FULL/LONG TITLE OF THE STUDY
Risk of Aneurysm Rupture Study

SHORT STUDY TITLE / ACRONYM
ROAR Study

PROTOCOL VERSION NUMBER AND DATE
Version 1.2 22/02/2021

RESEARCH REFERENCE NUMBERS

IRAS Number:
276144

SPONSORS Number:
RHM NEU0390

FUNDERS Number:
Not applicable

This protocol has regard for the HRA guidance and order of content from HRA guidance and template 1.1 March 2016

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: SDaviesDear
.....

Date:
..02/Mar/2021

Name (please print):
Sharon Davies-Dear

Position:
Clinical Trials Project Manager – UHS Sponsored Studies

Chief Investigator:

Signature:

Date:
22nd Feb 2021

Name: (please print):
Mr Diederik Bulters

LIST of CONTENTS

KEY STUDY CONTACTS

Insert full details of the key study contacts including the following

Chief Investigator	Mr Diederik Bulters Dbulters@nhs.net 02381205531
Study Co-ordinator	Mr Samuel Hall Samuelrichards.hall@uhs.nhs.uk 02381 205531
Sponsor	Mrs Sharon Davies-Dear sharon.davies-dear@uhs.nhs.uk 02381205146
Joint-sponsor(s)/co-sponsor(s)	Not applicable
Funder(s)	Not applicable
Key Protocol Contributors	Mr Diederik Bulters Dbulters@nhs.net 02381205531 Mr Samuel Hall Samuel.hall@doctors.org.uk 02381 205531 Mrs Jacqueline Birks Jacqueline.birks@csm.ax.ac.uk 01865 223463
Committees	Not applicable

STUDY SUMMARY

It may be useful to include a brief synopsis of the study for quick reference. Complete information and, if required, add additional rows.

Study Title	Risk of Aneurysm Rupture Study
Internal ref. no. (or short title)	ROAR Study
Study Design	Multi-centre retrospective cohort study
Study Participants	Adults with unruptured intra-cranial aneurysm
Planned Size of Sample (if applicable)	22,781
Follow up duration (if applicable)	Not applicable
Planned Study Period	2006-2020 (inclusive)
Research Question/Aim(s)	Validation of the PHASES score for estimation of rupture risk for unruptured intra-cranial aneurysms

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**

ROLE OF STUDY SPONSOR AND FUNDER

The Sponsor is University Hospital Southampton NHS Foundation Trust (UHS), which is the organisation that is taking legal responsibility for the trial.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Committee

The trial management committee will comprise:

Mr Diederik Bulters
- Chief Investigator
- Data custodian

Mr Samuel Hall
- Study co-ordinator
- Principal Investigator – University Hospitals Southampton site.

Mrs Jacqueline Birks
- Study statistician

Day-to-day trial management will be co-ordinated by a Trial Management Group. The Trial Management Group will meet regularly to ensure all practical details of the trial are progressing well, working effectively and all members of the trial team are appropriately trained. They will coordinate training and data collection at all participating sites.

In view that this is an observational study a decision has been made, in conjunction with the sponsor, that it is unnecessary for a separate trial steering committee, or data monitoring and ethics committee, to be appointed and these responsibilities will be assumed by the trial management committee. A copy of the TMG report will be provided to the Sponsor for review and comment during the course of the study.

PROTOCOL CONTRIBUTORS

This protocol was designed and constructed by Mr Diederik Bulters, Consultant Neurosurgeon, and Mr Samuel Hall, Registrar in Neurosurgery, both of Wessex Neurological Centre, University Hospital Southampton NHS Foundation Trust in conjunction with Jacqueline Birks, medical statistician at the University of Oxford. The expert input of the following individuals was sought and included:

Professor Issy Reading, Director of the Research Design Service South Central and Principal Medical Statistician within the Faculty of Medicine, University of Southampton, advised on study design.

Professor David Cromwell, Director of the Royal College of Surgeons Clinical Effectiveness Unit, advised on the process for matching patients with HES records.

Mr Adam Wahba, neurosurgery registrar and Royal College of Surgeons England research fellow, advised on techniques for processing HES data.

Professor James Batchelor, Fellow of Clinical Informatics and Healthcare Innovation at the University of Southampton, advised on the initial study design to involve national hospital admission databases.

Dr Mikayala King, R&D Quality Assurance Manager, University Hospitals Southampton NHS Foundation Trust, advised on patient contact, recruitment and governance.

Mrs Lisa Hall, Head of Data Protection and Disclosures, University Hospitals Southampton NHS Foundation Trust, advised on confidentially issues surrounding the acceptable use of identifiable patient information.

NHS Digital Contact Care Team, Julian Augley at Public Health Scotland, Ian Farr at the University of Swansea who advised on the process for applying to the HES, SMR and PEDW databases respectively.

Mr Patrick Grover, consultant neurosurgeon at the National Hospital for Neurology and Neurosurgery, for neurosurgical review of the protocol.

The British Neurovascular Group who held a research sandpit where the study design was critiqued and approved by members of the neurosurgical community.

Role of the sponsor:

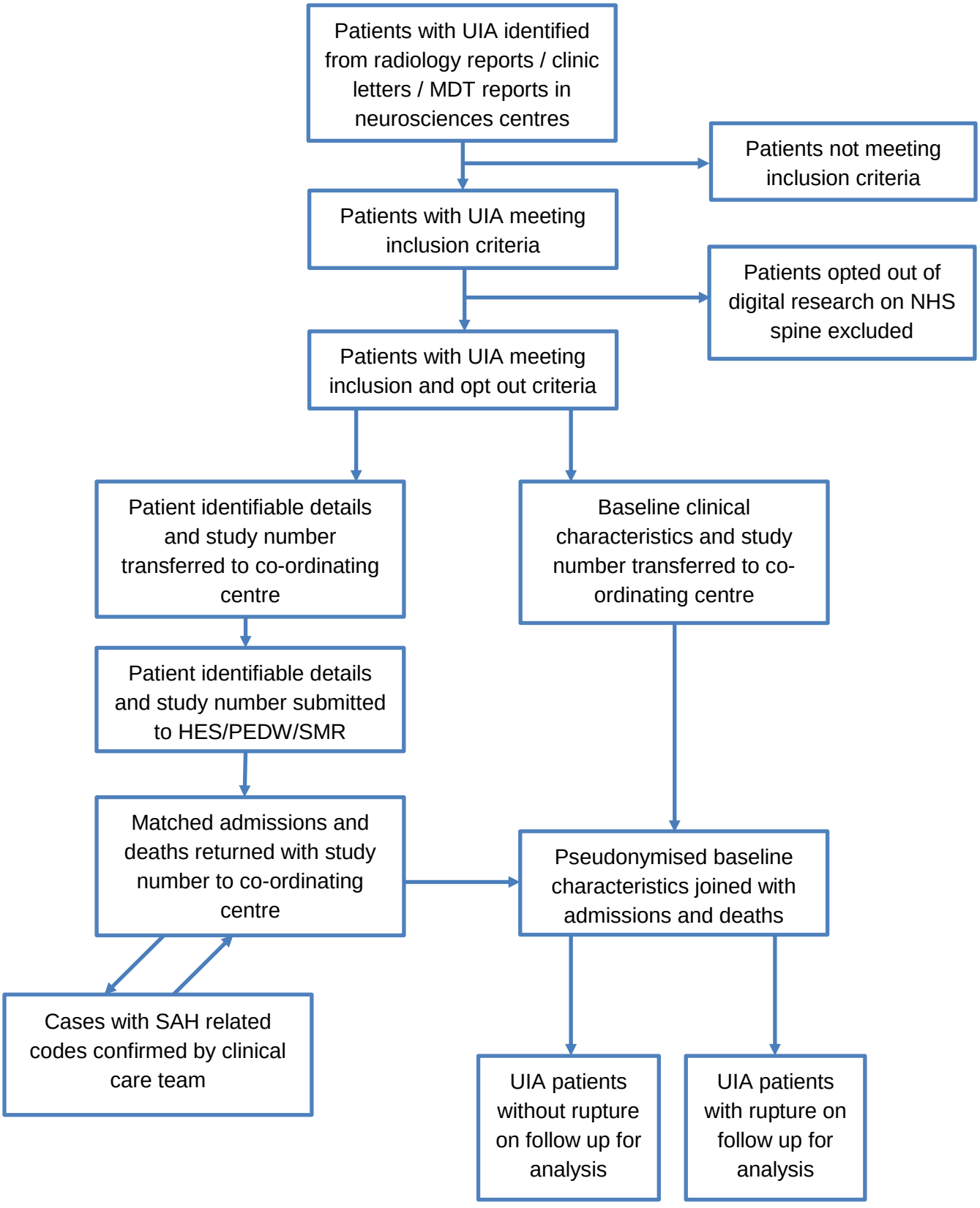
- The sponsor has no role in the conduct, data analysis and interpretation, manuscript writing, and dissemination of results of this study.
- The sponsor does not control the final decision regarding any of these aspects of the study.

Public involvement:

- The Wessex Subarachnoid Support Group has been running since 2012 and includes consultant neurosurgeons in their meetings. During discussions a frequently recurring theme is anxiety over treatment decisions for unruptured intracranial aneurysms (UIA).
- A research priority workgroup was conducted with invited members of the Subarachnoid Haemorrhage Support Group. This confirmed that better decision making on aneurysm treatment is the main concern for patients and the need for research into the risks posed by unruptured intracranial aneurysms ultimately led to the development of this study.
- Opinions have been solicited from patients with unruptured intracranial aneurysms attending clinic regarding their opinions on confidentiality and consent issues raised by this study. All would be happy for their data to be used for a natural history study but would not want to be in a randomised controlled trial of aneurysm treatment versus no treatment.

KEY WORDS:
Neurosurgery
Intra-cranial aneurysm
Sub-arachnoid haemorrhage
Rupture
Prediction

STUDY FLOW CHART



STUDY PROTOCOL
Risk of Aneurysm Rupture Study

1 BACKGROUND

Intracranial aneurysms (IA) are common. Their prevalence is 3.2% in healthy people aged 50 (Vlak 2011). They occur with increasing frequency from the third decade onwards. They are usually asymptomatic and are detected incidentally on scans (usually MRI or CT) done for other reasons. Some can rupture and cause subarachnoid haemorrhage (SAH). The incidence of SAH is much lower at 9.1 per 100,000 person years (de Rooij 2007), reflecting a relatively low rate of IA rupture estimated at 1.4% per annum (Greving 2014).

Unruptured IAs (UIAs) can be treated prophylactically to prevent rupture with open microsurgery to apply a clip to occlude the aneurysm neck, or endovascularly to insert coils to fill the aneurysm sac. However, it is hard to justify treating all UIAs given these procedures carry a 5% or more risk of permanent morbidity or mortality, and very few rupture. It is therefore necessary to identify UIAs at high risk of future rupture for treatment.

An international attempt at a randomized controlled trial to address which patients benefit from treatment was stopped due to poor recruitment (just 80 patients consented to the study over 3 years out of a planned study size of 2000 (Raymond 2011)) and is unlikely to repeated. Therefore, treatment decisions are made based on what is known about the natural history of UIAs. The problem is that data on the natural history of UIAs is inadequate to inform major treatment decisions such as this.

Only one large multicentre prospective cohort has studied a population of UIAs applicable to the UK. The International Study of Unruptured Intracranial Aneurysms (ISUIA) was an international multicentre prospective cohort study which documented a strong relationship between aneurysm size (maximum diameter in any dimension at baseline) and SAH (Wiebers 2003). Five year SAH rates were 0% and 2.6% for IAs <7mm and 7-12mm respectively. ISUIA received extensive criticism both before (Ausman 2002), and after publication of results (Raymond 2008). A large number of patients were selected for treatment (58%), and of those selected for conservative management, many went on to have their UIA treated (32%) so that overall 72% were treated. This selection was not random, and the study population was not representative of all UIAs.

The only study with no selection or follow up bias is based on a cohort of Finnish patients (Juvela 2013). This found markedly different rupture rates with 26% of small anterior aneurysms (the most common type) rupturing over 30 years (versus 0% extrapolating data from ISUIA). There are three possible explanations for these differences – genetic, environmental or methodological differences between the studies. Despite not one published genetic study, the results have largely been ignored based on an assumption that the difference is genetic. This has been driven by historical data showing a higher incidence of SAH in Finland (29.9 per 100,000). This historical data has recently been discredited, however, and SAH incidence has been shown to be similar in Finland to the rest of the world (8.9 per 100,000) (Korja 2016). The Finnish natural history studies may therefore be more representative than previously assumed.

The only other large studies were conducted in Japanese populations (Sonobe 2010, Morita 2012). They again differed enormously in their design. There are obvious differences in race (the Japanese population is the only other population proposed to have a different rupture rate to the rest of the world), length of follow up (1-30 years), loss to follow up (up to 71% in the largest study of 6697 patients). They also showed much higher rates of rupture than ISUIA. However, it is again unclear to what extent this relates to genetic differences, environmental differences or methodological differences.

