have played in that equipoise shift.[1,35] Although the National Clinical Guideline for Stroke[35] is clear that treatment within 48 hours refers to good-grade patients (as early coiling was proven in good-grade patients in the ISAT trial), it may well have influenced perceptions quite widely within NSCs, such that units may have been concerned that TOPSAT2 enrolment might make it appear that they were missing the '48 hours to secure aneurysm' target repeatedly. That was one of the contributory factors stated for not joining TOPSAT2 by some of the centres that declined to participate in the trial. The equipoise change is probably also due to a number of other reasons; all consultants and senior nursing staff managing a case had to be content with randomisation for this to be feasible. It transpired that a team consensus to clinical equipoise in participating centres was not the prevailing situation, whereas it might have tended to be so in the past if agreement to participate in a trial had been given by all relevant consultant groups. Indeed, even the understanding of the concept of clinical equipoise as it applies to an individual patient may have worsened with time, and/or a mindset of defensive medicine may affect clinical care trials such as this. Anything potentially perceived (even erroneously) as 'conservative management' is perceived as risky, although, of course, randomisation into a clinical care trial like TOPSAT2 is actually a very positive decision.[36,37]

Limitations

The TOPSAT2 trial aimed to compare a policy of securing a ruptured aneurysm in poor-grade patients early in all cases, with the aneurysm being treated expeditiously on neurological improvement (whether that was early or late was irrelevant). TONI had been the standard approach to management when aneurysm clipping was the main/only proven treatment (up until at least 2002). The trial PROBE design used in TOPSAT2 is a very well-validated and robust one that has proven successful in the neurointerventional field before. However, such an approach has been less successful in prior trials where neurointerventional treatment has been compared with 'conservative' management.[33,34]

Although TOPSAT2 was not a trial of conservative management, it was clear that the actual policy applied in most trial centres was ET in all cases, even though they had stated equipoise regarding the approach in response to pre-trial enquiries and in centre-declared expressions of interest. In other words, it seems that many clinicians in participating centres viewed TOPSAT2 as a de facto conservative management trial, even though it was not, and, therefore, they felt that they (or at least one of the team) were not in personal clinical equipoise to randomise.

This lack of equipoise was not seen in the earlier feasibility TOPSAT1 trial.[19] This change is probably for a number of reasons discussed above.

Relatives' assent was required for all TOPSAT2-screened eligible patients, and the relatives' approach to this may also have shifted towards ET. This is unsurprising given that they were often told that their relative was being transferred to a regional NSC for the aneurysm to be coiled, raising expectations of definite and early treatment. These factors combined led to an unfeasibly low recruitment rate (relative to time and target necessary), even though the conversion rate of screened, eligible patients was somewhat better than predicted.

The very modest sample size recruited is the major limitation of TOPSAT2. The preponderance of WFNS grade 5 patients would have been only a relatively minor limitation of the trial (as grade was a minimisation

criterion) if recruitment targets were able to have been met. The PROBE design and the multicentre/multinational recruitment with blinded outcome assessment are indeed strengths, but cannot negate the small sample size achieved.

Magnetic resonance imaging substudy

This was an exploratory and mechanistic component to the study and was intended to be run in the UK centres only. However, none of the UK centres that recruited patients was able to sign up to the substudy from the start of their participation. This was due to the logistical difficulties of performing detailed advanced MRI in this critically ill and unstable patient population (population as enrolled) on top of the effort required by centres to screen and enrol patients. This is despite all NSCs regularly performing MRI under general anaesthesia in children and some adults. However, general anaesthesia plus critically ill patient monitoring within the MRI environment is both technically challenging and very time-consuming of sparse human resources, such as critical care anaesthetists and nurses. Two centres did agree to the MRI substudy from the start but failed to enrol any patients into TOPSAT2, Newcastle being one of them. Several centres intended to enrol into the substudy once they had recruited 5–10 patients and they and their ITU had become familiar with the trial processes and protocol, etc. However, the trial closing very early precluded that extension.

Research MRI units exist in or near most UK university hospitals but they rarely have the facilities for general anaesthesia let alone the monitoring and care of critically ill patients, and they are most often not located within the main hospital building. Therefore, transport would be required as well, which would occupy even more extensively the time of a whole team of critical care staff to undertake MRI in research MRI facilities. Ultimately, no patients were enrolled in the MRI substudy. That of itself indicates that, at present, carrying out MRI in WFNS grade 5 aSAH patients in the UK is not feasible on a regular basis, and, thus, MRI biomarker studies in poor-grade SAH do not seem plausible currently within the UK NHS health-care environment.

