Efficacy and Mechanism Evaluation programme

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

TOPSAT 2
TREATMENT OF POOR-GRADE
SUBARACHNOID HAEMORRHAGE
TRIAL 2

TREATMENT OF POOR-GRADE SUBARACHNOID HAEMORRHAGE TRIAL 2

TOPSAT2

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the UK Policy Framework for Health and Social Care Research, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

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TRIAL SUMMARY

Trial Title	Treatment of Poor-Grade Subarachnoid Haemorrhage 2
Acronym	**TOPSAT2**
Summary of Trial Design	Prospective, randomised, controlled, parallel group study with blinded outcome evaluation (PROBE).
Summary of Participant Population	Participants will be patients with WFNS grade 4/5 aSAH.
Planned global sample size	346
Planned UK sample size	**246**
Planned number of sites	30 (20 UK sites)
Intervention Duration	Participants will be randomised to receive either the standard local treatment for aneurysm, as soon as possible within 72 hours of ictus, or receive it after neurological improvement (to WFNS grade 1-3).
Follow up Duration	Participants will be followed up for a period of 12 months
Planned Trial Period	**1st August 2016 – 31st March 2021** (44 months recruitment: 1st Aug 2016 – 31st March 2020) (12 months follow up: 1st April 2020 – 31st March 2021)
Primary objective:	To establish the efficacy of a strategy of early aneurysm treatment (within 72h of ictus) in a population of World Federation of Neurosurgical Societies grade 4-5 (high grade) aneurysmal subarachnoid haemorrhage (aSAH) patients in comparison with the conventional strategy of treatment of aneurysm after neurological improvement (to WFNS grade 1-3).
Primary outcome:	Primary outcome is functional outcome at 12 months determined by ordinal analysis of modified Rankin score (mRS). Ordinal analysis results in substantially greater statistical power to detect a treatment effect. 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. Score ranges from 0 (no symptoms or disability) to 6 (death).
Secondary trial outcomes:	- Dichotomised mRS 0-3 vs 4-6; 0-2 v 3-6

- Mortality rate (30 days and 12 months; survival analysis will be undertaken)

- Re-bleeding rate from randomisation

- Treatment related complication rate and SAE report rates – reported as per standard CTU procedures. Details of treatment related/all SAEs will be added to the CRF and followed until resolution.

- Time in hospital to discharge and length of ITU/HDU stay

- mRS at discharge

- Functional outcome at six months determined by ordinal analysis of modified Rankin score (mRS)

MRI Sub-study objective: To explore whether brain Magnetic Resonance Imaging (MRI) markers in patients with high grade (4/5) aSAH are related to outcome, and whether they might be used to identify patients who would benefit from each treatment strategy – i.e. to stratify the management of grade 4-5 aSAH patients.

MRI Sub-study outcomes:

- Lesion load on DWI

- Fractional anisotropy values on DTI

- Brain perfusion/CSF parameters

- Endothelial permeability

- Blood-brain barrier integrity on MRI

CONTENTS

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ADL	Activities of Daily Living
aSAH	aneurysmal Subarachnoid Haemorrhage
AR	Adverse Reaction
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
eCRF	electronic Case Report Form
EME	Efficacy and Mechanism Evaluation programme
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
HELPS	Hydrocoil Endovascular aneurysm occlusion and Packing Study
ISAT	International Subarachnoid Aneurysm Trial
ISF	Investigator Site File
ISRCTN	The International Standard Randomised Controlled Trial Number
ITU	Intensive Therapy Unit
LCRN	Local Clinical Research Network
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NCEPOD	National Confidential Enquiry in Patient Outcome and Death
NIHR	National Institute for Health Research
NHS	National Health Service
NSU	Neurosciences Unit
NRES	National Research Ethics Service

NUTH	The Newcastle upon Tyne Hospitals NHS Foundation Trust
PI	Principal Investigator
PIS	Patient Information Sheet
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAH	Subarachnoid haemorrhage
STICH	Surgical Trial in Intra-Cerebral Haemorrhage
TMG	Trial Management Group
TOPSAT	Treatment of Poor-grade Sub-arachnoid Haemorrhage Trial
TSC	Trial Steering Committee
WFNS	World Federation of Neurosurgical Societies

1. BACKGROUND

Aneurysmal Subarachnoid Haemorrhage (aSAH) is one of the major causes of haemorrhagic stroke; its incidence is ~80 per million population per year[1]. aSAH often affects young, previously fit people. Peak occurrence is in 40-60 age range, it often has a poor prognosis and so it carries a disproportionate socio-economic burden – aSAH accounts for just 5% of strokes, yet 20% of the quality adjusted life years (QALYs) lost to stroke, much of that loss concentrated in high grade aSAH patients[1-3]. 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 £8 billion per annum in the UK.[2]

Existing research

In order 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 being the most widely used.[4] Patients with WFNS grades 1 to 3 are considered "good grade" patients. 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 and 5 are considered poor or "high grade" and generally have considerably worse outcomes than grades 1-2. Traditionally neurosurgical clipping of aneurysms in these patients has been deferred until the patients' 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[5].

In more recent years, intracranial aneurysms have been treated primarily by endovascular coiling (85% coiling rate in recent National Confidential Enquiry into Patient Outcome and Death [NCEPOD] report[1]). Packing the aneurysm with platinum coils via 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.[6-8] 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 usually not considered for clipping unless they make substantial clinical improvement. The landmark, UK-led, ISAT trial compared coiling with clipping, but included predominantly grades 1-3. Just 5% of patients recruited into ISAT were in grades 4-5. The small numbers of high-grade patients enrolled, and likely differential centre enrolment bias around grade meant that no conclusions on poor grade management can be drawn. Overall 37% [46/123] of grade 4-5 patients enrolled in ISAT had a good outcome at one year (alive and independent) compared with 75% for grade 1-3 patients.[7] In the only other substantial trial of aneurysm coiling versus clipping, a more representative 19% (91/471) of patients were grade 4-5, but outcome data by individual clinical grade (on randomisation) were not presented; however, odds ratio for poor outcome was 3.51 (95% CI 2.21-5.68) for grades 3-5 inclusive, compared with grades 1-2, on multivariate analysis[8].

The conventional management strategy for grades 4-5 (treat on neurological improvement), incurs a risk of aneurysm re-bleed. Patient outcome if a re-bleed occurs prior to aneurysm treatment is dismal - >80% poor outcome[7, 8]. Grade 4-5 patients are also thought to have a higher aneurysm re-bleed rate than grade 1-2 patients, and this risk is highest soon after the first bleed[5].

Therefore, reducing the chance of re-bleeding 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[10-17]. One larger-sized (459 patients) heterogeneous population study found evidence that treatment of ruptured intracranial aneurysms within 24 hours of aSAH improves medium- and long-term clinical outcome[9]. The benefit of ultra-early treatment was even more apparent for patients treated with endovascular coiling.

Review of prior literature on early coiling published from 2002 (when coiling became a proven aneurysm therapy) until 2015 identified eight relevant studies[10-17]. Unfortunately, none of these studies have a control group and most are small, retrospective studies carried out in a single centre, and therefore suffer from inherent selection, review and recall bias. Overall, this is a very heterogeneous group of studies in terms of methodology, inclusion criteria, treatment timing, 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 is 15% better than ISAT results, despite studies in the summary analysis including more WFNS grade 5 patients than were enrolled in ISAT (1%). The primary and overriding difference between the ISAT trial and the subsequent acute aneurysm treatment literature is the timing of aneurysm treatment.

A Chinese Registry of high grade SAH (with a target of 226 patients) is ongoing – ChiCTR-TNRC-10001041. This is an observational rather than a randomised study, examining outcomes rather than management strategy. A randomised high grade trial protocol for a single Chinese centre has also been published recently– ChiCTR-TRC-12002917. However, this proposes a trial of 99 patients examining timing of clipping in three groups of 33 (at <3 days, 3-7 and >7 days) - none of which is truly early aggressive aneurysm treatment. On both grounds (treatment modality and timelines) it is not comparable with TOPSAT2.

Newcastle feasibility pilot – TOPSAT 1[18]

TOPSAT 1 was carried out in a single UK neuroscience centre (The Newcastle upon Tyne Hospitals NHS Foundation Trust). Adult patients with WFNS grade 4-5 aSAH were randomised within 24 hours of neuroITU admission to early treatment arm or treatment after neurological improvement arm with analysis on an intention to treat basis. If randomised to early treatment, 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 Score (GCS) [and thus derivation of WFNS grading] prior to intubation/ventilation was sought from the hospital transfer/referral letter.

