MANCHESTER 1824
The University of Manchester

| | |
|---|---|
| **Study title:** | **Does Interleukin-1 Receptor Antagonist Improve Outcome following aneurysmal Subarachnoid Haemorrhage (aSAH)? A Phase III trial** |
| **Short title:** | **SC IL-1Ra in SAH – phase III trial** |
| **Chief Investigator:** | Prof Andrew King<br>Department of Neurosurgery<br>Salford Royal NHS Foundation Trust<br>Salford M6 8HD<br>Tel: 0161 206 0631<br>Email: andrew.king@manchester.ac.uk |
| **Key Sponsor Contact:** | Mohammed Zubair<br>University of Manchester<br>Christie Building<br>Oxford Road<br>Manchester M13 9PT<br>Tel: 0161 275 2725<br>Email: mohammed.zubair@manchester.ac.uk |
| **Funder:** | National Institute for Health Research |
| **Protocol Version:** | 7.0; dated 20 Sep 2019 |
| **REC Ref:** | 17/NW/0581 |
| **EudraCT No:** | 2016-003725-42 |
| **IRAS Project ID:** | 214739 |
| **Trials.gov identifier:** | NCT 03249207 |

## Confidentiality Notice

**This document contains confidential information. This document must not be disclosed to anyone other than the trial staff and regulatory authorities. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Prof Andrew King (University of Manchester).**

**This protocol has regard for the HRA guidance and order of content.**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

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 clinical investigation without the prior written consent of the Sponsor.

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

**For and on behalf of the Trial Sponsor:**

Signature: Date: ...../...../.....

.....

Name (please print):

.....

Position:

.....

**Chief Investigator:**

Signature: Date: ...../...../.....

.....

Name: (please print):

.....

**Statistician:**

Signature: Date: ...../...../.....

.....

Name: (please print):

.....

Position:

.....

**KEY TRIAL CONTACTS**

| | |
|---|---|
| **Chief Investigator** | Professor Andrew King<br>Department of Neurosurgery<br>Salford Royal NHS Foundation Trust<br>Stott Lane<br>Salford M6 8HD<br>Tel: 0161 206 0631<br>Email: andrew.king@manchester.ac.uk |
| **Sponsor** | Mohammed Zubair<br>University of Manchester<br>Christie Building<br>Oxford Road<br>Manchester M13 9PT<br>Tel: 0161 275 2725<br>Email: mohammed.zubair@manchester.ac.uk |
| **Funder(s)** | National Institute for Health Research<br>Room 132<br>Richmond House<br>79 Whitehall<br>London SW1A 2NS<br>Key contact: Charlie Dukes**,** Research Manager<br>Tel: 02380 595 653<br>Email: charlie.dukes@nihr.ac.uk |
| **Clinical Trials Unit** | Manchester Clinical Trials Unit (Manchester CTU)<br>1st Floor, Jean McFarlane Building<br>University of Manchester<br>Oxford Road<br>Manchester M13 9PL<br>Tel: 0161 306 3144<br>Email: SCIL@manchester.ac.uk |
| **Key Protocol Contributors** | Mr Hiren Patel<br>Deputy CI<br>Consultant Neurosurgeon<br>Salford Royal NHS Foundation Trust<br>Email: hiren.patel@srft.nhs.uk<br><br>Mr James Galea<br>Consultant Neurosurgeon<br>University Hospital of Wales<br>Email: james.galea@manchester.ac.uk<br><br>Louise Dulhanty<br>SAH Specialist Nurse |

| | |
|---|---|
| | Salford Royal NHS Foundation Trust<br>Email: louise.dulhanty@srft.nhs.uk<br><br>Sharon Hulme<br>Research Manager<br>University of Manchester<br>Email: Sharon.hulme@manchester.ac.uk<br><br>Prof Audrey Bowen<br>Professor of Psychology<br>University of Manchester<br>Email: Audrey.bowen@manchester.ac.uk<br><br>Dr Ian Galea<br>Associate Professor in Experimental Neurology<br>University of Southampton<br>Email: I.galea@soton.ac.uk<br><br>Dr Kayode Ogungbenro<br>Lecturer in Cancer Pharmacometrics<br>University of Manchester<br>Email: kayode.ogungbenro@manchester.ac.uk |
| **Statistician** | Prof Andy Vail<br>Centre for Biostatistics<br>University of Manchester<br>Tel: 0161 275 1720<br>Email: andy.vail@manchester.ac.uk |
| **Trial pharmacist** | Beatriz Duran Jimenez<br>Manchester University NHS Foundation Trust<br>Wythenshawe Hospital<br>Pharmacy - Ground Floor<br>Southmoor Road<br>Manchester M23 9LT<br>Tel: +44 (0) 161 291 4193<br>Email: Beatriz.Duran-Jimenez@manchester.ac.uk / Beatriz.Duran@mft.nhs.uk |
| **Committees** | A trial management group, trials steering committee and independent data monitoring committee will be involved in the set-up and management of this trial.<br>Details of the committee members and details of their roles and responsibilities can be found in each committee charter. |

## SYNOPSIS

| | |
|---|---|
| **Title** | Does Interleukin-1 Receptor Antagonist Improve Outcome following aneurysmal Subarachnoid Haemorrhage (aSAH)? |
| **Trial Phase** | Phase III |
| **Hypotheses** | Treatment with IL-1Ra subcutaneously (SC) twice daily to patients with aSAH will improve clinical outcome at 6 months. |
| **Primary Outcome** | Ordinal shift in modified Rankin Score (mRS) at 6 months |
| **Secondary Outcomes** | Measurement of mood, fatigue and quality of life at 6 months using HADS, Fatigue score and EQ-5D-5L score and correlation of the effect of treatment on clinical outcome with its effect on plasma IL-6 concentration. |
| **Trial Design** | Multi-centre, parallel group, double-blind, placebo-controlled randomised phase III trial. In addition there is a single sub-study in patients who are entered into the main study to allow retention of the blood pellet from research blood samples taken at baseline and 3-5 days post randomisation, for use in future analysis of genetic influence on outcome after SAH if optional consent is given |
| **Sample Size** | Target total recruitment of 1000 patients (800 participants with confirmed aSAH). |
| **Summary of Participant Eligibility Criteria** | ***Inclusion Criteria:*** Patients with CT positive spontaneous SAH admitted to a participating neurosurgical centre within 72h onset of SAH; no concomitant serious health problems in the opinion of the PI (or designee); willing and able to consent, or consent available from patient representative; male or female aged 18 or over<br><br>***Exclusion Criteria:*** Unconfirmed or uncertain diagnosis of spontaneous SAH; known active tuberculosis or active hepatitis; known active malignancy; neutropenia (neutrophil count $<1.5 \times 10^9$/L ); abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 ml/minute); live vaccinations within the last 10 days; previous or concurrent treatment with IL-1Ra; previous or current treatment with medication suspected of interacting with IL-1Raknown at the time of trial entry or previous participation in this trial; known to be pregnant or breast feeding; clinically significant serious concurrent medical condition, pre morbid illnesses, or concurrent serious infection, at the PI's (or designee's) discretion; known allergy to IL-1Ra or any of the excipients; Known allergy to other products that are produced by DNA technology using the micro-organism E. coli |
| **Investigational Product Dosage and Administration** | Recombinant human IL-1Ra (manufactured as Kineret from Swedish Orphan Biovitrum Ab (Sobi), Sweden). Doses to be administered SC twice daily (12 hourly) starting within 72 hours of ictus (onset of symptoms) for a maximum of 21 days from ictus (or sooner if discharged from neurosurgical centre). |
| **Control groups** | Matched placebo obtained from Sobi will be used as control trial intervention |
| **Procedures** | Potential participants will be screened to ensure their eligibility for the trial. Consenting patients will be randomised to treatment group. Patients will undergo a |