Generalisability of trial findings

The low recruitment inevitably limits drawing any substantial conclusions about the management of poor-grade aSAH. However, the demographics in terms of sex and key comorbidities were as expected, although the population was, on average, older than is typical of aSAH patients. There were also some trends emerging within the population actually recruited into TOPSAT2 indicating that it may not reflect the generality of poor-grade aSAH. For instance, younger patients and those in WFNS grade 4 are under-represented in the TOPSAT2 RCT compared with the NCEPOD national sample.

The TOPSAT2 trial gives an indication of outcomes really only for WFNS grade 5 SAH patients and grade 4 patients aged > 60 years, neither group being well represented in either ISAT or the NCEPOD sample (regarding NSC admissions). Given that the clinical outcomes statistically are the same between arms, the results are likely to reflect the true clinical outcome for the sample population (WFNS grade 5 and older grade 4 patients).

Interpretation

Unfortunately, the low recruitment and early termination of TOPSAT2 preclude making many clear statements or recommendations. The subgroup of poor-grade SAH patients proved to be a difficult population in which to undertake a randomised trial, at least in the neurovascular field. The trial data do suggest that the care pathway for aSAH has improved in the 15 years since the ISAT trial, at least in part driven by a 48-hour target to treat aneurysms in good-grade patients. However, as a by-product, that 48-hour aspiration may have contributed to undermining equipoise to randomise patients into the trial. Younger patients, especially those in WFNS grade 4, were under-represented; this may well be because

the team/unit preference to treat immediately may have been more compelling given that, on average, both worse grade and older age are independent poor prognostic factors following aSAH.

However, if there are differences between the ET and TONI approaches they would appear to be modest at best, as no strong trends let alone statistically significant differences between the two management approaches were detected for mortality or functional clinical outcome in TOPSAT2 (or indeed in the preceding small TOPSAT1 feasibility study).

Although any interpretation of TOPSAT2 data must necessarily be limited, it is reassuring that no evidence was demonstrated that supported the hypothesis that ET would reduce mortality but lead to a large proportion of highly dependent survivors. The combined mRS 4–5 rate at 12 months was 2/11 for the ET arm compared with 1/12 for the TONI arm, and mortality was 6 versus 10 and not statistically different.

Chapter 5 Conclusions

Implications for health care

With regard to poor-grade aSAH management, at present, some units employ ET in nearly all patients routinely, some apply both ET and TONI on an ad hoc individual basis and others are (variably) selective in admissions regarding poor-grade SAH and some restrict admission to grade 4.[1] The TOPSAT2 data indicate no difference in outcome for the strategies of ET and TONI, albeit with the caveats discussed above (see *Chapter 4*). Therefore, the evidence suggests that TOPSAT2 is not able to provide data to indicate that the current heterogeneous approach to poor-grade management should change in one or another direction and, thus, that no service reconfiguration is necessary.

The use of MRI remains very challenging in aSAH patients, particularly in poor-grade patients. Therefore, caution should be employed when assessing any data on MRI in SAH – especially if generated on small sample sizes and/or extrapolating results from predominantly good-grade patients.

Future research implications

The RCT approach to poor-grade SAH management of TOPSAT2 proved unfeasible, and funding for a prospective observational study specific to this group was rejected by the National Institute for Health Research (NIHR) EME programme. It is also not likely to appeal to any other UK funder currently supporting studies in this clinical field given the scale of resources and study duration required, especially given the impact of the COVID-19 pandemic on charitable incomes. This leaves clinical audit approaches. A systematic comprehensive SAH patient audit has been proposed in the UK but does not yet exist. Anything less than a universal (all NSC units) and comprehensive (near 100% case ascertainment and inclusion) audit is inherently afflicted by many biases. These include admission and inclusion selection biases, data collection bias, transfer bias (losses to follow-up not random), interviewer bias, recall bias, outcome misclassification bias, confounding bias and performance bias. There is an ongoing voluntary UK and Ireland aSAH audit but it involves < 70% of NSCs; no measures exist to ensure 100% case ascertainment and all of the follow-up is undertaken and adjudicated by the clinical team looking after the patient, which is inherently open to major bias. Extension of the Stroke Sentinel National Audit Programme (SSNAP) to include SAH would probably be a better way to achieve that universal audit. However, no funding exists for such a development at present. Although it would not eliminate all the biases mentioned above, it could deal with some and ameliorate others. The linkage of SSNAP data to quality improvement markers, and thus NHS funding, has proven successful in the ischaemic stroke care setting.