Exclusion criteria were: a) age over 75 years b) signs of brainstem death not promptly reversed by anti-cerebral oedema treatment c) pure intra-ventricular haemorrhage d) large intra-cerebral haematoma requiring immediate surgical clot evacuation e) pregnancy f) cardiorespiratory instability g) lack of clinical equipoise.

An appropriate clinician (ITU consultant / registrar or neurosurgical consultant / registrar or neuroradiology consultant) discussed the trial and provided written information to the next of kin. The clinician returned after a maximum of four 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. A screening log was completed, recording the number of patients assessed, the number meeting inclusion criteria and the number excluded because of the presence of one or more exclusion criteria (and if excluded, the reason for it).

50 patients admitted to ITU with grade 4-5 aSAH were screened from August 2008 to January 2011. Fourteen patients were eligible for the TOPSAT 1 trial (28%). Eight out of 14 were randomised (57%); four male and four female with 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 early treatment arm and three patients were randomised to treatment after neurological improvement arm. Of patients in the early treatment arm, three patients had a WFNS grade of 5 and 2 had WFNS grade of 4. Of patients in the treatment after neurological recovery arm, two patients had WFNS grade of 5 while one had WFNS of grade 4.

There were no treatment-related adverse events related to endovascular aneurysm treatment in either arm. No patients were lost to follow-up or crossed over in TOPSAT 1.

Functional outcomes were assessed at the time of discharge and at six months following ictus using standard modified Rankin score (mRS) questionnaire. There was no statistical difference between the arms (but numbers in this feasibility pilot were very small and it was not powered for formal analysis of efficacy).

TOPSAT 1 demonstrated that recruitment into a randomised controlled trial of management policy for grade 4-5 aSAH patients is feasible. Recruitment rate among patients eligible for the study was encouraging at 57%. However, TOPSAT 1 did not have stroke research/comprehensive local research nurse/network support, which limited recruitment to five days per week, rather than seven; no specific trial funding was secured and TOPSAT 1 had narrower eligibility criteria than is proposed in TOPSAT 2. Also since TOPSAT 1 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 TOPSAT 1 screening log, we estimate that at least 12 additional patients would have been eligible for TOPSAT 2 (52% overall eligibility) - 10% by eliminating delays to randomisation by SRN/CLRN support, 6% by including patients up to age 80, 8% by utilisation of an appropriate consultee for assent. So we have good evidence to support an appreciably higher participation rate being achieved from the aSAH population in TOPSAT 2 than the TOPSAT 1 pilot.

Manchester audit of high-grade SAH

Additional data on grade 4-5 patients was sought from the earlier Manchester audit of high grade SAH (Mr H Patel, Consultant Neurosurgeon, Salford Royal NHS Foundation Trust; personal communication). 80 patients were admitted to Salford neuro ITU over a two year period, of whom 21 improved in neurological status quickly (25%); 44/59 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 TOPSAT 2 – so again an approximately 50% eligibility rate.

NCEPOD report

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

The NCEPOD report also highlights the heterogeneity of current UK management of grade 4-5 aSAH patients both in terms of admission rates and subsequent management. Grades 4-5 comprised between 8% and 50% of admissions and some units never admitted grade 5 patients. Overall, 22% of patients in NCEPOD report were WFNS grade 4-5 on admission to NSU, with approximately equal numbers in each grade. 38% of grade 4 and 15% of grade 5 patients had a good functional outcome on discharge. This indicates that the "real world" current good outcome rate in aSAH grade 4-5 patients admitted to NSU in the NHS averages only 24%, compared with case series literature indicating >50% good outcome with early aneurysm treatment.[1]

Biomarkers of aSAH outcome

One of the challenges in managing patients with grade 4-5 aSAH 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 SAH are not a homogeneous group, and some patients' true clinical grading is unknown because they have been previously ventilated and intubated for transfer. There could be other more accurate early predictors of outcome which 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 aneurysm early and aggressively. Neurological damage following SAH 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 three days following ictus, and then evolves to a variable degree of neurological damage up to around four 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 exploratory MRI mechanistic study proposed has two rationales. The first is to establish whether MRI can be used to guide the decision on early versus deferred treatment. The second is to measure the risks posed to nervous tissue by aneurysm repair and to relate this to timing.

Imaging biomarkers

We have identified a number of specific MR-based biomarkers, which may be hypothesised to have potential predictive power in this setting. These include changes in overall cerebral perfusion, the presence of increased intra-cerebral pressure with associated changes in cerebral tissue compliance, the presence of dysfunctional auto-regulatory hydrodynamics, and the presence of early inflammatory change. Diffusion-weighted magnetic resonance 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 grades 4-5 than grades 1-2[19]. Furthermore, studies suggest that the more extensive the changes on DWI in grade 4-5 aSAH patients, the worse the prognosis[20]. 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 cortico-spinal tract in patients with SAH who have focal limb weakness[21]. 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 MR has been demonstrated to reveal breakdown in the Blood Brain Barrier [BBB] (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.

2. RATIONALE

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

Although we have good evidence that significantly fewer rebleeds occur in patients in good clinical grades compared to those in high grade, there are additional procedural risks in high grade patients[22]. Therefore at present the management of high grade aSAH is based on individual or team experience, although there is a clear trend for these patients being treated more aggressively, mostly with early coiling. This is mainly because, with 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 haemorrhage is greatest. However, this is not an evidence-based approach and potentially exposes healthcare 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)
- costs of possibly unnecessary aneurysm coiling (staff, infrastructure and consumables)
- drive to deliver weekend coiling services locally rather than by potentially cheaper networking (networking may be a good option for grade 1-3 aSAH patients but not for grade 4-5 patients for whom extra transfer between centres may be risky, resource intensive and costly).

Conversely, if an early treatment strategy (primarily with coiling) of grade 4-5 aSAH patients was proven in a RCT to be superior, there is a compelling argument that it should be provided to all patients. Endovascular services would need to be extended to cover seven 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 due to lack of endovascular service. Currently approximately one quarter of UK neuroscience units offer a robust seven day coiling service (NCEPOD[1] + UK Neurointerventional Group [UKNG] survey 2013 - undertaken on behalf of the UKNG by Prof White).

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 CT study, 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 long-term care and rehabilitation. 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 socio-economic impact is also disproportionately high.

2.1 Risk Assessment

For many neurosurgeons / interventional neuroradiologists in UK neuroscience units (NSU) there is genuine uncertainty (clinical equipoise) regarding whether to treat all grade 4-5 aSAH patients as soon as possible or not; this also has service provision implications. The main risk in TOPSAT2 is 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. We estimate this would occur, related to early treatment procedure in no more than 10-15/170 patients enrolled into the early treatment arm.

The risk of modern aneurysm coiling related-morbidity/mortality is around 3-5%, although it may be slightly higher in grade 4-5 patients (unclear from existing RCT data).[15,23] However, we know that re-bleeding from an aneurysm has an awful prognosis (82% poor outcome in ISAT across all grades) and that the re-bleed rate is also higher in grade 4-5 patients.[5,7]

By contrast, due to current clinical uncertainty, the potential benefits of determining the optimum management strategy for aSAH are considerable. If early treatment is proved, service reconfiguration would be necessary but the outcome for grade 4-5 aSAH patients in UK could be transformed. Studies on early treatment for grade 4-5 patients indicate good outcome rates around 50%, yet NCEPOD found many grade 4-5 patients are not admitted to a NSU in the UK.[1] Even when patients are admitted, very few Neuroscience units provide treatment seven days per week. Furthermore, delays to treatment were correlated with poor outcome. There are almost 1300 grade 4-5 aSAH patients per annum in the UK, and NCEPOD data show that <25% currently have a good outcome, yet almost 50% might with early aggressive 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 high grade aSAH to be truly individualised, which imaging biomarkers can potentially help to deliver.

If treatment after neurological improvement was at least as good as early intervention, fewer patients would need NSU admission, savings on coils and other consumables could be made immediately and simpler options would be viable for coiling service reconfiguration – all considerable and tangible benefits of undertaking TOPSAT 2.