Despite the obvious limitations of combining studies with different populations, methodologies and results, the data from these studies have been pooled with ISUIA to produce the PHASES score (Greving 2014). From this a 6 item scoring system (population, hypertension, age, aneurysm site,

previous subarachnoid haemorrhage and aneurysm size) was developed to predict 5 year rupture risk in patients with a diagnosed UIA. It assumes the data is representative and accurate, and ascribes the differences in risk to population rather than study methodology.

It leaves UK clinicians with a practical conundrum. Should management of patients be based on:

A) *The only study with a genetically similar population* - accepting the likelihood that in a predominantly Northern American cohort with high treatment rates a disproportionate number of high risk aneurysms (for example with dome irregularity and blebs) were treated before entry to the study.
B) *The only study with no selection or follow up bias* – accepting that this study found a markedly higher rate of rupture (26% vs 0% in ISUIA over 30 years) for the most common types of aneurysm (Juvela 2013), but that this difference may also be due to genetic or environmental differences in the Finnish population.
C) *The largest available study* – accepting the inherent biases introduced by combining studies of different and non-overlapping populations all with markedly different risk profiles.

There is therefore a pressing need for more research into the natural history of unruptured aneurysms. Specifically, the PHASES score, whilst used by 24 out of 30 neurosurgery units in the UK (unpublished data), has never been validated for use in a UK population.
Aim 1 - To validate the PHASES score in a UK population.

The PHASES model only used 6 available patient and aneurysm characteristics for prediction. There are many more that are believed to have a large influence on risk but have not been considered. Examples include aspirin use, statin use, smoking, aneurysm irregularity, multiple aneurysms, family history of aneurysms/SAH and polycystic kidney disease. Therefore:
Aim 2 - To develop a new prediction model including all described predictors of risk.

Most clinicians believe that rupture risk is higher early after aneurysm formation and reduces with time. However, practically all clinical decisions are made by projecting estimates of short-term risk over a patient's lifetime (assuming a constant risk). For example, 68% of patients in PHASES came from a study with just 1.0 year of follow up which is reported as a 5 year risk in PHASES which is then extrapolated by clinicians to 30 year/lifetime risks. Therefore, very small errors in 1 year rates can lead to very large errors in lifetime risks. Moreover, none of the studies accounted for whether the aneurysm was a new diagnosis at time of recruitment or not. Data is therefore needed to determine the long-term risks of UIAs and assess if the early and late risks are the same. Therefore:
Aim 3 - To report long-term risk of aneurysm rupture.

2 RATIONALE

The aim of this study is therefore to describe the natural history of unruptured intracranial aneurysms in Great Britain. The condition is of great clinical importance because of the high prevalence of UIA with diagnoses continually increasing due to the widespread availability of imaging and increasing age of the population. Despite this there are great uncertainties as to how to manage patients with UIA. The management is fundamentally based on the balance of risk between treatment and the natural history of the UIA. However, as described above, our understanding of UIA natural history is flawed and thus currently patients are potentially being subjected to the risk of over- or under-treatment. The possible negative outcomes from either unnecessary prophylactic aneurysm treatment or from subarachnoid haemorrhage, include stroke, long term disability and death, and thus it is crucial that patients are provided with most accurate information possible for their treatment decisions.

3 THEORETICAL FRAMEWORK

The study is designed as a UK based multi-centre study which incorporates retrospective patient identification combined with outcomes recorded in a prospective database.

The first stage of the study is for individual neurosurgery units to identify their patients with an unruptured aneurysm and collect baseline data about that aneurysm. Most patients with unruptured aneurysms are managed as outpatients and assessed in a neurosciences unit in the UK. This should identify a large cohort of patients and the necessary aneurysm variables to predict risk are best recorded in local medical notes.

Searches will be done retrospectively over a period of up to 2006-2020. Patients can be identified from sources such as clinic letters, MDT discussions or radiology reports. A retrospective design allows the identification of patients diagnosed up to 15 years ago and thus the length of follow-up achievable will exceed the 5 years currently used in PHASES. Given that UIA can rupture at any point in a patient's lifetime the longer the follow-up achieved will make the results more translatable to the actual patient. Trying to achieve the same length of follow-up with a prospective study would take considerably more time and financial investment.

This study is best done as a multi-centre design because of the large number of patients required. UIA rupture is uncommon (approximately 1% per year) and thus to reach the minimum number of ruptures required to test the current PHASES model a much larger overall cohort of UIA will be required. This is only realistically achievable by many neurosurgical units pooling their patient numbers.

The second stage in this study is to compile the patients into a single cohort and link them to national databases for hospital admissions (HES/PEDW/SMR) for the UK. Every hospital admission in the country is recorded on one of these databases with the corresponding codes for diagnosis during that admission. Searching the cohort against these databases will return all admissions following diagnosis of a ruptured aneurysm.

The strength of using national databases is that they will capture any event of aneurysm rupture irrespective where it occurs in the UK. Rupture is a sudden severe event that always results in a hospital admission or death and it is not anticipated that there is a significant rate of SAH undiagnosed in the community. Rupture could not be identified from the neurosciences records however as many patients who suffer rupture of their aneurysm will be admitted to another hospital (e.g. their local hospital is not a neurosciences centre, or they have moved home, etc). These databases are also linked to ONS and so can capture causes of death for patients who die before reaching hospital. The comprehensive coverage offered by these admission databases will recreate the high follow-up rates that are normally only achieved with a prospective study.

In the third stage local neurosurgery units will confirm the admissions identified in stage 2 were correctly coded as a subarachnoid haemorrhage. This will be a final quality control to mitigate for any issues with miscoding in HES/PEDW/SMR to and ensure the data derived is accurate and meaningful.

4 RESEARCH QUESTION/AIM(S)

Primary Aims:
Aim 1 - To validate the PHASES score in a UK population.
Aim 2 - To develop a new prediction model including all described predictors of risk.
Aim 3 - To report long-term risk of aneurysm rupture.

Secondary Aims:
Aim 4 – To develop risk models of aneurysm growth.
Aim 5 – To evaluate the efficacy of aneurysm screening regimens.
Aim 6 – To develop and evaluate new radiological predictors of aneurysm growth and rupture.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

Data Collection – Baseline data – local neurosciences units
Patients will be identified by members of the clinical care team and record:

- NHS number
- Name
- Date of birth
- Post code

These patients will be allocated a study number for pseudonymisation. This data will not be otherwise kept or used for other research purposes.

Further data will be collected from patient's case notes (either electronic or paper based as appropriate). A separate data definitions manual will be produced. All data collectors will be provided with a mandatory education module and correctly collect data from test cases before data collection.