Randomised controlled trials of proven design overcome most biases. However, RCTs of management pathways or so called 'clinical care trials', although often called for, have proven difficult, certainly in the neurovascular field.[38] If we are to provide patients with optimal, prudent care in the context of uncertainty and perform such trials then it does seem to require a major change in the mentalities of clinicians, other health-care staff and patients/relatives alike. Recognition that the answer to a care question was valuable and needed (with supporting survey and indeed feasibility study evidence) no longer seems to be enough. Innovative trial methodologies, such as step-wedge or cluster RCTs, may not map well onto the sort of specialised management care pathways that TOPSAT2, TEAM[36] and ARUBA[39] have attempted to investigate – where units that perform the treatment are relatively few and where key team leaders will frequently interact regionally, nationally and internationally. These trials' collective experience does raise the question of whether or not it is appropriate that trials aimed at evaluating clinical care have a fixed, limited time period to provide an

answer (recruitment 'feasibility') while potentially unjustified clinical care continues 'unquestioned' over an unlimited time period. In such clinical care questions, it is more likely than not that one approach is indeed somewhat better than the other, but if both approaches continue in the long term it is clearly likely to be to the detriment of some of those receiving the clinical care in question.

The use of MRI biomarkers looks promising in aSAH but the TOPSAT2 experience indicates that, at least in the subgroup of poor-grade patients, routine use of such MRI in the UK remains some way off and is associated with major logistical barriers in any health-care system. More traction might exist for the investigation and validation of MRI biomarkers in good-grade patients (not requiring a critical care support team for scanning), but studies would need to be correspondingly much larger, given that the number of (poor) outcome events is much lower in good-grade patients, amplifying the costs of such studies, which per patient are already high.

Acknowledgements

Contributions of others

Professor Peter Andrews (Consultant and Honorary Professor) was chairperson of the DMC and reviewed the final report.

Professor Jens Fiehler (Director of Diagnostic and Interventional Radiology) was a member of the TSC and reviewed the final report.

Professor Alex McConnachie (Professor of Clinical Trial Biostatistics) was an independent statistician on the DMC and reviewed the final report.

Dr Andrew Molyneux (Consultant Neuroradiologist) was a member of the DMC and reviewed the final report.

Contributions of authors

Philip White (https://orcid.org/0000-0001-6007-6013) (Translational and Clinical Research Institute, Newcastle University) was chief investigator for TOPSAT2, helped conceive the multicentre trial and develop the trial protocol, chaired the Trial Management Group (TMG), helped draft the report and edited it for important intellectual content.

Barbara Gregson (https://orcid.org/0000-0003-4868-9137) (Principal Research Associate, Neurosurgical Trials Group) was co-investigator and statistician for TOPSAT2, helped conceive the multicentre trial and develop the trial protocol, analysed the data, helped draft the report and edited it for important intellectual content.

Elaine McColl (https://orcid.org/0000-0001-8300-3204) (Professor of Health Services Research, Newcastle University) helped finalise the trial protocol, was a TMG member and edited the report for important intellectual content.

Paul Brennan (https://orcid.org/0000-0002-7347-830X) (Senior Clinical Lecturer, Neurosurgery, University of Edinburgh) contributed to neurosurgical engagement and recruitment.

Alison Steel (https://orcid.org/0000-0003-1279-1455) (Senior Trial Manager, Newcastle Clinical Trials Unit) helped finalise the trial protocol, was a TMG member and edited the report for important intellectual content.

Philippa Watts (https://orcid.org/0000-0003-3523-5101) (Trial Manager, Newcastle Clinical Trials Unit) set up and worked with study sites, conducted trial management and contributed to drafting and editing the final report for important intellectual content.

Ruth Wood (https://orcid.org/0000-0002-8296-1774) (Data Manager, Newcastle Clinical Trials Unit) designed and set up the trial-specific database, managed central data processes, reviewed study results and edited the final report.

Clare Bowes (https://orcid.org/0000-0002-9212-5315) (Professional and Administrative Services Officer, Faculty of Medical Sciences, Newcastle University) carried out data collection, data entry and revision of the report manuscript for important intellectual content.

Mohsen Javadpour (https://orcid.org/0000-0001-9836-1741) (Consultant Neurosurgeon, National Neurosurgical Centre, Beaumont Hospital) was chairperson of the TSC and had input in and final approval of the version of the report.

Amanda Weston (https://orcid.org/0000-0002-8119-1050) (independent layperson) contributed to public and patient involvement and reviewed and edited the final report.