3. OBJECTIVES AND OUTCOME MEASURES

3.1 Primary Objective

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

3.2 MRI sub-study Objective (in 100 participants)

To explore whether brain Magnetic Resonance Imaging (MRI) markers in patients with high [4-5] grade aSAH are related to outcome, and whether they might be used to identify patients who would benefit from each treatment strategy – i.e. to stratify the management of grade 4-5 aSAH patients.

3.3 Primary Endpoint/Outcome

Primary outcome is functional outcome at 12 months determined by ordinal analysis of modified Rankin score (mRS). Ordinal analysis results in substantially greater statistical power to detect a treatment effect. 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. Score ranges from 0 (no symptoms or disability) to 6 (death).

3.4 Secondary Endpoints/Outcomes

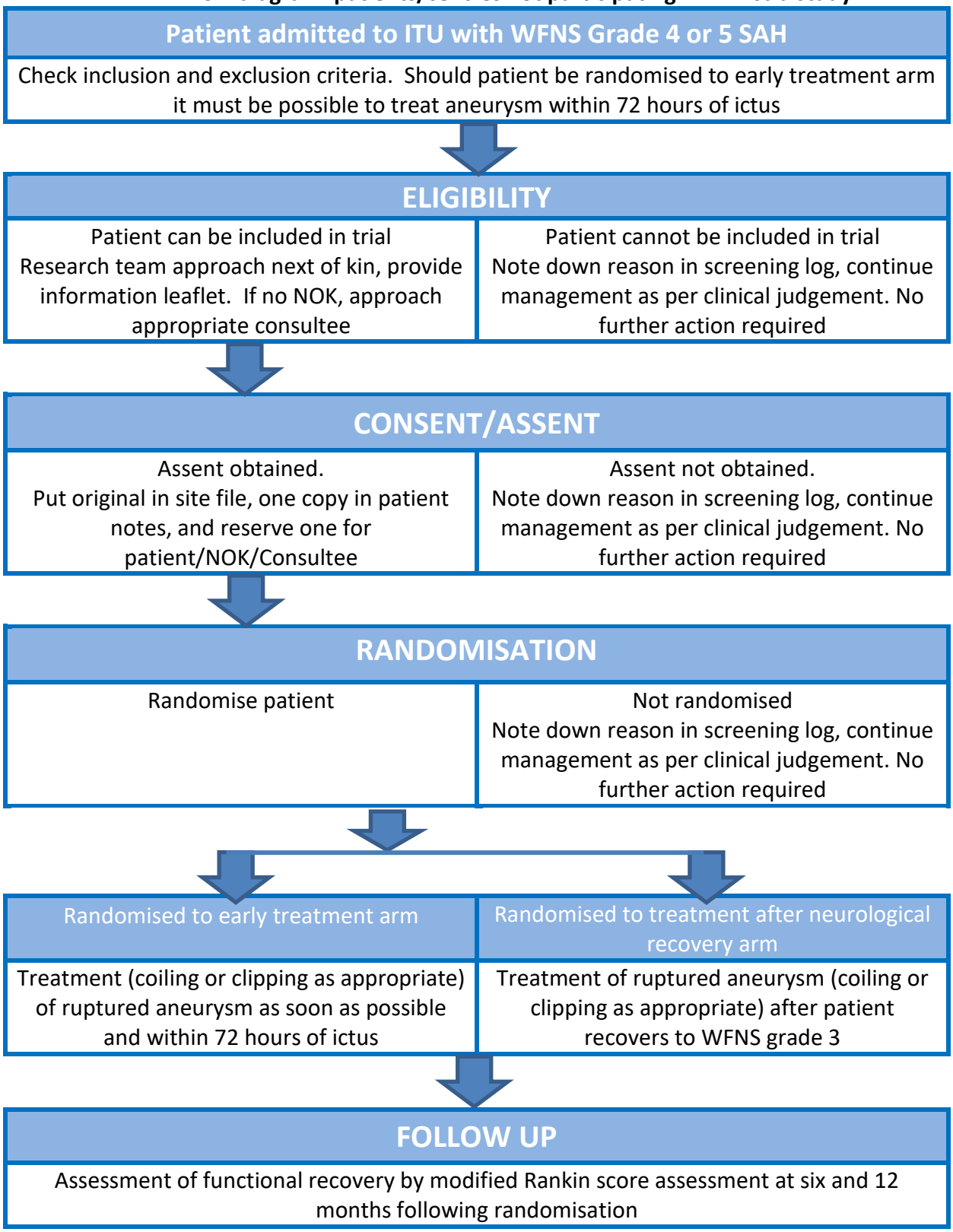
- Dichotomised mRS: 0-3 vs 4-6; 0-2 vs 3-6
- Mortality rate (30 days and 12 months; survival analysis will be undertaken)
- Re-bleeding rate from randomisation
- Treatment related complication rate and SAE report rates – reported as per standard CTU procedures. All SAEs, and their relatedness to treatment, will be added to the CRF and followed until resolution.
- Time in hospital to discharge and length of ITU and HDU stay
- mRS at discharge
- Functional outcome at six months determined by ordinal analysis of modified Rankin score (mRS)

3.5 MRI sub-study Outcomes

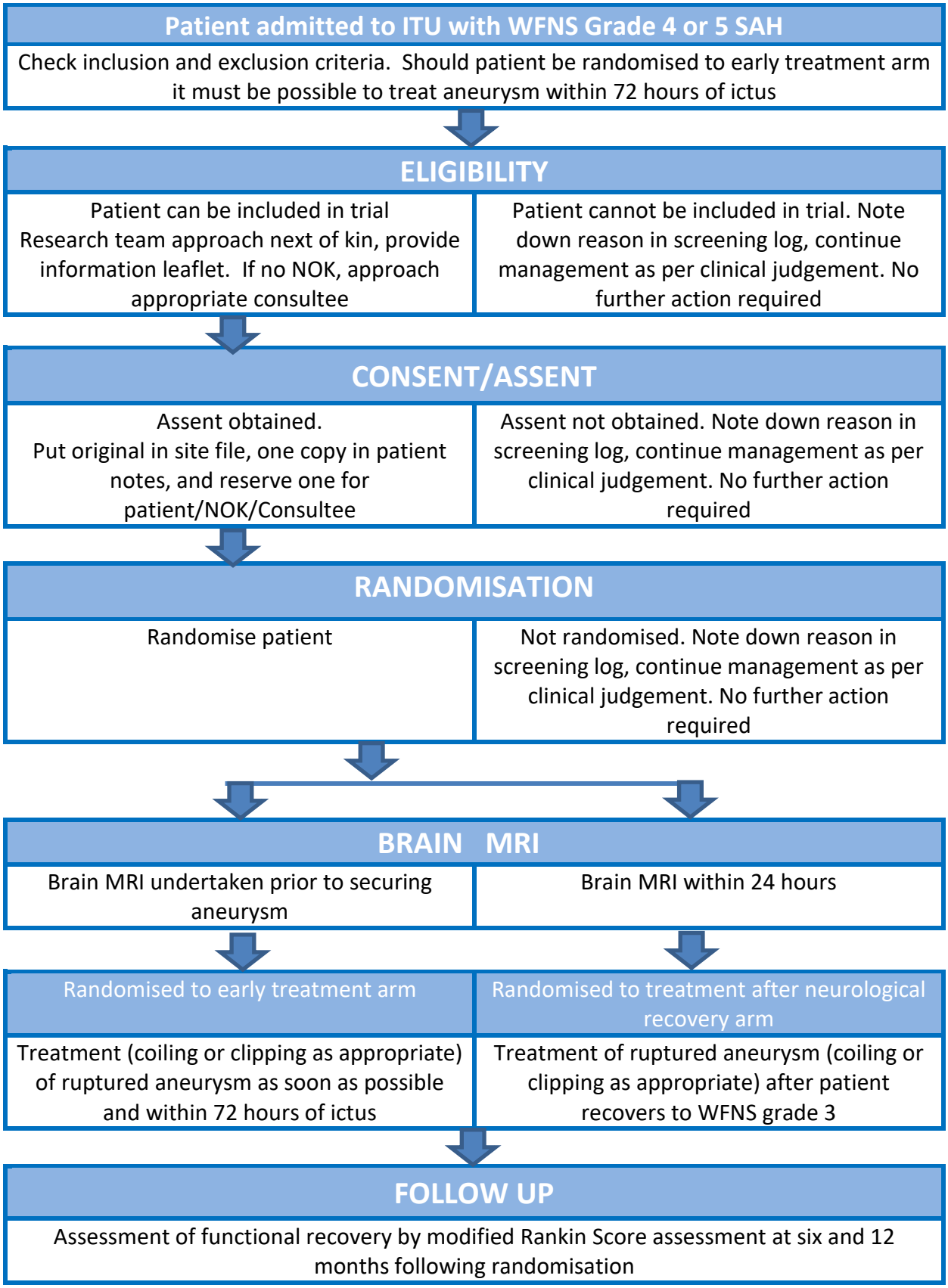
- Lesion load on DWI
- Fractional anisotropy values on DTI
- Brain perfusion and CSF parameters
- Endothelial permeability
- Blood-brain barrier integrity on MRI