The core covariates for each patient at time of diagnosis will be:

- Date of first diagnosis of aneurysm (date of first CTA/MRA/DSA or where not available date of first MDT or clinic appointment whichever is earlier)
- Date of inclusion in the study (date of first CTA/MRA/DSA or where not available date of first MDT or clinic appointment that lies within the unit's search period)
- Hypertension: a co-morbidity of hypertension or regular use of anti-hypertensive medication at time of diagnosis.
- Age: in years at time of diagnosis of aneurysm on angiographic imaging
- Gender:
- Site: anterior cerebral artery (including anterior communicating and pericallosal arteries), internal carotid (including bifurcation, ophthalmic, superior hypophyseal), MCA (including M1 segment and bifurcation), posterior communicating and posterior circulation (including vertebral, basilar, cerebellar and posterior cerebral arteries).
- Aneurysm size: the longest aneurysm dimension recorded to the nearest millimetre as described by the MDT discussion or where not available from the reporting radiologist at time of diagnosis or where not available from the clinic letter.
- Previous aneurysmal subarachnoid haemorrhage: confirmed diagnosis of aneurysmal SAH in the patient's medical history.
- Population: European/North American, Finnish, Japanese (where race cannot be confirmed it will be assumed to be non-Finnish and non-Japanese on the basis that there is a low incidence of these populations in the UK and their presence would usually be considered noteworthy in a clinical note.

The additional desirable covariates at time of diagnosis will include:

- aspirin use - any dose used >3* per week
- statin use - any statin use >3* per week
- smoking history - non-smoker, ex-smoker, current smoker
- Aneurysm multiplicity – record number of intra-dural aneurysms the patient has (treated or untreated)
- Family history – number of 1 first degree and second degree relatives with UIA/SAH
- History of Autosomal Dominant Polycystic Kidney Disease – yes, no
- Aneurysm location subclassification – ICA paraclinoid (ophthalmic and superior hypophyseal) ICA (PCom), ICA other (anterior choroidal and bifurcation), ACA ACOM, ACA pericallosal, MCA, Posterior (basilar termination), Posterior (SCA), Posterior (AICA) Posterior (PICA)
- Bleb or irregularity of aneurysm – recorded as present or absent from radiology report only. If not mentioned in report assumed to be absent. If no radiology report available, then recorded as NA.
- New/known diagnosis: patients in whom the aneurysm was known prior to the search period will be recorded as known diagnosis and otherwise as new diagnosis.

Data collection – aneurysm rupture/censoring events – local neurosciences units
At the time of baseline data collection locally available follow up will be recorded which will include:

- Date of last follow-up

- Date of death (if applicable)
- Cause of death (if applicable)
- Date of SAH (if applicable)
- Location of aneurysm causing SAH (if applicable)
- Date of aneurysm treatment (if applicable)
- Reason for aneurysm treatment (if applicable)

This data will be used for quality control of subsequent HES searches.

Data collection – aneurysm rupture/censoring events - central HES ONS data
Upon collection of all baseline data, a search of the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases using the patient's NHS numbers be conducted. The use of a HES and ONS search is designed to maximise the identification of rupture events which are not treated in neurosurgical unit as subarachnoid haemorrhage. It will thus identify events managed in a district general hospital or those who die pre-hospital.

This search will use ICD-10 codes as defined by the UK biobank Outcome Adjudication Group (Definitions of Stroke for UK Biobank Phase 1 Outcomes Adjudication Date: August 2017 Version: 1.1 https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/alg_outcome_stroke.pdf). This will identify the following events:

1. Admission to hospital with aneurysmal subarachnoid haemorrhage (I60.0-I60.7)
2. Occlusive treatment of aneurysm.
3. Death diagnosed as subarachnoid haemorrhage in parts 1a-c of the death certificate.

All patients identified from the HES search with any of the above events will then have their medical notes re-evaluated by the local neurosurgery unit to confirm the HES report has accurately identified the event as aneurysm rupture or treatment.

A similar search will be repeated in Wales using NWIS/PEDW where NHS numbers are also used. Scotland does not use NHS numbers making searches more complex. However, a further search of equivalent database (SMR01) will be performed in Scotland using name and date of birth for identification.

Data collection – quality assurance - central HES ONS data
Additionally, all patients will be checked for possible SAH events that could have been miscoded.

Therefore, any patients with the codes:

1. Subarachnoid haemorrhage (other and unspecified) (I60.8-60.9)
2. Intracerebral haemorrhage (including intraventricular haemorrhage (I61.0-61.9)
3. Non-traumatic subdural haemorrhage (I62.00-I62.02)
4. Traumatic subarachnoid haemorrhage (S06.6X0, S06.6X9A, S06.6X9, S06.6X8A)

will have their casenotes reviewed for evidence the haemorrhage was aneurysmal.

Any patients with the following codes:

5. I46.1 sudden cardiac death
6. R96 other sudden death cause unknown
7. R98 unattended death

will have their casenotes reviewed to assess if their death was likely due rupture of their aneurysm.

Additionally, in at least one pilot site, all patients with the code

8. Cerebral infarction (63.0-63.9 & I64.X)

will have their casenotes reviewed to estimate rates of missed diagnosis for the whole cohort.

Where verification cannot be established from medical notes, any patients with codes in the specified possible miscoded SAH events will be assumed to be non-aneurysmal unless they have a procedure code indicating occlusive treatment of aneurysm within 30 days after the event, or they were coded as

subarachnoid haemorrhage other or unspecified and they subsequently died within 30 days (based on the very low rate of mortality from non-aneurysmal SAH) and did not have any additional codes for trauma indicating a non-aneurysmal event.

Data collection – other considerations - central HES ONS data
Last follow-up for each patient will be set as the time at which the HES search was performed, or the patient was unregistered with a GP in the UK or date of death, or the aneurysm was treated, whichever is earliest.
Additionally, we will record

1. race
2. I10 essential (primary) hypertension
3. Z72.0 tobacco use
4. F17.2 tobacco dependence

And use these to complete any missing baseline data. Where baseline data and HES conflict, the baseline data will be used. Where neither is available, after assessment for any bias (missing completely at random MCAR, missing at random MAR, missing not at random MNAR) multiple imputation will be used.

Statistical analysis - Aim 1 - PHASES validation
The PHASES study provides the coefficients from their Cox regression model and baseline survival at 5 years that allows the absolute 5-year risk of rupture, to be calculated for all patients who are not censored before 5 years, using age, whether the patients has hypertension, history of SAH, size of aneurysm (3 categories) and location of aneurysm. The time to censoring will be calculated (death or date of HES search or date unregistered from GP practice whichever is first) to ensure 5 years of follow up if rupture has not occurred. Discrimination will be assessed using Harrell's C-index of concordance and Royston and Sauerbrei's D statistic. Calibration will be assessed at the 5 year time point using the method in Royston (2014). These will be used to calculate the number of SAH events per 5 years for each PHASES score (0 to 12+) and expressed as a percentage with 95% confidence interval to compare to the PHASES estimates.