Dipayan Mitra (https://orcid.org/0000-0002-1891-5415) (Consultant Neuroradiologist, Department of Neuroradiology, Royal Victoria Infirmary) contributed to the development of the study hypothesis, collection of pilot data, grant application, trial management, initiation of sites and writing of the manuscript.

Data-sharing statement

Fully anonymised data from this trial will be available to the scientific community subject to appropriate ethics approval and TSC agreement. Requests for anonymised data should be directed to the corresponding author.

References

1. National Confidential Enquiry into Patient Outcome and Death (NCEPOD). *Managing the Flow? A Review of the Care Received by Patients who were Diagnosed with an Aneurysmal Subarachnoid Haemorrhage*. London: NCEPOD; 2013.
2. Patel A BV, King D, Quayyum Z, Wittenberg R, Knapp M. *Executive Summary Part 2: Burden of Stroke in the Next 20 Years and Potential Returns from Increased Spending on Research*. London: Stroke Association; 2017.
3. Teasdale GM, Drake CG, Hunt W, Kassell N, Sano K, Pertuiset B, De Villiers JC. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurosurgical Societies. *J Neurol Neurosurg Psychiatry* 1988;**51**:1457. https://doi.org/10.1136/jnnp.51.11.1457
4. Whitfield PC, Kirkpatrick PJ. Timing of surgery for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2001;**2**:CD001697. https://doi.org/10.1002/14651858.CD001697
5. Li H, Pan R, Wang H, Rong X, Yin Z, Milgrom DP, *et al.* Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. *Stroke* 2013;**44**:29–37. https://doi.org/10.1161/STROKEAHA.112.663559
6. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P, international subarachnoid aneurysm trial (ISAT) collaborative group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005;**366**:809–17. https://doi.org/10.1016/S0140-6736(05)67214-5
7. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, Albuquerque FC. The barrow ruptured aneurysm trial. *J Neurosurg* 2012;**116**:135–44. https://doi.org/10.3171/2011.8.JNS101767
8. Bergui M, Bradac GB. Acute endovascular treatment of ruptured aneurysms in poor-grade patients. *Neuroradiology* 2004;**46**:161–4. https://doi.org/10.1007/s00234-003-1143-5
9. Bracard S, Lebedinsky A, Anxionnat R, Neto JM, Audibert G, Long Y, Picard L. Endovascular treatment of Hunt and Hess grade IV and V aneuryms. *AJNR Am J Neuroradiol* 2002;**23**:953–7.
10. Suzuki S, Jahan R, Duckwiler GR, Frazee J, Martin N, Viñuela F. Contribution of endovascular therapy to the management of poor-grade aneurysmal subarachnoid hemorrhage: clinical and angiographic outcomes. *J Neurosurg* 2006;**105**:664–70. https://doi.org/10.3171/jns.2006.105.5.664
11. Taylor CJ, Robertson F, Brealey D, O'shea F, Stephen T, Brew S, *et al.* Outcome in poor grade subarachnoid hemorrhage patients treated with acute endovascular coiling of aneurysms and aggressive intensive care. *Neurocrit Care* 2011;**14**:341–7. https://doi.org/10.1007/s12028-010-9377-7
12. van Loon J, Waerzeggers Y, Wilms G, Van Calenbergh F, Goffin J, Plets C. Early endovascular treatment of ruptured cerebral aneurysms in patients in very poor neurological condition. *Neurosurgery* 2002;**50**:457–64. https://doi.org/10.1097/00006123-200203000-00005
13. Pereira AR, Sanchez-Peña P, Biondi A, Sourour N, Boch AL, Colonne C, *et al.* Predictors of 1-year outcome after coiling for poor-grade subarachnoid aneurysmal hemorrhage. *Neurocrit Care* 2007;**7**:18–26. https://doi.org/10.1007/s12028-007-0053-5

14. Luo YC, Shen CS, Mao JL, Liang CY, Zhang Q, He ZJ. Ultra-early versus delayed coil treatment for ruptured poor-grade aneurysm. *Neuroradiology* 2015;**57**:205–10. https://doi.org/10.1007/s00234-014-1454-8

15. Weir RU, Marcellus ML, Do HM, Steinberg GK, Marks MP. Aneurysmal subarachnoid hemorrhage in patients with Hunt and Hess grade 4 or 5: treatment using the Guglielmi detachable coil system. *AJNR Am J Neuroradiol* 2003;**24**:585–90.