4. TRIAL DESIGN

Flow diagram: patients/centres not participating in MRI sub-study



Flow diagram: centres/patients participating in MRI sub-study



5. STUDY SETTING

This is a study of patients admitted with WFNS grades 4 and 5 aneurysmal SAH. As these patients usually have depressed GCS they frequently require airway protection and ventilation. Therefore all patients considered for recruitment in this study are likely to be admitted to an intensive therapy unit or neuro high dependency unit (ITU/HDU). In neurosciences centres these patients are likely to be in neuro ITU rather than general ITU, for management by a specialist neuro critical care team. Patients who are randomised to the early treatment arm are likely to remain in ITU/HDU prior to aneurysm treatment. Some patients who are randomised to the treatment after neurological recovery arm may be discharged from ITU/HDU prior to aneurysm treatment. However, as a large number of patients with high-grade SAH have multi-system disorders such as cardio-respiratory insufficiency, it is expected that a substantial proportion of patients randomised to the treatment after recovery arm will remain in ITU/HDU for a substantial proportion of their hospital stay, prior to aneurysm treatment.

6. ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

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

BEFORE INCLUDING A PARTICIPANT IN THE TRIAL, IT MUST ALSO BE CONFIRMED THAT IT WILL BE POSSIBLE TO TREAT THE PARTICIPANT WITHIN 72 HOURS OF ICTUS, SHOULD THEY BE RANDOMISED TO THE EARLY TREATMENT ARM.

6.2 Exclusion Criteria

- Age < 18 or > 80 years
- WFNS grade 1-3, or uncertain WFNS grade (where patient recovers quickly and proves not to be of true high grade)
    - Patients of uncertain grade on transfer to a neuroscience unit where a formal sedation hold is undertaken at the neurosciences centre and the patient is established to be truly grade 4 or 5 will be eligible for trial
    - This will also apply to patients of uncertain grade undergoing sedation hold after insertion of external ventricular drain (EVD) or other early intervention for hydrocephalus
- Signs of coning or brain death not promptly reversed by anti-cerebral oedema treatment
- Pure intraventricular haemorrhage (no SAH)
- Large intracerebral haematoma which requires immediate clot evacuation
- Significant aneurysmal SAH-related haemodynamic instability
- Lack of clinical equipoise
- Lack of assent/consent
- Pregnancy
- Pre SAH modified Rankin score >2
- Pre-existing severe co-morbidity such that clinical follow up at 12 months is judged unlikely
- Non-saccular, Mycotic, giant or other atypical aneurysm

For MRI sub study only

- Known absolute contra indication to MRI

7. TRIAL PROCEDURES

7.1 Recruitment

Once a high grade SAH patient is admitted to neuroITU/HDU (or equivalent) in a trial centre, the patient will be stabilised from neurological and cardio-respiratory points of view as per local protocol. If the patient was initially admitted to a different hospital, confirmation of the WFNS grade prior to intubation/ventilation will be sought from the referral letter or by directly contacting the referring team. If the WFNS grade before the patient was intubated/ ventilated could not be established, the patient will be considered to be of uncertain grade (WFNS U) and will be ineligible for the study unless subsequent formal sedation hold and re-assessment confirms high grade. However, there will be no requirement in the trial centre to confirm the patient's WFNS grade by reversing sedation in ITU. Once aneurysmal SAH is confirmed and the patient is stable, the admitting neurosurgical/anaesthetic team will assess the patient with regard to eligibility for the trial.

7.2 Consent

An appropriate clinician (ITU consultant/registrar, neurosurgical consultant/registrar or interventional neuroradiology consultant/registrar) with documented responsibility on the delegation log, will discuss the trial and provide written Participant Information Sheet). The PI is responsible for ensuring that informed assent for study participation is given by each patient's NOK or relative, or by a nominated consultee, for patients fulfilling TOPSAT 2 eligibility criteria. A delegated individual will then return after an appropriate interval (maximum four hours) to allow adequate time for reflection, and obtain assent for the trial from the appropriate consultee.

The consent process for England/Wales/Northern Ireland and Scotland are detailed below.

England, Wales and Northern Ireland

The incapacitating nature of the condition precludes obtaining prospective informed consent from all, or nearly all, participants. Wherever possible we will aim to establish the views of the patient with regard to involvement in research from a Personal Consultee (England/Wales) or Next of Kin (Northern Ireland). However, given the time pressures of the study, this process should not cause unnecessary delay. If no Personal Consultee/NOK can be identified, then the researcher must nominate a person who has no connection to the study, who is not listed on the delegation log, and who is willing to be consulted about the participation of the person who lacks capacity, to act as a Consultee, usually the ITU consultant. For patients in England and Wales, the nominated Professional/Personal Consultee will complete a Consultee Declaration Form, which will be countersigned by the PI or delegated personnel. For patients in Northern Ireland, a Close Relative/friend Assent Form will be completed and countersigned by the PI or delegated personnel.

The original signed Consent/Declaration/Assent Form and a copy of the Participant Information Sheet will be retained in the Investigator Site File (ISF), with copies provided to the Personal Consultee/NOK or Nominated Consultee and clinical notes. A copy will also be sent to the Newcastle Clinical Trials Unit for central monitoring purposes.

Scotland

Consent will be sought from a Relative/Welfare Attorney during a face-to-face meeting. In the event that a Relative/Welfare Attorney is unable to attend immediately, verbal consent will be obtained in a telephone conversion. This will be documented on a telephone consent form and countersigned by the PI or delegated personnel and witnessed by a second member of staff and should be recorded in the clinical notes. The Relative/Welfare Attorney will provide written consent at the next available opportunity.

If necessary, NHS translation services will be utilised to discuss the trial. Written informed consent should always be obtained prior to randomisation and prior to study specific procedures or investigations.

Non-UK sites

Comparable consent processes will take place in each of the following non-UK countries; any significant differences to this process will be discussed and noted at the SIV visits.

- Czech Republic
- Latvia
- Lithuania
- Estonia
- Poland
- Hungary
- Romania

The right to refuse to participate without giving reasons must be respected.

7.3 Regaining capacity

If a participant regains mental capacity they should be fully informed about the study and their consent sought to continue in it. If they do not wish to remain in the study they must be withdrawn. Any data collected so far will be retained and analysed unless they refuse consent, in which case these must be destroyed. This is in accordance with the Mental Capacity Act 2005 in England and Wales and The Adults with Incapacity (Scotland) Act 2000 in Scotland. In Northern Ireland this is currently governed by common law. This also applies if the consultee makes the decision to withdraw a participant from the study before they regain capacity.

A fully anonymised screening log will be completed at each site, recording the number of patients assessed, the number meeting inclusion criteria, WFNS grade, time from ictus to admission, the number excluded and reason(s). Screening logs will be sent to NCTU monthly.

A record will be kept of the actual intervention carried out and the time and date received, in both arms. Consent/assent will be sought from the participant/consultee to inform the patient's GP by letter about their participation in the trial as soon as practicable following the intervention.

7.4 Randomisation

Randomisation will be carried out by the research team at sites through the use of a web-based system accessed via the trial website (www.topsat2.co.uk), and hosted by the Health Services Research Unit, University of Aberdeen. This service is available 24/7. Further information is

available in the randomisation SOP. The randomisation will utilise a minimisation algorithm with 80% chance of being allocated to the minimisation group to reduce differences in two arms with respect to the following (with 20% following a totally random allocation):

- Grade 4 and 5 (so distributed equally in the two arms)
- Participant age at the time of randomisation (age bands 18-50, 51-65 and 66-80)
- Presence of clinically significant hydrocephalus requiring CSF drainage procedure (yes/no)
- UK/non-UK centre.

The randomisation service will automatically confirm randomisation details to the person carrying out the randomisation, and NCTU, by email.