There are multiple potential causes leading to underestimates of rupture risk. The magnitude of these will be estimated and corrected for. In view that all SAH events will be verified in clinical notes it is not expected that there will be any significant overestimation and consequently correction. Events may be missed due to migration. Any patients noted at time of baseline data collection to have emigrated will have this recorded and this will be used for censoring. Additionally, HES data will reveal any patients who have unregistered with their GP for emigration which will be used as a censoring event. Unfortunately, it is anticipated that not all patients will unregister on departure from the UK and therefore the observed emigration rate (that from the baseline data collection and HES data) will be subtracted from average national migration figures and this applied to the data.

Events may be missed due to miscoding. Aneurysmal SAH miscoded as:

1. Cerebral infarction (63.0-63.9 & I64.X)

Will be identified at one or more test sites by review of clinical notes to estimate any under-estimates due to miscoding and these estimates applied to the whole cohort.

In the event there are high rates of failed verification for the codes:

1. Intracerebral haemorrhage (including intraventricular haemorrhage (I61.0-61.9)
2. Subarachnoid haemorrhage (other and unspecified) (I60.8-60.9)
3. Non-traumatic subdural haemorrhage (I62.00-I62.02)
4. Traumatic subarachnoid haemorrhage (S06.6X0, S06.6X9A, S06.6X9, S06.6X8A)
5. I46.1 sudden cardiac death R98 unattended death
6. R96 other sudden death cause unknown
7. R98 unattended death

at some centres, then error estimates may be applied to the data from centres with robust code verification.

Additionally, at baseline data collection, any subsequent SAH events observed in the local notes will be recorded with their date, or date of last follow up. The SAH events observed during this follow up period will be compared to that for the similar period using HES data (after applying the above corrections), and the total risk estimates adjusted for any differences between these to give final 5 year risk estimates.

Discrimination will be assessed with the C statistic but is expected to be poor due to low event rates and therefore will be compared to the original PHASES data. Calibration will be assessed with calibration plots and Hosmer-Lemeshow tests.

Statistical analysis – Aim 2 - Additional prognostic factors
A new risk prediction model for rupture will be developed using the total data set, including the additional possible risk factors. The Cox regression model will be used for risk of rupture. The absolute risks can be estimated at relevant time intervals, 2, 5 and 10 years. Numbers of missing values will be summarised for each factor. Multiple imputation will be used to replace missing values. Discrimination of the final model will be assessed with the Harrell's c-statistic. Internal validity will be assessed by bootstrap resampling.

Additionally, the following sensitivity analyses will be performed:
In view that a significant number of aneurysms are anticipated to have grown and subsequently treated on follow up, any cases noted to have undergone treatment for aneurysm growth will be included in a model predicting the risk of rupture or treatment for aneurysm growth. In view that it is anticipated that a number of unexplained deaths will be captured where it will not be possible to resolve if the cause was SAH or not, a model predicting aneurysm rupture or unexplained or unattended death (R 96 and 98) will be built.

Statistical analysis – Aim 3 - Long term rupture rates
It is anticipated that initially follow up times will range from months to 15 years. This will be insufficient to definitively answer what the long term risks posed by aneurysms are. However, a model will be built including a term for new diagnosis vs known diagnosis. This will establish if rupture rates are similar between patients with new and prior diagnoses.

All patients, including those who underwent aneurysm occlusion, will be included in time-to-event analysis which will cover the whole duration of available follow-up. This will include Kaplan-Meier and proportional hazards models for univariate and multivariate survival curve fitting. A cumulative Hazard plot will be used to assess if rupture risk is constant or varies with time from diagnosis.

Longer term, HES searches will be repeated periodically using unique HES identifiers generated by DARS at the first HES search. These searches will identify any late events of SAH due to aneurysm rupture and models will be built to predict true long-term risk.

Data management
Patient confidentiality
Complete anonymisation of data is not possible due to HES and ONS searches and similar searches in Wales and Scotland. The minimum level of identifiable data for HES searches are NHS number and date of birth. Inclusion of name and post-code is highly advantageous for more reliable 3 point searches in view of likely typographical errors with large numbers of NHS numbers. Therefore, permission to use this limited identifiable data will be sought.

It is anticipated that as this represents research performed by a public body that is in the public interest and cannot viably be performed in another way, that explicit patient consent will not be required for GDPR. The reason it cannot be performed with explicit patient consent is that many patients who suffer SAH are left dead or without capacity. These patients would therefore not be able to consent and participate leading to an underestimate of aneurysm rupture rates. Under the NHS Act

2006, a section 251 waiver for consent to confidential data will be requested from CAG. In order to meet the requirements of proportionality and minimization of data use, the following methods will be used.

Patients will be identified by the local clinical care team. In view that the inclusion criteria for the study require review of the majority of variables that will be collected in the study, on identification patient details and clinical details will be collected at the same time and a study number allocated for pseudonymisation. These will be held securely on password protected local hospital computers.

Each recruiting unit will upload their patient NHS numbers to the NHS Spine to check for a patient's pre-registered wish to opt out of their data being used for research. The NHS Spine will return a list of NHS numbers for patients who have not registered to opt out of research. Each recruiting unit will destroy the details for any other their patients who are not on the list returned from NHS Spine.

All data will be transferred between investigators using secure NHS email communication (NHS.net). All data will be stored on NHS Trust servers or encrypted mobile data devices. No data will be saved to unsecured personal computers.

All data from participating units will be combined to produce two data sets, one of patient identifiable details with pseudonymisation number and one of clinical details with pseudonymisation number. The former will be submitted to the NHS digital Data Access Request Service (DARS) for searching against the HES database. Similar searches will be conducted in Wales and Scotland.

On return of data from DARS the patient identifiable data will be again removed and the HES results further analysed by the team at University Hospitals Southampton NHS FT against the clinical details using only pseudonymisation number.

The software used for performing the analysis will be Microsoft Excel, SPSS, SAS, STATA and R.

6 STUDY SETTING

The study will be conducted at up to 30 neurosurgery units in the UK. Patient identification and baseline clinical data will be collected from their locally held medical notes and stored on their own NHS servers. Access to patient medical records by the local direct clinical care team will be either electronic or manual depending the document storage method of the individual unit. The identification and baseline data collection by the direct clinical care team, in each neurosurgery unit maximises patient confidentiality and minimises the number of people who have access to identifiable medical records.