| | |
|---|---|
| | baseline assessment prior to administration of the study drug (either IL-1Ra or placebo). Blood samples will be taken at baseline and day 3-5 post randomisation. Blood pellets will be retained for use in future genetic analysis if optional consent is given.<br><br>Outcome measures will be recorded during their stay and at the 3-5 day/30 day/6-month follow-up. |
| **Statistical Considerations** | We will seek outcomes for all randomised participants with confirmed aSAH regardless of protocol adherence and include them in analyses under the allocated group. Primary analysis will apply proportional odds regression to the mRS at 6-months with adjustment for the randomisation stratification criteria. Secondary outcomes will be assessed using regression methods with similar adjustment. Causal inference will be applied to the possible mediation of treatment effect through reduction in plasma IL-6. |

## FUNDING AND SUPPORT IN KIND

| FUNDER(S) | FINANCIAL AND NON FINANCIAL SUPPORT GIVEN |
|---|---|
| National Institute for Health Research<br><br>**Acknowledgement**<br>This project is funded by the Efficacy and Mechanism Evaluation (EME)* Programme, an MRC and NIHR partnership.<br><br>**Disclaimer**<br>The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.<br><br>*The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D Division, Public Health Agency in Northern Ireland. | Funding of research costs (5 year project duration). |
| Swedish Orphan Biovitrum | Supply of study drug (IL-1RA and placebo) and shipping costs |
| University of Southampton | Costs associated with courier transfer of anonymised blood pellets from the Biomedical Research Facility at Salford Royal NHS Foundation Trust to University of Southampton for genetic sub-study analysis. |
| UKCRN | Nurse support for screening and approach |
| Central / local commissioning | Excess Treatment costs |

## LIST of CONTENTS

SIGNATURE PAGE ..... 1
KEY TRIAL CONTACTS ..... 3
SYNOPSIS ..... 5
FUNDING AND SUPPORT IN KIND ..... 7
LIST of CONTENTS ..... 8
LIST OF ABBREVIATIONS ..... 13
LIST OF DEFINTIONS ..... 15
TRIAL PROTOCOL ..... 16
1. BACKGROUND ..... 17
1.1 Existing research ..... 17
1.1.1 Brain Injury and Ischaemia ..... 17
1.1.2 Inflammation in aSAH ..... 18
1.1.3 Evidence for the benefit of IL-1Ra in aSAH ..... 18
1.1.4 Safety and Tolerability ..... 20
1.1.5 Brief Trial Outline ..... 20
2. RATIONALE ..... 21
2.1 Rationale for Target Population ..... 21
2.1.1 Justification of IMP dose and treatment duration ..... 22
2.1.2 Justification for inclusion prior to confirmation of aneurysm ..... 23
2.2 Assessment and Management of Risk ..... 23
3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS ..... 24
3.1 Aim ..... 24
3.2 Primary Objective ..... 24
3.3 Secondary Objectives ..... 24
3.4 Outcome Measures/Endpoints ..... 24
3.4.1 Primary outcome ..... 24
3.4.2 Secondary Outcomes ..... 25
4. TRIAL DESIGN ..... 25
5. TRIAL SETTING ..... 25
6. ELIGIBILTY CRITERIA ..... 26
6.1 Inclusion criteria ..... 26
6.2 Exclusion criteria ..... 26

7. TRIAL PROCEDURES ..... 27
7.1 Schedule of Assessments ..... 27
7.2 Recruitment ..... 28
7.2.1 Patient Identification and Screening ..... 29
7.3 Consent ..... 30
7.4 Randomisation ..... 31
7.4.1 Method for participant randomisation and the implementing the allocation sequence ..... 31
7.4.2 Management of kits at site ..... 31
7.5 Blinding ..... 32
7.6 Unblinding ..... 32
7.7 Trial Assessments ..... 33
7.7.1 Pre-randomisation evaluation ..... 33
7.7.2 Post-randomisation evaluations ..... 33
7.8 Withdrawal Criteria ..... 35
7.9 Storage and Analysis of Samples ..... 36
7.10 End of Trial ..... 36
8. TRIAL MEDICATION ..... 37
8.1 Investigational product ..... 37
8.1.1 Interleukin-1 receptor antagonist (IL-1Ra) ..... 37
8.1.2 Access to Treatment Assignments ..... 37
8.1.3 Compliance in Investigational Product Administration ..... 38
8.1.4 Concomitant medication ..... 38
8.1.5 Special warning and precautions for use ..... 39
8.1.6 Labelling of study drug (IL-1Ra / placebo) ..... 39
8.1.7 Supply of Study Drug (IL-1Ra / placebo) ..... 40
8.1.8 Ordering and Storage of Study Drug (IL-1Ra / placebo) ..... 40
8.2 Prescribing and allocation of study drug kit ..... 40
8.3 Dispensing of Study Drug (IL-1Ra / placebo) ..... 41
8.4 Administration of Study Drug (IL-1Ra / placebo) ..... 41
8.5 Post-trial Access to Study Drug (IL-1Ra) ..... 42
9. PHARMACOVIGILANCE ..... 42
9.1 Definitions ..... 42
9.1.1 Operational definitions for (S)AEs ..... 44