If the patient is randomised to the early treatment arm, the result of randomisation will be communicated to the neurovascular team who will treat the aneurysm. They will decide on the most appropriate treatment strategy but, as per the RCT evidence base, if the aneurysm is technically amenable to coiling, coiling will be the initial therapeutic option. The usual institutional surgical consent form for the procedure will then be completed and the aneurysm must be treated within 24 hours of randomisation, and 72 hours of ictal bleed that led to hospital admission.

If the patient is randomised to the treatment after neurological improvement arm, the result will be communicated to the ITU and neurovascular team who will carry on managing the patient as per established protocol. Once the patient's neurological status improves to WFNS grade 3 or better (or GCS 13-15 or equivalent if WFNS is not assessed), the aneurysm will be treated expeditiously (by coiling, if technically amenable to coiling). According to the natural history of the disease, this improvement may take several weeks and in some may never happen. On the contrary, in some cases this may happen soon after randomisation if the patient's improvement is rapid. There will be no specific time-delay criterion for aneurysm treatment in this arm. However, it is anticipated that aneurysm treatment beyond one month post-randomisation would be exceptional; both due to the lower risk of re-bleeding after that time and the very guarded prognosis if a patient has not recovered sufficiently neurologically for treatment within one month.

A record will be kept of the actual treatment received and the date on which received, in both arms. With the patients' consent their GPs will be informed by letter about their participation in the trial.

7.5 Blinding

Treatment allocation in TOPSAT 2 is not blinded. However follow-up for functional recovery at six and 12 months by postal questionnaire will be blinded to the participant's treatment allocation. The Trial Secretary responsible for entering questionnaire data will therefore be blinded to allocation. This follows the successful ISAT and STICH trials methodology.

Individuals carrying out assessments of MRI scans for those participants in the MRI sub-study will be blinded to treatment allocation.

7.6 Baseline Assessments and Data

Baseline data will include collection of the following information:

- WFNS grade
- Demographic data, including age and co-morbidities
- Hydrocephalus requiring drainage
- Estimated modified Rankin Scale prior to ictus
- Date and time of ictal bleed leading to admission/diagnosis
- Admission data, including GCS prior to intubation/ventilation, Fisher grade and hydrocephalus on admission CT

7.7 Trial Assessments

Assessments to be conducted on day of aneurysm procedure

- Details of procedure carried out, date and time
- Adverse events
- Details of any additional procedures carried out
- WFNS grade

Day 30

- Mortality data to be collected, to include date and cause of death

Day of discharge

NB. Day 30 will replace Discharge assessment if not discharged by day 30

- Modified Rankin Scale assessment
- Discharge details to include:
    - Date of discharge
    - modified Rankin Scale grades
    - Where the participant has been discharged to
    - Contact details for participant and Next of Kin
    - GP contact details

Six and 12 months

- Modified Rankin scale questionnaire
- EQ5-D
- Mortality data (at 12 months)

7.7.1 Schedule of Events

Time	Screening	Consent and Randomisation	MRI (in MRI substudy centres only)	Treatment within 24hrs of randomisation OR after neurological recovery (depending on treatment allocation)	Discharge (or day 30 if still in-patient)	6 months	12 months
			After consent, before treatment for aneurysm and within 72 hours of ictus			+6 months following ictus (+/- 2 weeks)	+12 months following ictus (+/- 2 weeks)
Study discussed/ PIS given	X						
Assent		X					
Randomisation		X					
MRI scan (in MRI sub-study centres only)			X			X[a]	
Aneurysm treatment				X			
mRS/EQ5-D (at 6 and 12 months; by post or online as per participant preference)					X (by Research Nurse)	X (Postal)	X (Postal)
Adverse events				X	X	X	X

a) Routine MRI scan performed at 5-6 months post-surgery as per routine clinical practice

7.8 Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Site staff should try to ascertain the reason for withdrawal and document this in the Case Report Form and participant's medical notes.

An Investigator may discontinue a participant from the trial at any time if he/she considers it necessary for any reason including:

- Participant withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- Termination of the clinical trial by the sponsor

Where a participant withdraws from the trial whilst recruitment is active, an additional participant will be recruited.

7.9 End of Trial

The end of the trial is defined as last patient last 12-month questionnaire.

8. TRIAL INTERVENTION

8.1 Name and Description of Interventions

Standard local procedures for coiling (or clipping) the aneurysm will be followed. If the patient has more than one aneurysm the neurovascular team will treat the aneurysm that, in their judgement, is most likely to have caused the SAH (this is normally done on the basis of distribution of blood on CT, and aneurysm morphology on angiogram). If such a decision cannot be made, an attempt will be made to treat all the possible responsible aneurysms together.

8.2 Known Risks

Standard care for grade 4/5 SAH patients will be provided to all study participants. Initially, this is likely to be in an Intensive Therapy Unit or Neurosciences High Dependency Unit. Outcome in SAH patients is often linked to severity of the initial haemorrhage and degree of neurological disability at the time of presentation.

No additional clinical intervention will be undertaken as part of the trial. The treatment to be undertaken in the majority of cases is endovascular aneurysm coiling. Average risk of serious morbidity and mortality in treatment of ruptured aneurysms with this method is approximately 10%. A small number of patients, not technically suitable for coiling, may have neurosurgical clipping of aneurysm(s). These methods are well−established in the treatment of aneurysms; no new treatment method will be used in this trial.

8.3 Assessment of Compliance

After hospital discharge, the GP may be contacted, to establish that the patient is still alive and to obtain information about the patient's clinical condition. If the patient is known to be alive, the study questionnaire will be sent by post with a reply postage paid envelope. Alternatively, patients can complete the questionnaire online via the trial website (www.topsat2.co.uk), if they wish. If no response is received within two weeks, an initial postal reminder will be sent. If no reply is received within a further two weeks, telephone contact will be made with the patient/next of kin (if next of kin gave assent) by the research team or one of the local investigators.

If the patient is unable to complete the questionnaire themselves, a relative or friend can complete it on the patient's behalf.

9. SAFETY REPORTING

9.1 Standard SAE Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under study.
Adverse Reaction (AR)	An untoward or unintended response in a participant to which is related to the intervention under study i.e. that a causal relationship between the trial intervention and an AE is at least a reasonable possibility and the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial intervention, based upon the information provided.
Unexpected Serious Adverse Reaction (USAR)	A serious adverse reaction, the nature and severity of which is not consistent with the known information about the intervention under study.

9.2 Recording and Reporting AEs and SAEs for the TOPSAT2 study

All adverse events related to the study intervention (randomisation to either the early treatment arm or treat on improvement arm) should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. A flowchart (figure 1) is given in Section 9.8 to aid reporting procedures.

- Adverse events will be collected and recorded in the medical notes and in the eCRF.
- Any serious adverse events will be recorded throughout the duration of the trial until the end of study follow-up (12 months) and tracked until the SAE is resolved.
- Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.
- The investigator does not need to actively monitor subjects for adverse events once the trial has ended.
- Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected.

Any change of condition or other follow-up information should be communicated to the Sponsor/ NCTU as soon as it is available or, at least within 24 hours of the information becoming available. SAE forms should be faxed via the SOHO66 fax-to-email service, which distributes the form as an email to CTU, the UK sponsor and the Chief Investigator. If sites are unable to fax the form, it should be scanned and sent as an encrypted email attachment to topsat2soho66@newcastle.ac.uk. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3 Causality

The assignment of causality should be made by the investigator delegated this task on the site delegation log using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e. definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant

views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the REC and other bodies will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Expected adverse reactions:

Most adverse events that occur in this study, whether they are serious or not, will be expected due to the interventions and study procedures. Expected AEs are summarised in the following table.

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

AEs related to acute sub-arachnoid haemorrhage:

- Neurological
- Systemic

Condition	Common	Uncommon	Very Rare
Neurological	Death, impaired cerebrospinal fluid drainage-related, vasospasm-related, re-bleed, 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	

AEs related to aneurysm treatment:

- Coiling
- 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; re-bleed death; myocardial infarction	

9.4 Recording and Reporting Unexpected Serious Adverse Reactions

All Unexpected Serious Adverse Reactions (USARs) occurring in the 30 days post-intervention must be reported to the NHS REC. The Sponsor will perform this reporting. A separate procedure for non-UK sites is given in the non-UK protocol.

The assessment of expectedness will be performed by the Sponsor/CI against the known information for the trial.