The coordinating unit (University Hospitals Southampton NHS FT) will be the site at which patient information is uploaded to HES/PEDW/SMR. It will also be the site where pseudonymised data is analysed. There are no site specific requirements dictating these be done in Southampton however this site has been chosen for analysis as it is the base where Mr Diederik Bulters and Mr Samuel Hall currently work as clinicians. Pseudonymised data may also be analysed by Jacqueline Birks at the University of Oxford although she will have access to the pseudonymised list only. Similarly, pseudonymised data may also be analysed by contributors at participating centres.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

1. Age 18 years or older.
2. Intracranial intradural unruptured aneurysm.
3. Confirmed on angiogram (CTA/MRA/DSA).

4. Diagnosis of UIA between January 2006-December 2020.

7.1.2 Exclusion criteria

1. Mycotic or vasculitic aneurysms.
2. Aneurysm diagnosed on CT or MRI alone.
3. AVM associated flow aneurysms.
4. Extradural aneurysms (e.g. intra-cavernous).
5. Aneurysms previously treated by either microsurgical or endovascular techniques.
6. Small lesions uncertain as to whether they are truly aneurysmal ("dilatation", "bulge", 'Infundibulum", etc)

7.2 Sampling

7.2.1 Size of sample

Sample Size

There are no accepted methods for power calculation for validation studies of prognostic models. Therefore, usually the rule of thumb to have ten events for every covariate tested is applied.

For Aim 1, 6 covariates will be tested suggesting at least 60 SAHs will need to be captured. ISUIA recorded 51 ruptures in 1692 patients over 4.1 years. Sixty events may therefore be expected in 1,990 patients with 8,161 years of follow up.

For Aim 2, 120 events will need to be observed to account for the 6 additional commonly occurring covariates which would be expected in 3,981 patients with 16,332 years of follow up.

For autosomal dominant polycystic kidney disease (ADPKD) which has a low incidence, larger numbers of patients will be needed. Ten events in ADPKD are expected in 1360 patient years of follow up assuming the risk of SAH is not elevated and similar to the general population. However, 16,332 years follow up would only yield 195 years in patients with ADPKD (based on a population study which found 53/4436 IAs had ADPKD (Nurmonen 2017) and consistent with pilot data where 11/1025 cases examined to date had ADPKD). Therefore 113,905 years of follow up would be required to capture 10 ruptures amongst 1,340 years follow up in ADPKD patients. This would equate to 22,781 patients with 5 years of follow up (or applying the slightly looser rule of 5 events per prognostic factor this would require 56,952 years of follow up with 11,391 patients).

In a local pilot 1,415 cases were identified over 14 years in a population of 3 million with an anticipated 6,000 years of follow up. Extrapolating to England, Wales and Scotland 31,130 patients with 132,200 years follow up are available - well in excess of the target of 8,161 to validate PHASES in the general population, as well as the 16,332 to test the additional variables, but only just sufficient to answer the role of rarer predictors such as ADPKD. For reference PHASES was based on 29,166 years of patient follow up. Therefore, all cases that can be identified in England and Wales will be sought up to a maximum of 22,781.

7.2.2 Sampling technique

All patients who are identified using the retrospective searches, and who meet the eligibility criteria, will be included. Sampling techniques to reduce this cohort size will not be used because rupture events are uncommon and sampling may lead to an underrepresentation of the true rupture rate if these patients are missed. Furthermore, the final cohort size needs to be as large a possible in order to accurately include uncommon prognostic factors such as APCKD in the final model.

7.3 Recruitment

7.3.1 Sample identification

Patient identification

Due to most UIAs being detected during investigation for other conditions, HES coding for outpatient appointments cannot reliably identify patients with intracranial aneurysms and a local review suggested this may lead to a large underestimate of cases.

Therefore, patients will be identified by the direct clinical care teams at adult tertiary neurosurgical units in the UK treating patients with UIAs. All patients will be eligible whether seen in the centre, scanned in the centre or only discussed with the centre at MDT or on-call. Therefore, more than one search method may be applicable. Search methodology may be adapted to suit local case note and radiology records. We would recommend sequentially performing the following searches:

1. Electronic keyword searches of clinic letters, discharge summaries and MDTs. These capture most patients but risk missing patients not formally discussed with neurosurgery.
2. Electronic searches of cranial CTA, MRA and DSA reports for the term “aneurysm” excluding “no aneurysm”. These searches capture all patients at the parent hospital but may miss regional patients scanned in district hospitals.
3. Searches of on call referrals may capture any further conservatively managed UIAs.

In some units, paper records of MDT or vascular clinics may be searched where electronic systems are not in place. Additionally, some units maintain prospective neurovascular databases which could be used for patient identification.

To reduce selection bias all participating centres will produce a written search strategy for their unit and perform a search over a locally prespecified time period. This period will be within the range of 1 January 2006 – 31 December 2020 (representing the implementation of PACS and the present), but may be shorter. The date of inclusion will be the date of the first document to identify the patient in that locally prespecified date range. Where aneurysms were diagnosed before the study dates, the aneurysm will be marked as “known diagnosis” and the date of inclusion remains that of the first document in the study date range.

Patients will not be contacted as part of the identification process. There will also not be any payments made to the patients. There will not be any recruitment through publicity adverts. The study will have a dedicated website which will contain details of the study designed for investigators but this will not be used as a source of recruitment.

7.3.2 Consent

Informed consent will not be sought from the patients included in this study. The practicalities of approaching over 10,000 patients for consent would be logistically challenging and in attempting to obtain consent from such a large group of patients it would be expected there will be a significant number of patients in whom no consent can be obtained for practical reasons. We would expect it much less likely to be possible to obtain consent in patients who had suffered a bleed from an unruptured aneurysm as they are likely to be left either incapacitated, or dead. Therefore, if the study only included patients with informed consent, it would include far fewer cases who suffered a rupture leading to underestimates of the risk of bleeding and give misleading results – i.e. the requirement for full informed consent would heavily bias the study and invalidate the results.

Whilst informed consent won’t be sought we will be respecting a patient’s right to opt out of having their data used for research. All patients identified by the recruiting unit will be screened against the NHS Spine for patients who have registered as part of the National Data Opt-Out.

8 ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor will ensure that the trial protocol and submitted supporting documents have been approved by the appropriate regulatory body, Health Research Authority (HRA), main research ethics committee (REC) and that local permission has been obtained prior to any subject identification.

All substantial amendments and non-substantial amendments (as determined by the sponsor) will not be implemented until HRA/REC have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial amendments and non-substantial amendments. Relevant approvals must be obtained before any substantial amendment and non-substantial amendments may be implemented at sites.

All correspondence with the HRA and the REC will be retained in the Trial Master File and the Investigator Site File (maintained by the site).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within 90 days after the end of the trial (as defined in section 7.10), the CI/Sponsor will ensure that the HRA and the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

All results will be published on a publicly accessible database.