16. Phillips TJ, Dowling RJ, Yan B, Laidlaw JD, Mitchell PJ. Does treatment of ruptured intracranial aneurysms within 24 hours improve clinical outcome? *Stroke* 2011;**42**:1936–45. https://doi.org/10.1161/STROKEAHA.110.602888

17. Zhao B, Tan X, Yang H, Zheng K, Li Z, Xiong Y, Zhong M, AMPAS investigators. A multicenter prospective study of poor-grade aneurysmal subarachnoid hemorrhage (AMPAS): observational registry study. *BMC Neurol* 2014;**14**:86. https://doi.org/10.1186/1471-2377-14-86

18. Zhang Q, Ma L, Liu Y, He M, Sun H, Wang X, *et al.* Timing of operation for poor-grade aneurysmal subarachnoid hemorrhage: study protocol for a randomized controlled trial. *BMC Neurol* 2013;**13**:108. https://doi.org/10.1186/1471-2377-13-108

19. Mitra D, Gregson B, Jayakrishnan V, Gholkar A, Vincent A, White P, Mitchell P. Treatment of poor-grade subarachnoid hemorrhage trial. *AJNR Am J Neuroradiol* 2015;**36**:116–20. https://doi.org/10.3174/ajnr.A4061

20. Hadeishi H, Suzuki A, Yasui N, Hatazawa J, Shimosegawa E. Diffusion-weighted magnetic resonance imaging in patients with subarachnoid hemorrhage. *Neurosurgery* 2002;**50**:741–7. https://doi.org/10.1097/00006123-200204000-00010

21. Sato K, Shimizu H, Fujimura M, Inoue T, Matsumoto Y, Tominaga T. Acute-stage diffusion-weighted magnetic resonance imaging for predicting outcome of poor-grade aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2010;**30**:1110–20. https://doi.org/10.1038/jcbfm.2009.264

22. Yeo SS, Choi BY, Chang CH, Kim SH, Jung YJ, Jang SH. Evidence of corticospinal tract injury at midbrain in patients with subarachnoid hemorrhage. *Stroke* 2012;**43**:2239–41. https://doi.org/10.1161/STROKEAHA.112.661116

23. Rosenørn J, Eskesen V, Schmidt K, Rønde F. The risk of rebleeding from ruptured intracranial aneurysms. *J Neurosurg* 1987;**67**:329–32. https://doi.org/10.3171/jns.1987.67.3.0329

24. Naggara ON, White PM, Guilbert F, Roy D, Weill A, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy. *Radiology* 2010;**256**:887–97. https://doi.org/10.1148/radiol.10091982

25. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, *et al.* Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (STICH): a randomised trial. *Lancet* 2005;**365**:387–97. https://doi.org/10.1016/S0140-6736(05)70233-6

26. Mendelow AD, Gregson BA, Rowan EN, Francis R, McColl E, McNamee P, *et al.* Early surgery versus initial conservative treatment in patients with traumatic intracerebral hemorrhage [STITCH(trauma)]: the first randomized trial. *J Neurotrauma* 2015;**32**:1312–23. https://doi.org/10.1089/neu.2014.3644

27. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, STICH II investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet* 2013;**382**:397–408. https://doi.org/10.1016/S0140-6736(13)60986-1

28. Great Britain. *Mental Capacity Act 2005*. London: The Stationery Office; 2005. URL: www.legislation.gov.uk/ukpga/2005/9/contents (accessed 25 May 2021).
29. Bath PM, Gray LJ, Collier T, Pocock S, Carpenter J, Optimising Analysis of Stroke Trials (OAST) collaboration. Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials. *Stroke* 2007;**38**:1911–15. https://doi.org/10.1161/STROKEAHA.106.474080
30. Sarrafzadeh A, Haux D, Küchler I, Lanksch WR, Unterberg AW. Poor-grade aneurysmal subarachnoid hemorrhage: relationship of cerebral metabolism to outcome. *J Neurosurg* 2004;**100**:400–6. https://doi.org/10.3171/jns.2004.100.3.0400
31. White PM, Lewis SC, Gholkar A, Sellar RJ, Nahser H, Cognard C, *et al.* Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. *Lancet* 2011;**377**:1655–62. https://doi.org/10.1016/S0140-6736(11)60408-X
32. Coley S, Sneade M, Clarke A, Mehta Z, Kallmes D, Cekirge S, *et al.* Cerecyte coil trial: procedural safety and clinical outcomes in patients with ruptured and unruptured intracranial aneurysms. *AJNR Am J Neuroradiol* 2012;**33**:474–80. https://doi.org/10.3174/ajnr.A2836
33. Reeves BC, Langham J, Lindsay KW, Molyneux AJ, Browne JP, Copley L, *et al.* Findings of the international subarachnoid aneurysm trial and the national study of subarachnoid haemorrhage in context. *Br J Neurosurg* 2007;**21**:318–23. https://doi.org/10.1080/02688690701534748
34. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R, international subarachnoid aneurysm trial (ISAT) collaborative group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;**360**:1267–74. https://doi.org/10.1016/S0140-6736(02)11314-6
35. Royal College of Physicians (RCP) Intercollegiate Stroke Working Party. *National Clinical Guideline for Stroke*. 5th edn. London: RCP; 2016.
36. Raymond J. Reflections on the TEAM trial: why clinical care and research should be reconciled. *Can J Neurol Sci* 2011;**38**:198–202. https://doi.org/10.1017/S0317167100011343
37. Gifford F. So-called 'clinical equipoise' and the argument from design. *J Med Philos* 2007;**32**:135–50. https://doi.org/10.1080/03605310701255743
38. Raymond J, Darsaut TE, Molyneux AJ, TEAM collaborative group. A trial on unruptured intracranial aneurysms (the TEAM trial): results, lessons from a failure and the necessity for clinical care trials. *Trials* 2011;**12**:64. https://doi.org/10.1186/1745-6215-12-64
39. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, *et al.* Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicenter, non-blinded, randomized trial. *Lancet* 2014;**383**:614–21. https://doi.org/10.1016/S0140-6736(13)62302-8