USARs must be reported no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a USAR they must contact the CI, sponsor representative and the Trial Manager immediately. The reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- Patient trial number and date of birth
- Name of intervention
- Date of notification of the event
- Medical description of the event
- Date and time of onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g. Principal Investigator)

This information can be reported by telephone, email or fax. The site is expected to fully co-operate with the Sponsor so that a full and detailed report can be submitted to the NHS REC within the required timelines.

PIs will be informed of all USARs by the Sponsor.

9.5 Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events
- Ensuring that all SAEs and SARs, including USARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and providing further follow-up information as soon as available
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment
- Using medical judgement in assigning expectedness to SARs
- Immediate review of all USARs
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Sponsor

- Assessment of expectedness of any USARs
- Expedited reporting of USARs to the REC within required timelines
- Notification of all investigator sites of any USAR that occurs.

TSC/DMC

- Review of safety data collected to date to identify any trends

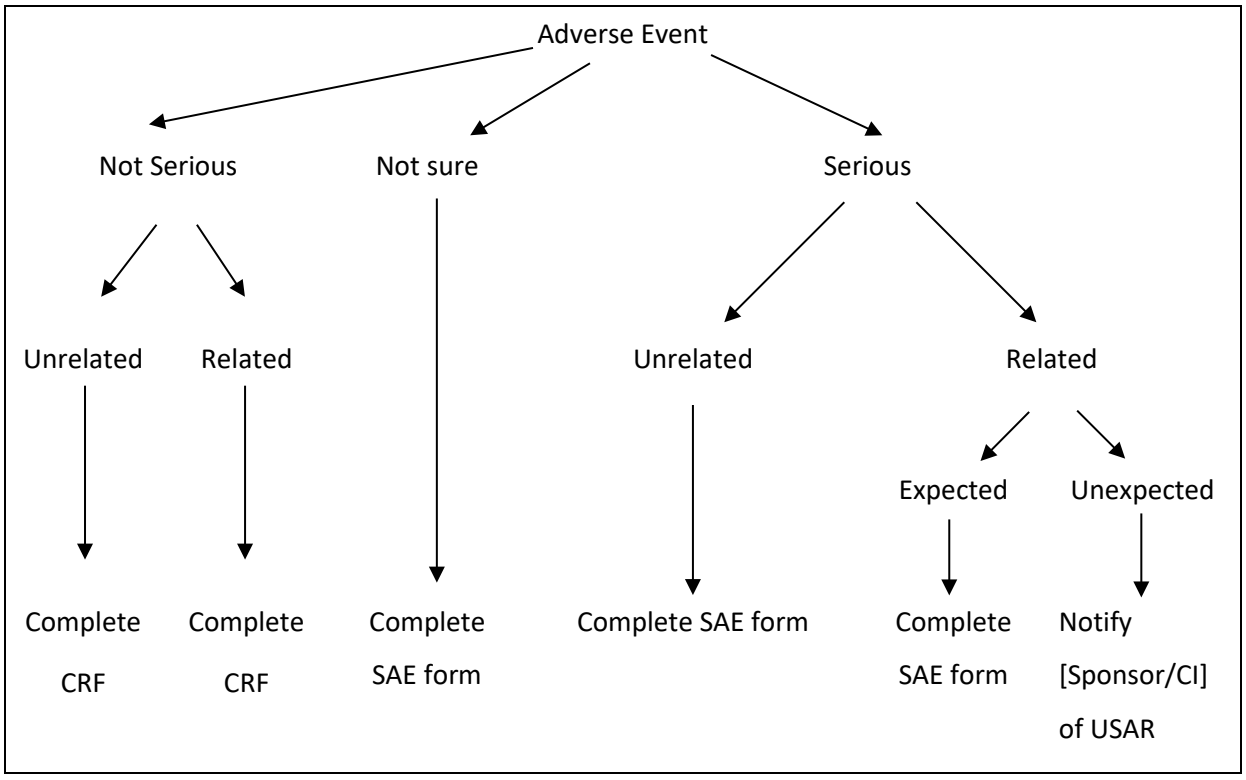
9.6 Notification of Deaths

Death is a common outcome in grade 4-5 aSAH, therefore REC will not be notified of these events unless due to serious, related and unexpected AE (USAR). All deaths occurring during the study that the site staff become aware of should be reported as SAEs.

9.7 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the CI and NCTU must be notified immediately and details of the USM given. The CI or NCTU must inform the Sponsor immediately. The Sponsor must inform the NHS REC within three days of the USM taking place in accordance with NCTU standard operating procedures.

9.8 Safety Reporting Diagram



Contact details for reporting SAEs and USARs

Please fax SAE form(s) via SOHO66 fax-to-email service on 0191 5800992
Or
If for any reason sites are unable to fax the SAE form, they must scan and email the form securely encrypted to topsat2soho66@newcastle.ac.uk.

10. STATISTICAL CONSIDERATIONS

10.1 Analysis Population

The aim is to collect outcome on all patients randomised to the study who do not withdraw consent.

10.2 Statistical Analyses

10.2.1 Analysis of the Primary Outcome Measure

Outcome analysis will take place once all data has been collected, cleaned and the database locked. Trial analysis will be on a modified intention-to-treat basis. Where patients are lost to follow-up they will be removed from the primary outcome analysis; however a sensitivity analysis will be performed to assess the effect of missing data. The primary outcome will be 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 proportional odds model. A sensitivity analysis will be undertaken of the proportional odds model (of primary outcome), adjusting for the minimisation criteria (WFNS grade, age band, hydrocephalus requiring drainage, and whether the patient is randomised within the UK or not). Per protocol analysis will also be performed. If a subject withdraws, all data collected up until that point will be used in trial analysis, unless he/she specifically refuses. In that case, if the trial is still recruiting an additional subject will be randomised.

10.2.2 Analysis of Secondary Outcome Measures

Secondary outcomes of dichotomised mRS (0-3 v 4-6; 0-2 v 3-6) at discharge, six and 12 months, mortality rate at 30 days, six and 12 months, re-bleeding rate and treatment-related complication rate between the arms will be compared using a chi-squared test; odds ratios will be reported. MRS at discharge and six months will be compared using a proportional odds model. These will further explain differences between the two treatment policies. Survival, time to discharge and length of ITU/HDU stay will be compared between arms using survival plots, and the log rank test will be reported. The latter two highlight differences between the two treatment arms in the NHS costs of the two treatments.

10.2.3 MRI sub-study Outcome Measures

Analysis of MRI data will be exploratory. Further details will be included in the Statistical Analysis Plan.

10.2.4 Subgroup Analyses

Odds ratios and 95% confidence intervals will be reported for the following subgroups: WFNS grade at randomisation (4/5), age band (18-50/51-65/66-80), whether there is clinically significant hydrocephalus requiring CSF drainage (yes/no), location of the site (UK/non-UK) and treatment actually received (coil vs clip). Interaction tests will be undertaken and relevant p-values will be reported.

10.2.5 Interim Analyses and Criteria for the Premature Termination of the Trial

There are no planned interim primary outcome analyses.

Interim analyses will be conducted at intervals predetermined by the DMC but will include two specific time points. As there is a stop/go remit at 30 months, to ensure that the trial recruits to target, the DMC will meet at approximately 28 months to review the data for all patients recruited to 24 months. It will not be possible for them to review primary outcome as there will be few patients who will have reached the one-year primary outcome point. Patients with this condition and severity have a high mortality rate and hospital discharge is often delayed due to poor outcome. The DMC will therefore review 30-day mortality and discharge rates. The DMC will also be asked to review 30-day mortality and discharge rates after 36 months of recruitment. The results of interim analyses will be strictly confidential and the trial will only be stopped early if one or other treatment policy shows an advantage at a very high significance level.

10.3 Statistical Size Calculations

The outcome measure in TOPSAT2 is based on the mRS. This is a seven-point scale with values 0 to 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 (OAST) Collaboration and other authors have recently shown the benefit of ordinal analysis in the field of stroke [24-26]. Using an ordinal analysis achieves substantially greater statistical power to detect a treatment effect with equal sample size. The sample size calculation is therefore based on a proportional odds regression ordinal analysis of the mRS.