9.2 Recording and Reporting of SAEs, SARs AND SUSARs ..... 49
9.3 Responsibilities ..... 50
9.4 Criteria for Intervention and Discontinuation ..... 52
9.5 Notification of Deaths ..... 52
9.6 Pregnancy Reporting ..... 53
9.7 Overdose Reporting ..... 53
9.8 Urgent Safety Measures ..... 54
9.9 New Safety Findings ..... 54
9.10 The type and duration of the follow-up of subjects after adverse events ..... 54
9.11 Periodic Safety Reports ..... 54
9.11.1 Development safety update reports (DSUR) ..... 54
9.11.2 Annual progress reports (APR) ..... 54
10. TRIAL MANAGEMENT AND OVERSIGHT ARRANGMENTS ..... 55
10.1 Roles and Responsibilities ..... 55
10.1.1 Trial sponsor ..... 55
10.1.2 Manchester CTU ..... 55
10.1.3 Funder ..... 56
10.2 Oversight Committees ..... 56
10.2.1 Trial Management Group (TMG) ..... 56
10.2.2 Trial Steering Committee (TSC) ..... 56
10.2.3 Independent Data Monitoring Committee (IDMC) ..... 57
11. STATISTICS AND DATA ANALYSIS ..... 57
11.1 Sample Size Calculation ..... 57
11.2 Planned Recruitment Rate ..... 58
11.3 Statistical Analysis Plan ..... 58
11.3.1 Summary of baseline data and flow of patients ..... 58
11.3.2 Primary outcome analysis ..... 58
11.3.3 Secondary outcome analysis ..... 58
11.3.4 Mechanistic analysis ..... 59
11.4 Subgroup Analyses ..... 59
11.5 Adjusted Analysis ..... 59
11.6 Interim Analysis and Criteria for the Premature Termination of the Trial ..... 59
11.7 Subject Population ..... 60

11.7.1 Procedure(s) to account for missing or spurious data ....60
12. DATA HANDLING ....60
12.1 Data Collection Tools and Source Document Identification ....60
12.1.1 CRFs as Source Documents....61
12.2 Data Handling and Record Keeping....61
12.2.1 Data Handling at Manchester CTU ....61
12.3 Access to Data ....61
12.3.1 Trial performance and monitoring ....62
12.3.2 Clinical study report....62
12.4 Archiving....62
13. MONITORING, AUDIT & INSPECTION ....62
14. ETHICAL AND REGULATORY CONSIDERATIONS....63
14.1 Research Ethics Committee (REC) Review & Reports ....63
14.2 Regulatory Compliance ....63
14.2.1 Local capability and capacity review ....64
14.3 Peer Review....64
14.4 Public and Patient Involvement (PPI)....64
14.5 Protocol Compliance ....65
14.6 Notification of Serious Breaches to GCP and/or the protocol ....65
14.7 Data Protection and Patient Confidentiality ....65
14.8 Financial and Other Competing Interests....66
14.9 Indemnity ....66
14.10 Amendments ....67
14.11 Post-Trial care....67
15. DISSEMINATION POLICY ....67
15.1 Dissemination Policy....67
15.2 Authorship Eligibility Guidelines....68
16. APPENDICES....70
16.1 Appendix 1: List of live vaccinations commonly used in the UK ....70
16.2 Appendix 2: Safety Reporting Flow Chart ....71
16.3 Appendix 3: Amendment History....72
17. REFERENCES ....79

**Figure 1:** Trial Flow Chart ..... 16
**Figure 2:** Summary of distribution of inflammatory markers, IL-6 and CRP, on the natural logarithm scale up to Day 21 post ictus ..... 19
**Figure 3:** PK profiles of Kineret in plasma following o.d. (real) and b.d. (simulated) SC administration ..... 22

Table 1 Schedule of Assessments ..... 27
**Table 2:** Definitions of Adverse Events ..... 43
**Table 3:** Assessment of Severity ..... 45
**Table 4:** Events related to normal diseases processes in SAH (Expected events) ..... 46
**Table 5:** Responsibilities relating to AE reporting ..... 51

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ANC | Absolute Neutrophil Count |
| AR | Adverse Reaction |
| aSAH | Aneurysmal Subarachnoid Haemorrhage |
| CA | Competent Authority |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTA | Clinical Trial Authorisation |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| CTPM | Clinical Trial Project Manager |
| DMC | Data Monitoring Committee |
| DSUR | Development Safety Update Report |
| EC | European Commission |
| eGFR | estimated Glomerular Filtration Rate |
| EMA | European Medicines Agency |
| EU | European Union |
| EUCTD | European Clinical Trials Directive |
| EudraCT | European Clinical Trials Database |
| EudraVIGILANCE | European database for Pharmacovigilance |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| MA | Marketing Authorisation |

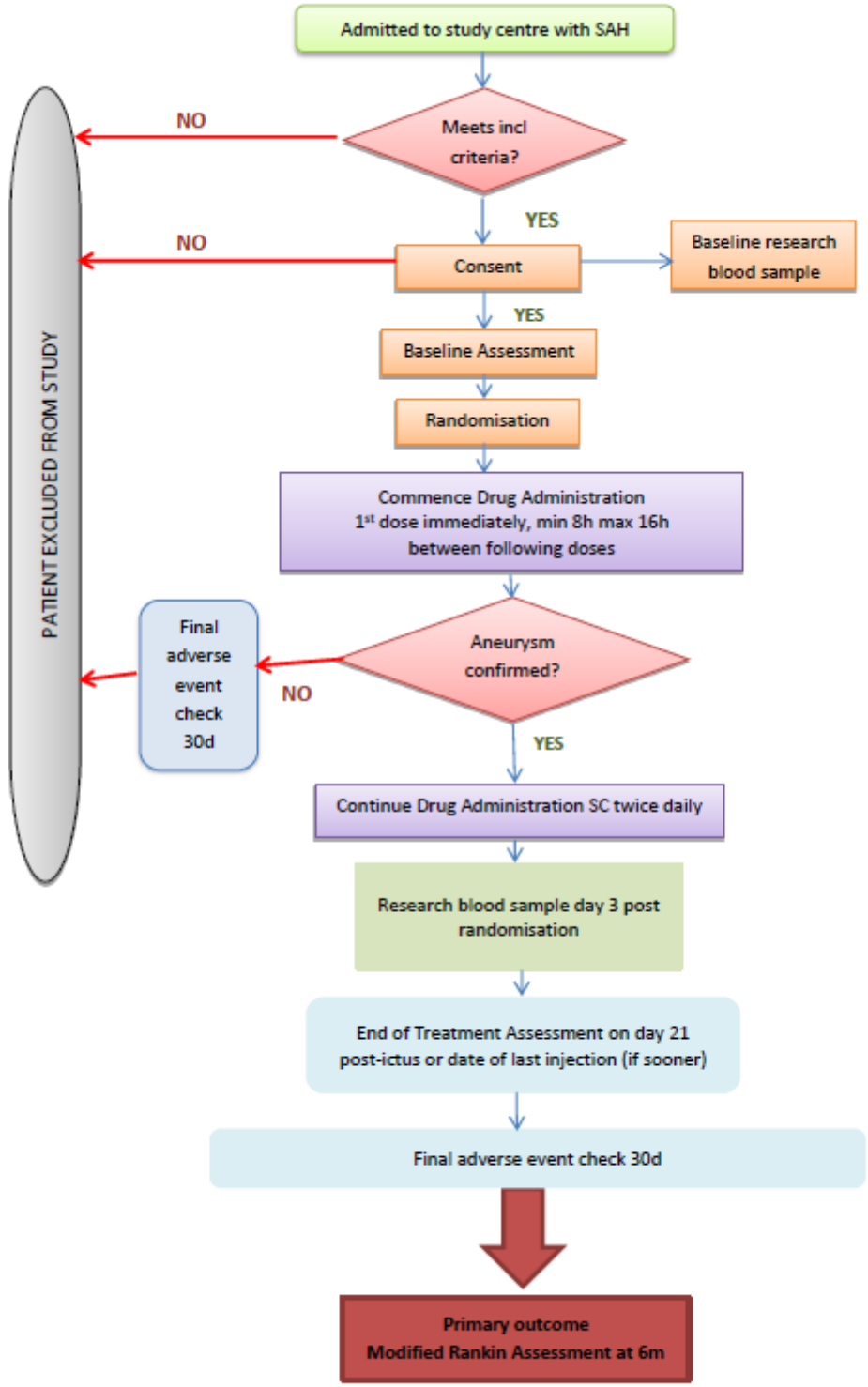
| | |
|---|---|
| Manchester CTU | Manchester – Clinical Trials Unit |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| mRS | modified Rankin Score |
| MS | Member State |
| NHS R&D | National Health Service Research & Development |
| NIMP | Non-Investigational Medicinal Product |
| PI | Principal Investigator |
| PIC | Participant Identification Centre |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| QC | Quality Control |
| QP | Qualified Person |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SC | Subcutaneous |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SmPC | Summary of Product Characteristics |
| SSI | Site Specific Information |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| TMF | Trial Master File |