8.1 Assessment and management of risk

This research proposal is based on retrospective data collection from already established medical records. There will be no direct patient contact. The retrospective design means that the conduct of this study cannot alter the treatment they have already received. Thus, there are no direct risks nor burdens to their health.

The risk to patients from this study is associated with breach of confidentiality and any harm this could cause. Most access to patient identifiable data will be by the direct clinical care team who would have routine access to the patient's medical records and poses minimal risk. There is a small risk of data being exposed during transfer to the coordinating centre. We have attempted to minimise risk/burden to the patient from confidentiality breach by separating clinical details and patient identifiable details into different datasheets. These datasheets will be transferred independently with the patient identifiable details transferred using a separate AES-256 bit end-to-end encryption software such as Slack. Therefore, in the unlikely event of a breech, clinical data could not be linked to patients. Outside of the direct clinical care team only the co-ordinating centre will have access to both the clinical and identifiable details which will be minimised as much as possible by deleting the identifiable details as soon as they have been uploaded to HES/PEDW/SMR.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol.

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance
Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as relevant. For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments
The decision to amend the protocol will be made by the CI who will inform the sponsor of the need for amendment. The history of any amendments to the protocol will be held in the Trial Master File.

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. Confidentiality Advisory Group (CAG)) need to be notified about substantial amendments in case the amendment affects their opinion of the study. Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

8.3 Peer review

The protocol has been reviewed by two expert reviewers. The first is a Professor of Clinical and Experimental Neurology with a special interest in haemoglobin scavenging after subarachnoid haemorrhage. The second is a doctor of medical statistics with a special interest in survival analysis. Both have at least 20 years experience in their respective fields. Furthermore, both reviewers are independent of the study and do not work for the department of neurosurgery. Two reviewers was felt an appropriate number based on the straight-forward study design and it does not involve experimentation on patients. Neither reviewer found issue with the protocol.

8.4 Patient & Public Involvement
University Hospitals Southampton has run focus groups to identify research priorities for patients with unruptured aneurysms and with subarachnoid haemorrhage since 2012. These focus groups have been drawn together by advertising at meetings of the Wessex SAH support group and on Facebook and email with previous patients. Mr Bulters, the Chief investigator, also has experience of working with the James Lind Alliance, who represent the gold standard in patient and public involvement, through his membership of the Stroke Association Steering Committee for the Stroke Priority Setting Partnership.

This study has developed from multiple meetings with the Wessex Subarachnoid Haemorrhage Support Group to prioritise research questions for patients with SAH and UIA. The support group is a forum for patients and carers with SAH and UIA established in 2001 and available to over 2000 patients during that time. It runs bimonthly meetings with typically 30 to 50 participants and has been on Facebook since 2016 (187 current members). Recurrently the main themes at Q&A are around anxiety, and more specifically "what is the risk I will have a haemorrhage". Anxiety over the risk of rupture of unruptured aneurysms is routinely cited as the greatest concern for both patients with

unruptured aneurysms (and patients who have suffered subarachnoid haemorrhage and had one aneurysm treated but have further untreated unruptured aneurysms). It is also a major concern for relatives and carers who fear losing loved ones. These observations of patient concerns were mirrored closely in an analysis of online discussion groups of patients with UIA.

The majority of patients are advised not to undergo treatment based on our existing understanding of the condition, however, knowledge of the presence of their aneurysm and uncertainty as to exactly what risk it poses and whether it should be treated can have devastating effects on people's lives who frequently describe an inability to move on or enjoy life again. Conversely in patients undergoing treatment of their aneurysms there is huge concern whether they are making the right decision to undergo a procedure with risk of death or major disability when we don't know exactly what risk their aneurysm poses. There is therefore huge support for further studies of unruptured aneurysm risk and most are amazed to hear how most of our decisions are based on disputed data from Finland and Japan.

We therefore organised a workgroup to discuss UIA research (advertised via the support group Facebook page) where it was confirmed that better decision making on aneurysm treatment is the main concern for patients, but patients do not want to their management to be randomised and therefore an RCT is unlikely to succeed. Consequently, a better understanding of the natural history of UIA, was deemed the top priority and that long term, ideally lifetime risks, are what is relevant to patients.

Since COVID it has not been possible to run our focus groups face to face. Therefore, to specifically evaluate the acceptability of the study design and its proportionality to the problem, over the course of 2020 we have asked a series of patients seen in outpatients with unruptured aneurysms their views. All patients strongly supported a study of the natural history of UIA. The overwhelming majority view the need to better define the aneurysm rupture risk outweighs the risks posed by use of patient identifiable data in this study. Although some declined participation in imaging or interventional studies, all confirmed they would be happy for their records to be searched for a natural history study, without full informed consent, as we propose.

8.5 Protocol compliance

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the sponsor. Frequent non-compliances could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles. Storage and handling of confidential data and documents will be in accordance with the Data Protection Act UK (2018) and General Data Protection Regulation 2016/679/EU.

Personal information required for the national admission database searches will be collected by the direct clinical care teams at each of the neurosurgery units in the UK. This data will be collected at the point of patient identification/confirmation of eligibility as it is included on all hospital documents. This information will be held at the respective neurosurgery unit on secure NHS servers in password

protected documents. At the point of patient identification each patient/aneurysm will be assigned a pseudonymisation code which is unrelated to any other identifiable details. This pseudonymisation code will be used to reunite the HES admissions with the original patient.

Identifiable details will be transmitted from the recruiting units to the co-ordinating unit using AES-256bit end-to-end encryption software. Mr Diederik Bulters and Mr Samuel Hall at the co-ordinating unit (University Hospitals Southampton NHSFT) will be the only people outside of the direct clinical care teams to have access to the patient identifiable details.

Once the identifiable details have been uploaded to HES by the co-ordinating unit (University Hospitals Southampton NHS FT) this data will be deleted and identifiable details only maintained by the direct clinical care team. From this point all correspondence between HES, the co-ordinating unit and the recruiting units will be done using the pseudonymisation code.

Combining the patients from each of the recruiting units into a single list for upload to DARS is at the recommendation of NHS Digital who advise that if each unit uploaded their own data it would be classed as separate data linkage events with the £10,000 fee applicable to each unit, i.e. increasing the search fees 20 fold.

Storage of personal data after the study has ended will only done by the direct care team within their NHS hospital (no personal data will be stored outside of the direct care team's hospital). This will initially be for 10 years and reviewed every 10 years thereafter for its ongoing need. The justification for such long periods is that little is known about the risk of rupture of aneurysms beyond the first 5 years after diagnosis. We would therefore like to repeat the HES/PEDW/SMR01 search at 5-10 year intervals in the future to track longer term rupture rates.

The data custodian will be Mr Diederik Bulters, study CI.