The best available literature, a non-randomised study, was used to provide the expected distribution of mRS after grades 4 and 5 aSAH[27]. Detecting a difference in clinical outcome (i.e. favouring one treatment strategy over the other) by an odds ratio 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%; 6, dead 27%) was entered into the “Sample size for ordered categories” routine of the Compare2 program in WinPepi version 11.43 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 odds ratios (where the odds ratio 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, gives a cumulative Odds Ratio (OR) in favour of better mRS in one treatment arm of 1.7 at 5% significance level and 80% power. A margin is built in to allow for losses to follow-up and crossovers meaning a total sample size of 346 will be recruited (173 per arm). Loss to follow-up of <2% is based on data from multiple UK-based aneurysm coiling trials.

Using the expected distribution from the best available evidence 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 can be calculated as the inverse of the (proportion of pairwise comparisons with a better result in the treatment group – the proportion with a worse result). This gives an NNT of 5.7 (95%CI 5.61 – 5.88).

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

If equal numbers of grades 4 and 5 patients are recruited, with 346 patients overall, the trial is powered to detect a statistically significant odds ratio 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; the optimum management strategy may differ between grades.

Statistical Analysis

The Statistical Analysis Plan will be published prior to the completion of recruitment and data analysis. All randomised patients will remain in the trial whether they receive the allocated treatment or not, and will be accounted for in the final analysis. The trial is powered to account for a certain level of cross-over and drop-out from follow-up, based on ISAT/HELPS trials experience, predominantly in UK aSAH subjects. It is anticipated that there will be very few crossovers from early treatment allocation but there may be some from “treatment on neurological recovery” to “early treatment” arm – we have estimated 2% based on the TOPSAT pilot and other UK led trials involving coiling. Loss to primary outcome follow-up in ISAT at one year was 1%. In the HELPS trial for UK SAH subjects it was <2% at 18 months. We anticipate a similar or lower level of loss in TOPSAT2, particularly as the principal outcome at grades 4 and 5 will be mortality. Fairly complete death ascertainment from combined primary and secondary care electronic records is anticipated, but letter/telephone contact with a GP followed by death certification will be pursued, should any uncertain cases be identified.

11. DATA HANDLING

11.1 Data Collection Tools and Source Document Identification

Data for individual patients will be collected on source data worksheets by each PI or his/her delegated nominee. These are retained in the medical notes, with all data transferred to the eCRF (the secure, validated clinical data management system, MACRO) as soon as possible following the visit. Patient identification on the eCRF will be via a unique study identifier number. A record linking the patient's name to the unique study identifier number will be held only in a locked room at the study site, and is the responsibility of the PI. As such, patients cannot be identified from eCRFs. The CI or nominated designee will continually monitor completeness and quality of data recording in CRFs and will correspond regularly with site PIs (or their delegated assistants) to capture any missing data where possible, and ensure continuous high-quality data.

The CDMS (MACRO) used for this trial is fully compliant with all regulatory frameworks for research of this nature. It uses a secure web-based interface for data entry; no data are stored on computers at site. The system has an inbuilt back-up facility, through Elsevier's hosting partner Rackspace's secure premises in London, and is managed and supported by the Rackspace team.

11.2 Data Handling and Record Keeping

Overall responsibility for data collection lies with the Chief Investigator. Data will be handled, computerised and stored in accordance with the General Data Protection Regulation 2018. Identifiable data will be stored in a separate, limited-access database, to allow follow-up questionnaires to be sent. Paper copies of study-related results will be annotated, signed and dated, and filed in the medical notes. The overall quality and retention of study data is the responsibility of the Chief Investigator. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

11.3 Access to Data

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the Data Monitoring Committee (DMC) or the REC. Secure anonymised electronic data will be released to the Study Statistician for analysis. The PI and study site staff may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information to which they have access, in order to carry out the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

11.4 Archiving

Archiving will be carried out according to NCTU and Sponsor SOPs.

12. MONITORING, AUDIT AND INSPECTION

The trial will be managed through the Newcastle Clinical Trials Unit. The study will be co-ordinated by a Trial Management Group (TMG) that will include those individuals responsible for the day-to-day management of the trial. The TMG will monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself. TMG meetings will occur at least monthly and include a teleconference link to Manchester, where required. Progress will be monitored proactively according to timelines and any issues addressed. The TMG will liaise with the Trial Steering Committee (TSC), providing updates on trial progress and highlighting any issues arising.

The Principal Investigators will be responsible for highlighting day-to-day study conduct at site. The NCTU will provide day-to-day support for the sites and training, via Investigator meetings, site initiation visits and routine monitoring visits.

Quality control will be maintained through adherence to Newcastle Joint Research Office SOPs, study protocol, GCP principles, the UK Policy Framework for Health and Social Care Researchand clinical trial regulations.

An independent Data Monitoring Committee (DMC) will be established to oversee safety of participants in the study. During the recruitment period, interim analyses of baseline, follow-up data and any other analyses requested by the committee, will be supplied, in strict confidence, to the DMC chair. The DMC will include an independent neurointensivist and statistical representation. This committee will monitor efficacy and safety endpoints. Only the DMC will have access to un-blinded study data. At the first meeting, the DMC will agree on its charter of operation, and discuss and advise on the inclusion of an interim analysis and possible adoption of a formal stopping rule for efficacy or safety.

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial, and will oversee trial conduct and progress. Its chair is an independent consultant neurosurgeon, and the committee includes one lay member. Additional external (independent) members include a stroke neurologist and neurointerventionist. The CTU Senior Trial Manager or nominated Deputy will also attend these meetings. The TSC terms of reference and members' names and contact details will be published ahead of its first meeting.

The committee will meet every six months during recruitment, and annually thereafter for the duration of the trial.

Clinical management of participants will remain subject to individual centres' internal audit procedures. Monitoring to ensure appropriate study conduct and data collection will be carried out by the Newcastle CTU. Patient-identifiable information will be removed prior to presentation to a conference or journal publication. Electronic data will be stored in secure, password-protected computers. NCTU staff will use a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP.

The following will be monitored at UK sites:

- Presence of completed original consent forms in the Investigator Site File (ISF), and copies in patients' notes
- Existence of patients, by comparison of original consent forms with patient identification (enrolment) list
- Reported serious adverse events, by verification against patient notes (source data verification)
- Presence of essential documents in the ISF and study files
- Primary endpoint data and eligibility data, 10-20% of study participants, by source data verification.

For non-UK sties, monitoring will be in accordance with the non-UK Monitoring Plan and non-UK protocol. The following will be monitored centrally at UK sites:

- Original consent forms
- Applications for study authorisations and submissions of progress/safety reports, for accuracy and completeness, prior to submission
- Documentation essential for study initiation, prior to site authorisation
- Reported adverse events for 10-20% of participants, by source data verification
- Primary endpoint data, by source data verification
- Eligibility data for <see monitoring plan> % of study participants, by source data verification.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The study in the UK may be subject to inspection and audit by The Newcastle upon Tyne Hospitals NHS Foundation Trust under its remit as Sponsor, and other regulatory bodies, to ensure adherence to GCP. The investigator(s) / institutions will permit study-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data and documents.

The trial may be subject to audit by representatives of the Sponsor or inspection by EME. Each PI will permit study-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the study.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee Review and Reports

The CI, supported by NCTU, will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) in the UK prior to the start of the study. All parties will conduct the study in accordance with this ethical opinion.

The CI, supported by NCTU, will notify the REC of all required substantial amendments to the study and those non-substantial amendments that result in a change to documentation (e.g. protocol or Participant Information Sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this is obtained. The CI/NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or USARs that occur during the trial.

An annual progress report will be submitted each year to the REC by the CI/NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The CI/NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Favourable ethical opinion from an appropriate REC and NHS Permission will be sought prior to commencement of the study in the UK. Local approvals will be sought before recruitment may commence at each site. The NCTU will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Due to the nature of high grade aSAH, TOPSAT 2 will, of necessity, entirely recruit participants who are unable to consent for themselves. However, the need for trials on such patients to answer crucial clinical questions is now well recognised in stroke, brain injury and other acute neurological conditions. Written information sheets (PIS) and trial SOPs will be tailored to this patient population. Written informed consent or a signed Consultee Declaration Form will be provided by an appropriate consultee as defined by (and in accordance with) legislation pertaining to each participating country of the UK. Information sheets for participants who regain capacity and consent forms for them to sign to remain in the trial will also be developed (please refer to Section 7 for a more detailed description of the consent process). Copies in other languages will be developed as required.