## LIST OF DEFINTIONS

| | |
|---|---|
| Manchester CTU | The company delegated the management of the study including trial management, data management and monitoring. |
| Trial Centre | The Chief Investigator's own team (including Principal Investigators) who will be delegated the responsibility to conduct specified trial procedures. |
| Study drug | Either IL-1Ra or placebo. |
| Woman of childbearing potential (WOCBP) | A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. |

**TRIAL FLOW CHART**

**Figure 1:** Trial Flow Chart



**TRIAL PROTOCOL**

**Does Interleukin-1 Receptor Antagonist Improve Outcome following aneurysmal Subarachnoid Haemorrhage (aSAH)? A Phase III trial**

# 1. BACKGROUND

## 1.1 Existing research

Aneurysmal subarachnoid haemorrhage (aSAH) is an acute cerebrovascular event characterised by the rupture of an aneurysm within the subarachnoid space and release of blood over the surface of the brain. Patients may present with sudden collapse, severe headache or acute neurological dysfunction. Initial management is supportive together with securing of the aneurysm by endovascular or surgical means. The incidence is around 9 cases per 100,000 person years, largely unchanged over the last 4 decades[1]. Up to 35% of patients with aSAH do not survive the initial bleed[2] and a significant proportion of survivors suffer a secondary ischaemic insult, resulting in overall high morbidity and mortality. People may be left with physical disabilities, including speech, motor, balance sensory or visual perceptual problems, which affect their ability to care for themselves. There is now increasing recognition of the impact of longer term cognitive and higher mental dysfunction which also poses a significant socioeconomic burden[3]. A systematic review of studies of the long term cognitive and psychological sequelae of aSAH demonstrates the difficulties experienced by many long term survivors including cognitive function, language, mood, anxiety and fatigue, impacting on activities of daily living and, in particular, return to work[4]. Moreover, patients with aSAH tend to be younger than those with ischaemic stroke or primary intracerebral haemorrhage so that the socioeconomic effect may be more significant[5]. In one recent prospective study of 200 survivors of aSAH, only 46.5% reported return to previous leisure activities and 61.5% reported return to usual social interactions[6] after 4-10 years. Depression and fatigue scores were the best predictors of poor outcome.

### 1.1.1 Brain Injury and Ischaemia

Although aSAH differs from other forms of stroke in its presentation and management, most of the pathological sequelae in terms of brain damage are similar and underlying mechanisms are common to many other neurological disorders such as vascular dementia, birth asphyxia and secondary ischaemia resulting from head trauma. Following the acute aneurysmal bleed, global hypoperfusion results from a loss of cerebral perfusion pressure and a concomitant, acute rise in intracranial pressure. Some patients may have an associated intracranial haematoma which exerts a pressure effect and exacerbates injury through haem-related toxicity. Ischaemic brain damage following aSAH can present clinically as a sudden deterioration in neurological function, often called delayed cerebral ischaemia (DCI), occurring in up to 30% of patients. This most commonly occurs between the fourth and tenth day after aSAH[7]. More recently the term “early brain injury” has been used to describe the mechanisms underlying acute neurological deterioration following aSAH[8] that include the cell death, cerebral oedema and neuronal dysfunction that occur following the initial bleed. Preclinical and autopsy studies illustrate the heterogeneity of pathological phenomena that may manifest as neurological dysfunction after aSAH[9]. The causes of brain injury after aSAH are multifactorial and include classic angiographic spasm, microvascular spasm, micro thromboembolism, direct inflammatory neuro-toxicity and spreading depolarisation[10]. Treatment to prevent or limit brain injury is focused on high dependency care including maintenance of cardiac output, early recognition of infection, avoidance of hyperglycaemia and maintenance of high cerebral blood flow with hypervolaemia and induced hypertension[11].

The only evidence-based pharmacological intervention is the reduction of vascular spasm using calcium channel antagonism with nimodopine[12]. These limited treatments reveal a pressing need to develop additional therapies that treat the underlying pathophysiological mechanism of brain injury following aSAH.

### 1.1.2 Inflammation in aSAH

Inflammation is a key factor following aSAH associated with vasospasm, oedema and neuronal loss. There is now both experimental and clinical evidence that inflammation is a major contributor to brain injury and ischaemia and holds significant promise as a therapeutic target[13]. A number of potential anti-inflammatory strategies have been suggested or trialled in aSAH[8], including clazosentan and cilostazol, but none have shown the anti-inflammatory activity of IL-1Ra or have its extensive preclinical data. Statins have an anti–inflammatory activity and have been trialled recently, most notably in the recent STASH study, but showed no evidence of clinical effectiveness[14]; it is of note that statins in this study did not reduce the inflammatory mediator C-reactive protein (CRP)[15] which contrasts with our proposed intervention.