8.7 Indemnity

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

8.8 Access to the final study dataset

The final (pseudonymised) study dataset will be held by the CI at University Hospitals Southampton. Only the steering committee will have access to the final dataset during data analysis, up to the submission of the final study report. The steering committee will also have access to conduct secondary analysis. The steering committee may share pseudonymised data with participating centres to assist with analysis as appropriate.

The fully anonymised data set will be available to collaborators either nationally or internationally upon reasonable request. Requests to access the dataset will by via written application and approval from the study CI. All requests and approvals will be recorded in the Trial Master File.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The data arising from this study will be owned by the Sponsor.

On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared. The mains study findings will be made available through a peer reviewed manuscript.

All participating investigators will have the rights to present analysis of their local data at scientific meetings. Where possible without prejudicing the findings of the main study report, they may also publish their local findings, after discussion with the trial steering committee. Participating investigators may access the full anonymised dataset for publications as set out in 8.8. There are no time limits on when publications can be submitted based on this data.

There are currently no funders who require acknowledgement in publications. However, if external funders support this project their involvement will be acknowledged in all publications. The funders will not have publication rights over the data produced in this study.

The individual patients will not be directly notified of the results in the study. Much of the clinical decision making will have been completed many years before the results are published and approaching patients may induce undue anxiety over their previous decision. The study results will however be made available to the direct clinical care teams and once the final study manuscript is published it is expected that neurosurgeons in the UK, and worldwide, will review their practice based on the results and should they wish to change previously made treatment decisions on the basis of the new results, they can contact their patients at their discretion.

Requests from participants for final results will be directed to the final study report.

The study protocol may be published in a peer reviewed open access journal or in a public protocol repository before publication of the full study report. It is expected that the final study report will also be published in a peer reviewed journal.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The authorship on the final study report will follow International Committee of Medical Journal Editors guidelines. All contributors will be included as MEDLINE searchable authors. How authors will be listed in the byline will depend on the relevant journal policies at the time of publication. This could mean all authors personally listed in the byline, selected authors listed in the byline and the remainder grouped as “The ROAR Study Group” and listed individually at the end of the publication or in a supplement, or all authors grouped as “The ROAR Study Group”. Any manuscripts reporting on the primary study endpoints will be published following this principle. Any publications on secondary endpoints will be handled flexibly depending on the dataset utilised and contributors to the analysis.

All publications arising from this work will acknowledge the organisations involved in the research. This will specifically include University Hospital Southampton NHS Foundation Trust and its partner organisation the University of Southampton acknowledging the success of each organisation resulting from working in partnership.

10 REFERENCES

Ausman, J. I. (2002). Why the International Study of Unruptured Intracranial Aneurysms has lost credibility with neuroscientists. Surgical Neurology, 58(3-4), 287–290. http://doi.org/10.1016/s0090-3019(02)00891-1

Darsaut, T., Fahed, R., & Raymond, J. (2017). PHASES and the natural history of unruptured aneurysms: science or pseudoscience? *Journal of Neurointerventional Surgery*, *9*(6), 527–528. http://doi.org/10.1136/neurintsurg-2016-012295

de Rooij, N. K., Linn, F. H. H., van der Plas, J. A., Algra, A., & Rinkel, G. J. E. (2007). Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time

trends. Journal of Neurology, Neurosurgery & Psychiatry, 78(12), 1365–1372. http://doi.org/10.1136/jnnp.2007.117655
Greving, J. P., Wermer, M. J. H., Brown, R. D., Morita, A., Juvela, S., Yonekura, M., et al. (2014). Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurology, 13(1), 59–66. http://doi.org/10.1016/S1474-4422(13)70263-1
Juvela, S., Poussa, K., Lehto, H., & Porras, M. (2013). Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Stroke, 44(9), 2414–2421. http://doi.org/10.1161/STROKEAHA.113.001838
Korja, M., Lehto, H., Juvela, S., & Kaprio, J. (2016). Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. Neurology, 87(11), 1118–1123. http://doi.org/10.1212/WNL.0000000000003091
Nurmonen, H. J., Huttunen, T., Huttunen, J., Kurki, M. I., Helin, K., Koivisto, T., et al. (2017). Polycystic kidney disease among 4,436 intracranial aneurysm patients from a defined population. Neurology, 89(18), 1852–1859. http://doi.org/10.1212/WNL.0000000000004597
Morita, A., Kirino, T., Hashi, K., Aoki, N., Fukuhara, S., et al. (2012). The natural course of unruptured cerebral aneurysms in a Japanese cohort. The New England Journal of Medicine, 366(26), 2474–2482. http://doi.org/10.1056/NEJMoa1113260
Raymond, J., Guillemin, F., Proust, F., Molyneux, A. J., Fox, A. J., Claiborne, J. S., et al. (2008). Unruptured Intracranial Aneurysms. A Critical Review of the International Study of Unruptured Intracranial Aneurysms (ISUIA) and of Appropriate Methods to Address the Clinical Problem. Interventional Neuroradiology, 14(1), 85–96. http://doi.org/10.1177/159101990801400111
Raymond, J., Darsaut, T. E., Molyneux, A. J., TEAM collaborative Group. (2011). A trial on unruptured intracranial aneurysms (the TEAM trial): results, lessons from a failure and the necessity for clinical care trials. Trials, 12, 64. http://doi.org/10.1186/1745-6215-12-64
Rinkel, G. J. E., Algra, A., Greving, J. P., Vergouwen, M. D. I., & Etminan, N. (2017). PHASES and the natural history of unruptured aneurysms: science or pseudoscience? *Journal of Neurointerventional Surgery*, *9*(6), 618–618. http://doi.org/10.1136/neurintsurg-2016-012436
Royston, P. (2014). Tools for checking calibration of a Cox model in external validation: Approach based on individual event probabilities. The Stat Journal, 14(4),738-755.
Sonobe, M., Yamazaki, T., Yonekura, M., & Kikuchi, H. (2010). Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. Stroke, 41(9), 1969–1977. http://doi.org/10.1161/STROKEAHA.110.585059
Wiebers, D. O., Whisnant, J. P., Huston, J., Meissner, I., Brown, R. D., Piepgras, D. G., et al. (2003). Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet, 362(9378), 103–110. http://doi.org/10.1016/s0140-6736(03)13860-3

11. APPENDICIES

11.1 Appendix 1- Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	15/2/2021	Sam Hall	Correction of a typographic error. The signature date for the Chief investigator on page ii was 2011 which has been corrected to 2021.
2	1.1	15/2/2021	Sam Hall	Several textboxes in the study flow chart (page viii) had cut off some of the text. The textbox sizes have been reformatted.
3	1.2	22/02/21	Sam Hall	Page 5 – conversion of SAIL to NWIS

List details of all protocol amendments here whenever a new version of the protocol is produced. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.