Appendix 1 Twelve-month follow-up questionnaire

12-month follow-up questionnaire

This study is funded by the Efficacy and Mechanism Evaluation Programme
NIHR 13/29/83

About this Questionnaire

These questions ask about your health.

Please think carefully about each question. They can be answered by ticking the box next to the answer which applies to you.

If you are unsure how to answer any question, please give the best answer you can and write in any comments you want to make.

If you are unable to answer the questions yourself please ask a relative, friend or carer to help you.

If you make any errors whilst completing this form, please strike through the incorrect data with a horizontal line and initial and date any changes.

Please contact the study team if you have any uncertainty regarding completion.

If you would prefer to complete this questionnaire online please log on to the study website (www.topsat2.co.uk) using your study randomisati on number

Section 1

First some details about yourself and where you are living since completing your 6 month questionnaire.

1. Today's date? ☐ / / ☐

DD / MMM / YYYY

2. Please indicate who is completing this questionnaire:

Yourself ☐

Yourself with help ☐

Someone else ☐ (please specify relationship) _____

3. At present are you living:

Please tick only ***one*** of the boxes

At home alone ☐

At home not alone ☐

In a residential home ☐

In a nursing home ☐

In a hospital ☐

4. If you are living in a residential or nursing home when did you move there?

☐ / / ☐

DD / MMM / YYYY

Please could you read the following descriptions from people who have similar medical problems to you and choose the one which most closely describes your present state today?

Tick one box only below		mRS (Office use only)
	I have no symptoms at all and cope well with life.	0
	I have few symptoms but these do not interfere with my everyday life.	1
	I have symptoms which have caused some changes in my life but I am still able to look after myself.	2
	I have symptoms which have significantly changed my life and prevent me from coping fully, and I need some help in looking after myself.	3
	I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night.	4
	I have major symptoms which severely handicap me and I need constant attention day and night.	5

(Please tick ***one*** of the boxes only)

Section 2

These questions concern your health state today.

Please indicate which statement best describes your own health state today.

Mobility (Please tick ***one*** of the boxes only)

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self Care

(Please tick ***one*** of the boxes only)

I have no problems with self-care ☐

I have some problems washing and dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

(Please tick ***one*** of the boxes only)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

(Please tick ***one*** of the boxes only)

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

(Please tick ***one*** of the boxes only)

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Section 3

These questions concern the contacts you have had with hospital since completing your 6 month questionnaire.

1. The date that you completed your 6 month questionnaire was: ☐☐ / ☐☐ / ☐☐☐☐

DD / MMM / YYYY

2. Have you needed to go to hospital since your last questionnaire?

Yes ☐

No ☐

(Please tick ***one*** of the boxes only)

3. Was this for a routine follow-up appointment or for another reason?

Routine follow-up regarding your brain haemorrhage ☐

Emergency admission regarding your brain haemorrhage ☐

Something different not concerning your brain haemorrhage ☐

4. Did you have to stay in hospital?

Yes ☐ Number of days ☐☐☐

No ☐

5. What was the reason for your stay in hospital?

_____

_____

_____

_____

6. Have you experienced any other serious medical problems since your last questionnaire?

Yes ☐
No ☐

If yes, please give details:

_____

_____

_____

_____

Your answers to these questions will help us improve treatment for brain haemorrhage in the future. If there are any queries, we may contact you directly.