Due to the relative clinical urgency of the management of aSAH the time for reflection is necessarily limited; however, a reasonable time period of between 1 and 24 hours will be available to consider the provision of assent. Appropriate consultees can discuss risks and benefits with clinical investigators. Investigators involved in recruiting subjects will be listed on a delegation log for this purpose, will attend site initiation visits/training and have up to date GCP training. During the consent/assent process official translators may be used if required.

The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant or consultee. A copy of the consent form will be sent by secure fax or email to NCTU. Participants/consultees will specifically consent to the subject's General Practitioner (GP) being informed of their/the patient's participation in the study.

It is inevitable that a significant number of the subjects recruited into TOPSAT 2 will die before hospital discharge, and many survivors will make only a limited recovery. Information sheets for appropriate consultees and discussions with them will make the prognosis of grade 4-5 aSAH clear. It will be made clear verbally and in the PIS that participants have the right to withdraw from the study at any time for any reason, and without giving a reason. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Consent will be sought to retain data collected up to the point of withdrawal. Patients who withdraw and want all data deleted can be replaced if recruitment remains ongoing.

13.2 Peer Review

The study has undergone considerable and extensive peer review as part of the funding application process.

13.3 Public and Patient Involvement

Patient involvement is central to developing TOPSAT2. The NIHR Stroke Research Network Acute Clinical Studies Group lay members attended a SAH workshop in Oct 2012. This identified four priority areas for research; this proposal incorporates two - management of high grade patients and MRI biomarkers. CSG members also commented on the protocol.

The Newcastle SAH survivors support group meets monthly and multiple TOPSAT presentations have been made to this group. Several useful responses were received about the study. Patients provided advice on: a) process of obtaining assent b) assessing functional outcome including the most relevant issues to be addressed c) reassurance that structured telephone interview by research nurses for follow-up would be appropriate. These were incorporated when refining the research protocol. Eleven people who were interested in more active participation commented on the revised protocol. We have asked one to join the TSC. A plan is in place, with expert support from the trial team, to maintain engagement with lay members, and we will continue to do so throughout the trial.

13.4 Regulatory Compliance

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care. Before any site can enrol patients into the study, that site must have received NHS permission from its NHS Research & Development Department.

13.5 Protocol compliance

Protocol deviations, non-compliances and breaches are departures from the approved protocol.

- Unintentional protocol deviations will be documented and reported to the CI and sponsor. Where necessary, Corrective and Preventive Actions (CAPA) will be implemented. These will also be documented and reported to the CI and sponsor

- Deviations found to frequently recur at a site are not acceptable and could be classified as a serious breach

13.6 Notification of Serious Breaches to GCP and/or Protocol

A serious breach is a breach which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial or
(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The sponsor will notify the NHS REC within the required timelines in accordance with the sponsor SOP.

13.7 Data Protection and Patient Confidentiality

Personal data will be regarded as strictly confidential. All data retained at site and sent electronically to the main co-ordinating centre will contain Study ID and initials only. The secure password-protected eCRF database (MACRO) also requires initials and date of birth. This is essential for participant identification and verification. This information is also required for the randomisation system and fax-to-email SAE reporting system. A copy of each completed consent form will be transmitted to the main coordinating centre (NCTU) via a secure fax or dedicated NHS.net email account. This basic check forms part of the processes to confirm the quality of trial conduct and the integrity of data collected. Specifically, this allows remote verification of informed consent has taken place, version control checks, and verification of the consenting clinician/researcher against our delegation records. Personnel with access to this will be named on the delegation of duties document. All personnel are qualified and trained in, and will comply with ICH GCP. Justification for all such electronic transmissions is covered in the Caldicott application approved by Sponsor.

A Participant Identification List will be the only document retained within the ISF which contains full details of hospital number, patient name and study ID.

The study will comply with the General Data Protection Regulation 2018. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

13.8 Indemnity

The NHS Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability with respect to negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is the Sponsor and through the Sponsor, NHS indemnity is provided with respect to potential liability and negligent harm arising from study management. Indemnity with respect to potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS, and by

Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with Newcastle University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

13.9 Amendments

It is the responsibility of the Sponsor in the UK to determine whether an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Steering Committee.

Substantial amendments will be submitted to the REC and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File. Any non-substantial amendment that requires an update to the trial documentation will be submitted to the NHS REC for acknowledgement of the revised version of the document.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification, to determine whether the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by the NCTU.

13.10 Post-Trial Care

This will be as per standard care for patients with aneurysmal SAH.

13.11 Access to Final Dataset

After publication of the main results and initial subsidiary papers from the research team, an anonymised dataset will be lodged with an appropriate archive such as the Virtual International Stroke Trials Archive (VISTA) (http://www.vista.gla.ac.uk/)

14. DISSEMINATION POLICY

Data will be the property of the Chief Investigator and Co-Investigators. Publication will be the responsibility of the Trial Management Group in partnership with the Chief Investigator and authorship agreed with the Co-Investigators and Principal Investigators who have entered ≥ 10 patients into the study.

Progress and final outcomes will be disseminated at relevant neurosurgical, stroke, neuroradiology, MRI and critical care conferences by platform and poster presentations. We expect five to six research publications based on the findings to be published in international peer reviewed journals. Results will also be reported to the Sponsor and Funder, and will be available on their websites. Manuscripts, abstracts and other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identifiable in any study report.

Based on previous experience from Newcastle Neurosciences/Stroke research groups, primary trial publication/acceptance is expected within six months of database locking. A procedural safety paper will be submitted within weeks of the end of randomisation. There will also be multiple outputs around MR imaging techniques in high grade SAH. More detailed subgroup analysis and modelling of care are additional papers, identified as likely outputs of the TOPSAT2 study. The Stroke Research component embedded within NIHR Research Division 2, Newcastle University, professional societies (British Society Neurological Surgeons, British Society Neuroradiologists, UK Neurointerventional Group, British Neurovascular Group), Royal Colleges and contacts with the Clinical Senates, UK Stroke Forum and the Stroke Association will be utilised to disseminate the findings more widely to the public. This will include use of web-based information, newsletters and press releases.

We will feed back to centres via newsletters, the website and trial close down meetings and publications, and to participants via website, newsletter and the publicity generated. More direct personal or small group feedback will be given to the PPI groups involved in developing, contributing to and supporting TOPSAT 2. Feedback in the form of a lay summary will be provided to participants via the general section of the trial website, participant-specific newsletter at the end of trial (if they indicated they wished to receive it) and by wider publicity generated.

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16. APPENDICES

16.1 Appendix 1 - Addresses of Key Trial Contacts

1 Stroke Research Group, Institute of Neuroscience and Newcastle University, Institute for Ageing,3-4 Claremont Terrace, Newcastle upon Tyne, NE2 4AE

2 Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP

3 Newcastle Clinical Trial Unit, Newcastle University, 1-4 Claremont Terrace, Newcastle upon Tyne, NE2 4AE

4 University of Newcastle upon Tyne, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL

5 Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN

6 The Wolfson Molecular Imaging Centre, 27 Palatine Road, Withington, Manchester, M20 3LJ

7 Oxford University Hospitals NHS Foundation Trust, Headley Way, Headington, Oxford OX3 9DU

8 Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ

9 The University of Edinburgh, Crewe Road South, Edinburgh, EH4 2XR

10 Beaumont Hospital, Beaumont Road, Dublin, Ireland

11 Ground Floor, Office Block, Queen Elizabeth University Hospital,Glasgow, G51 4TF

12 University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg

13 Joint Research Office, The Newcastle upon Tyne NHS Foundation Trust, Regent Point (Level 1), Regent Farm Road, Gosforth, Newcastle upon Tyne , NE3 3HD

14 Evaluation, Trials and Studies Coordinating Centre, University of Southampton, Alpha House, Enterprise Road, Southampton, SO16 7NS

15 Deanery of Clinical Sciences, NHS Lothian, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU

16 Robertson Centre for Biostatistics, University of Glasgow, Level 11, Boyd Orr Building, University Avenue, Glasgow, G12 8QQ

17 Oxford University Hospitals NHS Foundation Trust, Headley Way, Headington, Oxford OX3 9DU

16.2 Appendix 2 - Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0		J Parker	Page 1 – version and date Page 2 – ISRCTN number Page 4 – addition of PI signature page Pages 7-10 - amendments to Key personnel Page 30 – addition of new non-UK country Page 31 – clarification of comparative GCS and WFNS grades Page 37 – updated information regarding SAE reporting Pages 38-39 – amendment to adverse event definitions