Interleukin-1 (IL-1) is a pro-inflammatory cytokine that is produced in response to brain injury and triggers a cascade of events that leads to further pro-inflammatory cytokine expression, increased vascular activation, increased numbers of circulating leucocytes, activation of glial mediated neuronal toxicity and increased neuronal excitability[13]. The naturally occurring antagonist of IL-1, interleukin-1 receptor antagonist (IL-1Ra) blocks these effects by competitively binding to the IL-1 receptor. In experimental SAH, IL-1Ra inhibits the IL-1α driven inflammation induced partly by haem released from lysed red blood cells[16]. A number of clinical studies that demonstrated a correlation between elevated levels of inflammatory markers (including cytokines such as IL-1 and its downstream mediator interleukin-6; IL-6) in cerebrospinal fluid (CSF) of people with aSAH that are related to poor neurological outcome. Plasma CRP is an independent predictor of clinical outcome as measured by the modified Rankin Scale (mRS) in good grade (World Federation of Neurosurgical Societies; WFNS grade 1 and 2) patients[15]. Plasma IL-6 levels are also associated with poor functional outcome[17]. Plasma inflammatory cytokines may reflect intracerebral processes, or may contribute to brain injury via the damaged blood brain barrier[8]. Rodent studies using bone marrow transplantation indicate that both central and peripherally derived IL-1 are involved in ischaemic brain injury[18].

### 1.1.3 Evidence for the benefit of IL-1Ra in aSAH

IL-1Ra is a competitive and highly-selective antagonist that blocks all known actions of interleukin-1 alpha (IL-1α) and IL-1 beta (IL-1β)[19]. It blocks all IL-1 signal transduction and actions. Preclinical studies in stroke and SAH have clearly demonstrated the efficacy of IL-1Ra in reducing neuronal damage in multiple models, in different laboratories[20] and in co morbid animals[13] and improving outcome in experimental models and the potential use of this drug in improving outcome in patients.

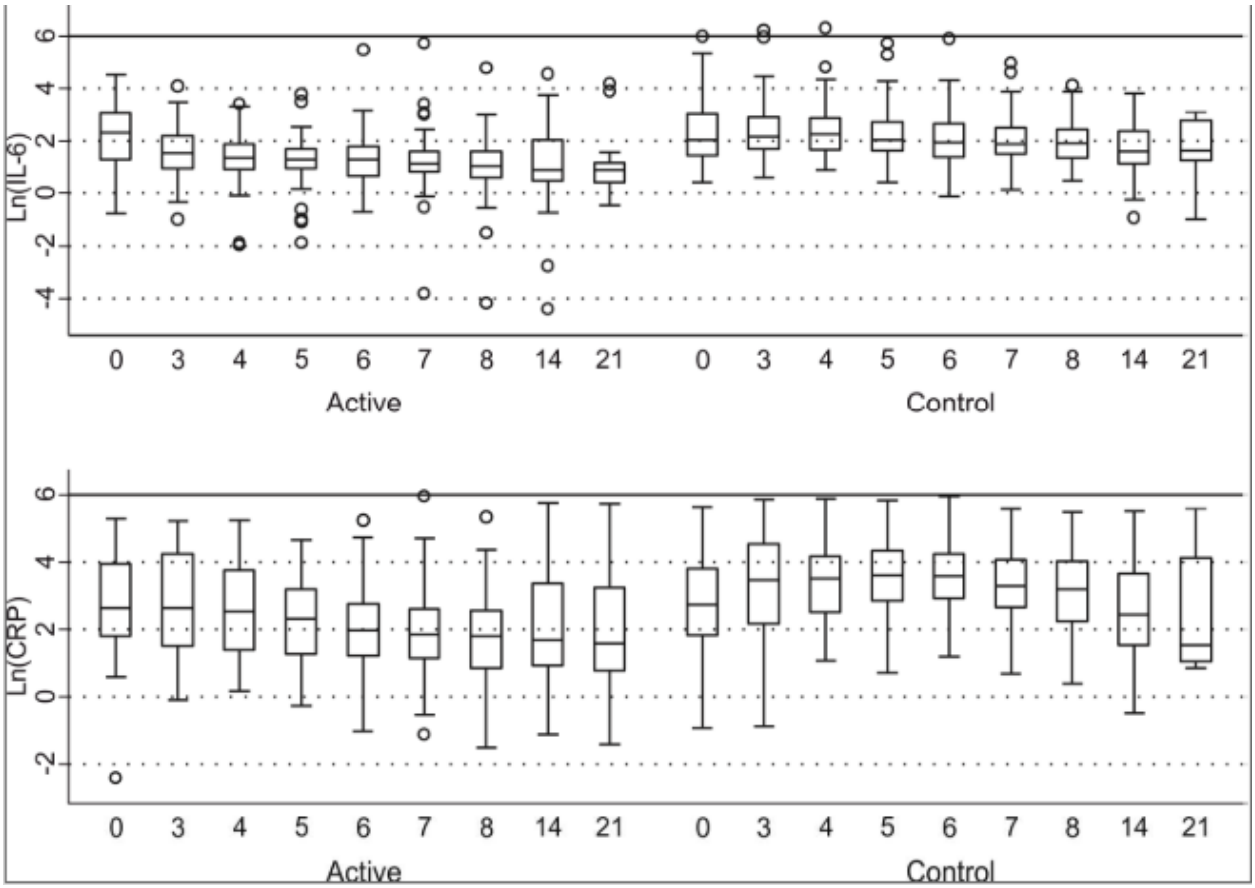
Recombinant subcutaneous (SC) IL-1Ra is effective in patients in reducing inflammation associated within various disease states including rheumatoid arthritis[21-23]. In an open-labelled pharmacokinetic (PK) study, performed in our centre, IL-1Ra was administered intravenously (IV) to a group of eight aSAH patients with external ventricular drains (EVDs) *in situ*. Simultaneous plasma and drain sampling of cerebrospinal fluid (CSF) showed that IL-1Ra did penetrate the blood-CSF barrier to achieve concentrations in the CSF that were experimentally therapeutic[24].

In a further open-labelled PK study in 25 patients with aSAH and EVDs, we demonstrated that the rate of entry into the CSF can be modulated to safely achieve a therapeutic time window of 45 minutes[25]. This

demonstrates early penetration of IL-1Ra into the brain compartment, however our experimental studies using mouse chimaeras show that both peripheral and brain IL-1 contribute to ischaemic brain damage[18].