Thank you very much for filling in this questionnaire.

Please return it to:

in the stamped addressed envelope enclosed

If you need the help of a study team member to complete this questionnaire please telephone XXXX

Appendix 2 Expected adverse reactions

Frequencies are defined as common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); or not known (cannot be estimated from the available data).

Adverse events related to acute subarachnoid haemorrhage (neurological or systemic)

Condition	Common	Uncommon	Very rare
Neurological	Death, impaired CSF drainage related, vasospasm related, rebleed, brain swelling/oedema, neuropsychological and cognitive, stroke, epilepsy (and sequelae); depression	Additional aneurysm related, visual, cranial nerve palsy	Visual loss
Systemic	Cardiorespiratory; renal; infections (including pneumonia, urinary tract infection, cellulitis, ventriculitis and hospital-acquired infections); complications of prolonged immobility including falls (and sequelae), deep-vein thrombosis, pulmonary embolism, pressure sores, spasticity, pain; fluid balance and electrolytic disturbances including syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting; frailty	Myocardial infarction	

Adverse events related to aneurysm treatment (coiling or clipping)

Procedure	Common	Uncommon	Very rare
Coiling	Rupture, dissection/vessel perforation, anaesthetic related, arterial puncture site related, adjunctive drug related (such as heparin, aspirin, nimodipine), stroke, coil prolapse/parent vessel occlusion, vasospasm	Epilepsy, myocardial infarction, contrast media related, radiation related, death	Visual loss
Clipping	Stroke, infection, anaesthetic, drain insertion related, epilepsy, vasospasm	Brain retraction related, rebleed death, myocardial infarction	

Appendix 3 Baseline characteristics of participants by World Federation of Neurosurgical Societies grade

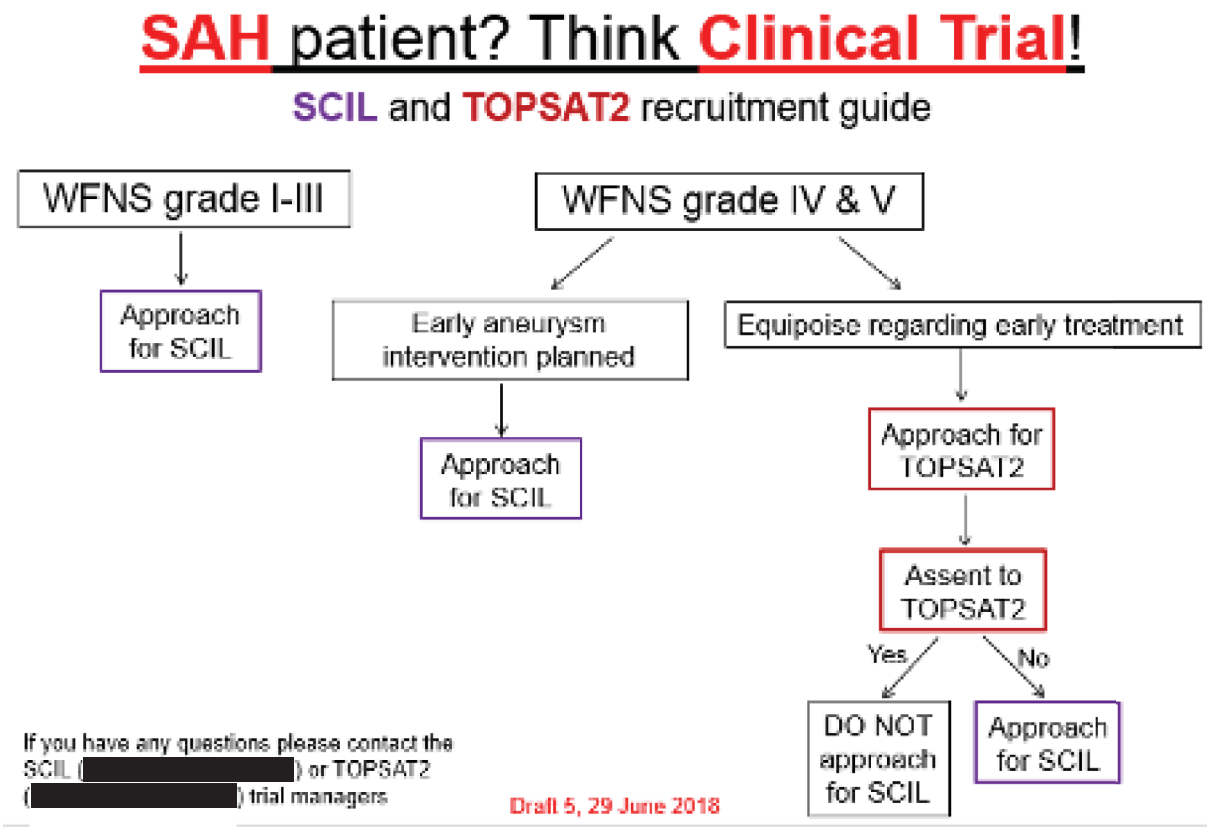
Randomised	WFNS 4 (*N* = 6)	WFNS 5 (*N* = 17)	Total (*N* = 23)
Age band (years), *n* (%)			
18–50	0	4 (24)	4 (17)
51–65	2 (33)	7 (41)	9 (39)
66–80	4 (67)	6 (35)	10 (43)
Sex, *n* (%)			
Male	2 (33)	6 (35)	8 (35)
Female	4 (67)	11 (65)	15 (65)
Site location, *n* (%)			
UK	3 (50)	13 (76)	16 (70)
Non-UK	3 (50)	4 (24)	7 (30)
Pre-stroke residence, *n* (%)			
At home alone	1 (17)	5 (65)	6 (26)
Home with family/friends	5 (83)	11 (29)	16 (70)
Sheltered housing	0	0	0
Other	0	1 (6)	1 (4)
Previous medical history, *n* (%)			
High blood pressure	4 (67)	6 (35)	10 (43)
Smoker	1 (17)	8 (47)	9 (39)
Fisher grade, *n* (%)			
1	0	0	0
2	0	0	0
3	1 (17)	2 (12)	3 (13)
4	5 (83)	15 (88)	20 (87)
Pre-stroke mRS, *n* (%)			
0	5 (83)	11 (65)	16 (70)
1	1 (17)	5 (29)	6 (26)
2	0	1 (6)	1 (4)
3	0	0	0
4	0	0	0
5	0	0	0

Randomised	WFNS 4 (*N* = 6)	WFNS 5 (*N* = 17)	Total (*N* = 23)
Time from ictus to randomisation			
Median (hours)	23.4	17.9	20.9
Minimum, maximum	13.8, 47.8	2.1, 47.5	2.1, 47.8
Q1, Q3	19.1, 45.5	8.1, 31.2	8.8, 39.2
Planned treatment, *n* (%)			
Endovascular	1 (17)	6 (35)	7 (30)
Neurosurgical	3 (50)	9 (53)	12 (52)
Other (not yet planned)	2 (33)	2 (12)	4 (17)

Appendix 4 Baseline characteristics of participants by location of centre (UK/non-UK)

Randomised	UK (*N* = 16)	Non-UK (*N* = 7)	Total (*N* = 23)
Age band (years), *n* (%)			
18–50	3 (19)	1 (14)	4 (17)
51–65	7 (44)	2 (29)	9 (39)
66–80	6 (38)	4 (57)	10 (43)
Sex, *n* (%)			
Male	4 (25)	4 (57)	8 (35)
Female	12 (75)	3 (43)	15 (65)
Pre-stroke residence, *n* (%)			
At home alone	3 (19)	3 (43)	6 (26)
Home with family/friends	12 (75)	4 (57)	16 (70)
Sheltered housing	0	0	0
Other	1 (6)	0	1 (4)
Previous medical history, *n* (%)			
High blood pressure	4 (25)	6 (86)	10 (43)
Smoker	7 (44)	2 (29)	9 (39)
WFNS, *n* (%)			
Grade 4	3 (19)	3 (43)	6 (26)
Grade 5	13 (81)	4 (57)	17 (74)
Fisher grade, *n* (%)			
1	0	0	0
2	0	0	0
3	2 (13)	1 (14)	3 (13)
4	14 (88)	6 (86)	20 (87)
Pre-stroke Rankin, *n* (%)			
0	9 (56)	7 (100)	16 (70)
1	6 (38)	0	6 (26)
2	1 (6)	0	1 (4)
3	0	0	0
4	0	0	0
5	0	0	0
Time from ictus to randomisation			
Median (hours)	21.9	17.9	20.9
Minimum, maximum	2.1, 47.8	4.4, 44.7	2.1, 47.8
Q1, Q3	8.5, 39.5	8.8, 25.1	8.8, 39.2
Planned treatment, *n* (%)			
Endovascular	7 (44)	0	7 (30)
Neurosurgical	5 (31)	7 (100)	12 (52)
Other (not yet planned)	4 (25)	0	4 (17)

Appendix 5 The SCIL/TOPSAT2 recruitment flow chart



EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library