In this clinical aSAH study, we demonstrated a decrease in peripheral levels of IL-6, although the administration period of IV IL-1Ra was only four hours. Another small study from our group demonstrated a reduction in CSF IL-6 concentration in people with aSAH who received intravenous IL-1Ra[26]. We recently completed a Medical Research Council (MRC) phase II study (G1001252/1 ISRCTN25048895) in 3 neurosurgical centres where SC IL-1Ra was administered to people with aSAH. It randomised 136 patients with aSAH within 72 hours of symptom onset to receive IL-1Ra and standard care or standard care alone in an open label randomised study. Participants continued treatment until discharge from the neurosurgical unit or day 21 (whichever was earlier). Primary outcome was plasma IL-6 concentrations. We showed a very significant reduction in plasma IL-6 in patients receiving IL-1Ra (geometric mean of IL-6 was 65% lower at 5 days post ictus in the treatment group than in the control group; area under the curve for logged values of IL-6 days 3-8 was 42% lower in the treated group). There was a similar difference in CRP between the two groups, although, as would be expected from the biology of CRP, the reduction in IL-6 occurred earlier than CRP. We also showed that the treated group had very consistent plasma levels of drug throughout 24 hours with twice daily SC injection of 100mg of IL-1Ra.

**Figure 2:** Summary of distribution of inflammatory markers, IL-6 and CRP, on the natural logarithm scale up to Day 21 post ictus



The study was not powered for a clinical outcome. However, extended Glasgow Outcome Score (GOS-E) was recorded at 6 months post randomisation as a secondary outcome measure. GOS-E is an 8-point scale, commonly used as an outcome in neurosurgical trials, which provides a measure of overall functional outcome but probably does not address the specifics of functional limitations[27]. The mRS has been used as a clinical outcome in other clinical studies in aSAH, including the STASH trial, because it shows finer discrimination among participants classified as "Good Recovery" using GOS-E. In our phase II study we found, a common odds ratio (95% confidence interval; CI) of 0.92 (0.50-1.7) in favour of treatment using ordinal regression for GOS-E. A logistic regression of sliding dichotomy to allow prognosis-based definition of favourable outcome gave odds ratio (95% CI) of 0.6 (0.31 to 1.3); p=0.419. Target for phase III is a common odds ratio of 0.65 on the mRS and would indicate a 7% increase in favourable primary outcome, a proportion that would have been considered clinically significant in the STASH trial in aSAH[14]. Data from our phase II study also add to a substantial safety profile for IL-1Ra in aSAH. We have now demonstrated conclusively that twice daily SC administration of IL-1Ra feasible following aSAH, is well tolerated and reduces plasma levels of inflammation significantly and reliably.

### 1.1.4 Safety and Tolerability

IL-1Ra has been evaluated in several clinical trials and is well tolerated with a consistent safety profile. Clinically significant adverse events in our stroke and aSAH studies were no more common with IL-1Ra than with placebo (with 102 patients treated with IL-1Ra). There is evidence of an increased frequency of serious infections in people treated with IL-1Ra long term, for example in conditions such as rheumatoid arthritis, but we have now treated patients with both ischaemic stroke and aSAH with IL-1Ra without safety concerns (no SARs and no SUSARs have been observed in over 70 patient with ischaemic stroke and 130 patients with aSAH). We have found no difference in infection rates between treated and non-treated/placebo patient groups even though patients with aSAH are at an increased risk of infection, as they may require intensive or high dependency care and be at risk of pneumonia. Indeed we have evidence that IL-1Ra appears to reverse the immune suppression associated with ischaemic stroke[28] *in vitro*.

The DSUR for IL-1Ra trials in stoke and aSAH had been complied by the trial centre and Sobi and includes confirmation of review by IDMCs for all trials. The conclusion of the latest DSUR (2016) is that the safety profile of IL-1Ra is consistent with the current SmPC. No issues have been highlighted by the MHRA during their review of the DSURs of IL-1Rs in phase II stroke and aSAH trials.

### 1.1.5 Brief Trial Outline

This phase III trial will establish whether IL-1Ra, administered SC twice daily for up to 21 days post aSAH, improves clinical outcome as measured by ordinal shift in mRS at 6 months.

Patients with SAH transferred to a neurosurgical centre will be identified and approached for study participation. Following consent, patients will be randomised to receive either IL-1Ra or placebo for a maximum of 21 days from ictus. Patients who are found to be non-aneurysmal following randomisation will be withdrawn from the study treatment. Blood samples for plasma IL-6 will be obtained prior to randomisation and at day 3-5 post randomisation for IL-6 & IL-1Ra measurement. Safety will be measured at 30 days post randomisation and outcome assessed at 6 months post randomisation. A sub-study will allow retention of blood pellet from research blood samples to be retained for use in a future, ethically-approved project of genetic influence on outcome after SAH.

## 2. RATIONALE

**Hypothesis:** SC IL-Ra improves clinical outcome for people with aneurysmal subarachnoid haemorrhage.

There is an urgent need to improve outcomes for people with aSAH who, while they may survive the initial bleed and go on to have their aneurysm successfully coiled or clipped, remain at risk of further neurological damage in the 3 weeks following ictus (onset of symptoms). People with aSAH may have significant neurological damage in terms of disability, but also may appear to have made a full physical recovery but remain affected by fatigue, low mood, and poor concentration and attention. This significantly impacts on return to normal life and in particular return to work.

The only guidelines based treatments aimed at improving neurological function are supportive care, hypervolaemia and induced hypertension, and the calcium channel antagonist nimodopine (www.strokeaudit.org; www.rcplondon.ac.uk). There is clearly a pressing need to develop new treatments to avoid the neurological damage that has such a significant impact on survivors.

Inflammation is associated with neurological damage following aSAH. Clinical, preclinical and autopsy studies of plasma and cerebrospinal fluid inflammatory markers demonstrate that following both experimental and clinical aSAH there is pro-inflammatory cytokine expression and increased vascular activation, increased numbers of circulating leucocytes, activation of glial mediated neuronal toxicity and increased neuronal excitability[13]. Reducing inflammation caused by aSAH is widely recognised as a key therapeutic target.

We have now shown that we can significantly, reliably and quickly reduce plasma levels of inflammation in people with aSAH using twice daily subcutaneous (SC) injections of 100mg IL-1Ra. We have shown that this approach is feasible in UK neurosurgical centres, that it is well tolerated and there are no significant safety concerns with this drug in this patient group (see 1.1.4). We have also shown the secondary clinical outcomes in this study although the study was not powered to show a significant change in clinical outcome. There is therefore a pressing case to test the effectiveness of this intervention in aSAH in a larger, double blind placebo controlled trial by finding out whether it improves clinical outcome. We propose a phase III trial with clinical outcome (ordinal shift in mRS) at 6 months post randomisation as the primary outcome.

### 2.1 Rationale for Target Population

The aim of this clinical trial is to evaluate whether or not treatment with IL-1Ra improves clinical outcome following aSAH. This research builds on our recent phase II study of IL-1Ra in aSAH that has shown significant reductions in plasma inflammatory markers in the treatment compared with control. It will provide definitive evidence of the efficacy or otherwise of this treatment.

Patients with aSAH even after acute management and securing of the aneurysm to prevent rebleeding, have significant mortality and morbidity with 25% dead or disabled at one year[29]. They may have symptoms associated with early brain injury which may include acute neurological deterioration, often occurring between 3 and 21 days following ictus and affecting mainly those with poor grade SAH. A higher proportion of patients experience problems such as fatigue, memory and concentration difficulties that contribute significantly to their difficulties returning to work and normal family life[9]. In a post -hoc analysis of the STASH trial, CRP at baseline was associated with clinical outcome in 'good grade' (WFNS 1&2) patients[15].

Our trial is needed now because pharmacological attempts to improve outcome to date have been disappointing, with only nimodipine, a selective calcium channel blocker, shown to improve outcome in the acute management of aSAH[30]. Prevention of cerebral ischaemia remains a key target[9]. Reducing the impact of cerebral ischaemia following aSAH would make a very significant societal and economic impact[5].

### 2.1.1 Justification of IMP dose and treatment duration

Patients will be randomised to receive study drug or placebo for a maximum 21 days from ictus. The length of treatment reflects the time course for risk of vasospasm that is generally accepted through the neurosurgical community[31]. Moreover, there is evidence that breakdown products of extravasated blood that are associated with IL-1 mediated inflammation are present in the cerebrospinal fluid for three weeks in 70% of patients following SAH[32].

The dose of SC IL-1Ra has been chosen following extensive pharmacological research. The peak plasma concentration achieved by injection of 100 mg of SC Kineret® is achieved within a maximum of 7 hours. This results in a significant variation (peak-trough) in plasma concentration when a once daily dose is administered. While this may not be an issue for treatment of chronic inflammatory diseases such as rheumatoid arthritis, it was our objective to achieve steady plasma concentrations when antagonising the acute inflammatory response following aSAH.

Using PK and safety data from Amgen, with whom we have collaborated for a number of years before the patent transfer to SOBI, we modelled different dosing regimens of the drug. A twice daily injection of 100 mg of Kineret® was predicted to achieve steady concentrations of the drug (Fig 3). This dose was subsequently used in a phase II study funded by the MRC (EudraCT 2011-001855-35). We have since published the results that demonstrated that the plasma concentrations achieved using this regime were within our predicted intervals and that the administration was feasible[33]. During our proposed study, we will be using this same dose and duration of drug that was shown to be effective in reducing inflammation in our patient cohort.

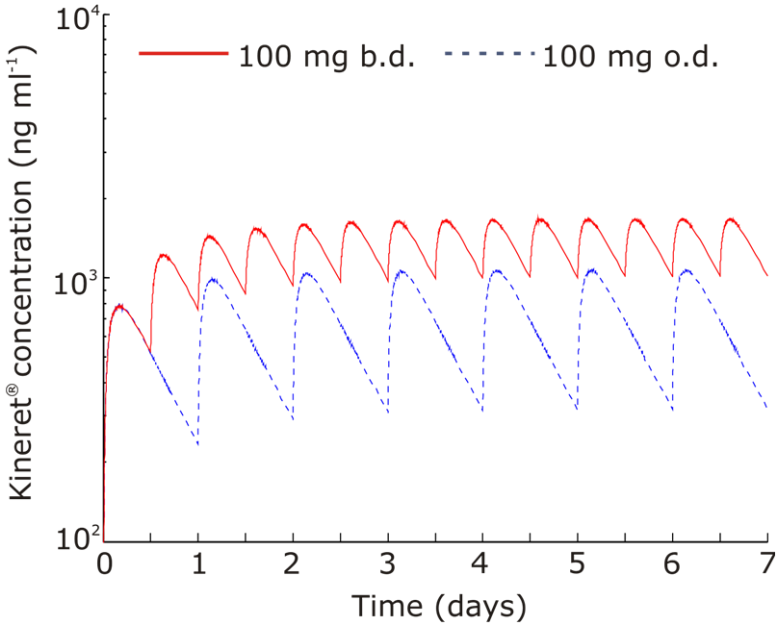



**Figure 3:** PK profiles of Kineret® in plasma following o.d. (real) and b.d. (simulated) SC administration

### 2.1.2 Justification for inclusion prior to confirmation of aneurysm

The initial clinical and computed tomography (CT) scan diagnosis on arrival in the neurosurgical centre is normally of SAH (not aSAH) because a proportion (around 20%) of patients with confirmed SAH is subsequently found on angiography not to have aneurysm. These non-aneurysmal SAH (non-aSAH) patients usually have mesencephalic bleed which has a much better outcome than aneurysmal bleed. Diagnosis of aneurysm requires an angiogram (usually CT angiogram; CTA) which may not be performed immediately.

Earlier treatment is known to be associated with better outcome in preclinical studies[34,35] so to avoid delay, we propose to randomise following the diagnosis of SAH which may be prior to confirmation of aneurysm. People subsequently found to be non-aneurysmal (usually angiogram is performed within 48 hours or less of arrival at the neurosurgical centre) will be withdrawn from the trial. We will encourage early approach to allow people as much time as they need to consider participation and so approaching as soon as the initial SAH diagnosis is made seems most logical. Patients for whom aneurysm is not confirmed will not be included in outcome analysis although they will be included in Adverse Event monitoring.

## 2.2 Assessment and Management of Risk

aSAH is a common cause of stroke related death and disability affecting younger people than the more common ischaemic stroke. Clinical outcome remains relatively poor and even those who survive the initial bleed rarely feel back to normal when they return home. Many survivors report ongoing symptoms e.g. fatigue, attention and memory deficits for months or years following ictus and return to work is often problematic. aSAH in 2005 was estimated to cost £205 million annually in the NHS including hospital care costs and care after discharge. Community health and social service care costs were estimated to be around 18% of the total cost[5]. Any treatment that improves modified Rankin score (mRS) could reduce length of hospital stay and will reduce the patient's dependence on formal and informal carers following discharge. It would be cost effective.

IL-1Ra has been evaluated in several clinical trials and is well tolerated with a consistent safety profile. Clinically significant adverse events in our stroke and aSAH studies were no more common with IL-1Ra than with placebo. There is evidence of an increased frequency of serious infections in people treated with IL-1Ra long term, for example in conditions such as rheumatoid arthritis, but we have now treated patients with both ischaemic stroke and aSAH with IL-1Ra without safety concerns. We have found no difference in infection rates between treated and non-treated/placebo patient groups even though patients with aSAH are at risk of infection, as they may require intensive or high dependency care and be at risk of pneumonia. Indeed we have evidence that IL-1Ra appears in vitro to reverse the immune suppression associated with ischaemic stroke[28].

IL-1Ra is contraindicated in people who are already taking Tumour Necrosis Factor-alpha (TNF-α inhibitors) so a medication history will be taken prior to inclusion.

The drug Summary of Product Characteristics (SmPC) states that IL-1Ra should not be administered in renal failure (Creatinine clearance < 30ml/min) or in neutropenia (absolute neutrophil count (ANC) < 1.5 x $10^9$L). Blood will be taken and results medically reviewed prior to inclusion in the trial. Injection site reactions may occur with IL-1Ra administered SC but we have found that by administering the injections in different anatomical sites each time these are generally well tolerated; just two patients (n=68 receiving IL-1Ra) withdrew from our phase II study because of injection site reactions. All adverse events will be reported.

# 3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

## 3.1 Aim

- To determine whether there is clinical efficacy of treatment with IL-1Ra following aSAH;

## 3.2 Primary Objective

Our primary objective is to answer the specific question:

- Does 100 mg twice daily SC injection of IL-1Ra commenced within 72 hours of ictus and administered for a maximum of 21 days from ictus in patients with aSAH improve their clinical outcome as assessed by the modified Rankin Scale at 6 months?

## 3.3 Secondary Objectives

- Does this treatment improve patient-reported outcomes such as mood, fatigue and quality of life?
- Is any effect of this treatment on clinical outcome correlated with its effect on plasma IL-6 concentration?

## 3.4 Outcome Measures/Endpoints

Primary outcome:

- Ordinal shift in modified Rankin Scale (mRS) at 6 months.

Secondary outcomes:

- Hospital Anxiety and Depression scale at 6 months (HADS)[36]
- Fatigue score (GM-SAT Fatigue question and Fatigue Severity Score)
- EQ-5D-5L score at 6 months[37]
- Correlation of the effect of treatment on clinical outcome with its effect on plasma IL-6 concentration

### 3.4.1 Primary outcome

We will assess the effect of intervention on the mRS (a 7 point ordinal measure of disability from 0 (no symptoms) to 6 (dead)) at 6 months following randomisation.

We have reviewed other clinical outcome measures studied in aSAH including the landmark ISAT trial[29] which used GOS-E as primary outcome measure. More recent studies, including STASH[14] and the ongoing ISAT II trial use the mRS. The proposed TOPSAT study being coordinated from the University of Newcastle will also use mRS as primary outcome. mRS is the outcome of choice in ischaemic stroke studies. Both mRS and GOS-E measure disability, i.e. the ability of a person to look after themselves. We have reviewed both of these outcome measures with our PPI group who felt the mRS better described their symptoms following aSAH. The mRS should also give finer discrimination among participants with “Good Recovery” as assessed by the GOS-E. We have experience of using both tools at phase II (GOS-E in our aSAH study and mRS in our ischaemic stroke studies) and find that mRS is much easier to complete and includes all activities of daily living. mRS is well validated including for use over the phone. We have therefore opted to use mRS as primary outcome in our proposed study.

### 3.4.2 Secondary Outcomes

We will measure quality of life, mood and fatigue as we know that fatigue and mood are the best predictors of poor outcome following aSAH[6]. We will also assess correlation between the effect of treatment on clinical outcome and the effect of treatment on plasma IL-6 concentration.

1. Mood: We will explore mood using the HADS[36] which is well validated in screening for anxiety and depression. This scale is widely used as an outcome measure, validated for telephone completion and is widely used clinically in people with aSAH.

2. Quality of Life: We have chosen EQ-5D-5L as a patient reported quality of life measure following advice from our patient user group. This is a well validated measure[37] that has been used in various types of stroke and subarachnoid haemorrhage. The EQ-5D-5L is also used by NICE for reference case analyses (www.euroqol.com).

3. Fatigue: We will screen for the presence of post aSAH fatigue with a single question "Do you feel tired all the time or get tired very quickly since your stroke?" which was developed in conjunction with community dwelling stroke survivors and their carers as part of the development of the GM-SAT[38]. This question identified fatigue as the most common problem (34%) in people 6 months post stroke, a proportion which is consistent with the proportion of stroke patients with post stroke fatigue (33%) as identified by a formal case definition of post stroke fatigue in a longitudinal cohort study[39] and with the proportion of people with aSAH who identified feeling tired on a daily basis (31%)[40].

   The GM-SAT fatigue question has now been used to screen for post stroke fatigue in a feasibility intervention study by Wu and colleagues (Wu, S, PhD University of Edinburgh). It is a simple and unambiguous question which can easily be answered as part of a telephone assessment. We will also measure the Fatigue Severity Score which is validated in stroke and takes 2-3 mins to complete[38].

## 4. TRIAL DESIGN

The trial design is a double-blind, randomised, placebo-controlled, multi-centre, parallel group phase III trial.

## 5. TRIAL SETTING

Up to 1000 patients with SAH will be recruited from up to 20 secondary/tertiary neurosurgical centres in the UK (a list of the participating sites can be found on clinicaltrials.gov). Adults admitted to a participating neurosurgical centre with a clinical diagnosis of acute SAH will be considered for trial participation. The care for all patients in the trial will be identical to the standard care pathway which will continue as normal including diagnosis of the aneurysm by imaging, endovascular coiling or clipping of the aneurysm, intensive or high dependency care, oral nimodipine, rehabilitation, clinical follow-up. No treatment will be withheld as a result of participating in the trial and participation will not affect clinical care.

# 6. ELIGIBILTY CRITERIA

## 6.1 Inclusion criteria

1. Patients with CT positive spontaneous SAH admitted to a participating neurosurgical centre where written informed consent can be obtained and study drug can be administered within 72 hours of ictus.
2. No concomitant health problems that, in the opinion of the PI or designee, would interfere with participation, administration of study drug or assessment of outcomes including safety. Please see precaution of use section 8.1.5 for further guidance.
3. Willing and able to give informed consent or consent available from a patient representative for trial inclusion including agreement in principle to receive study drug and undergo all study assessments.
4. Male or female aged 18 years or above.

## 6.2 Exclusion criteria

1. Unconfirmed or uncertain diagnosis of spontaneous SAH.
2. Known active tuberculosis or active hepatitis.
3. Known active malignancy.
4. Known Still's Disease
5. Neutropenia (ANC $<1.5 \times 10^9$/L ).
6. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 ml/minute) documented in the last 3 months prior to this SAH.
7. Live vaccinations within the last 10 days (please see appendix 1) of this SAH.
8. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial.
9. Current treatment with TNF antagonists (please see section 8.1.4 for the prohibited medication).
10. Known to have participated in a clinical trial of an investigational agent or device in the 30 days prior to ictus.
11. Known to have participated in a clinical trial of an investigational agent or device within 5 half-lives (of the previous agent or device) prior to ictus.
12. Known to be pregnant or breast feeding or inability to reliably confirm that the patient is not pregnant (Please see further guidance on pregnancy prevention in section 7.2.1).
13. Clinically significant serious concurrent medical condition, pre morbid illnesses, or concurrent serious infection, at the PI's (or designee's) discretion, which could affect the safety or tolerability of the intervention. Please see precaution of use section 8.1.5 for further guidance.
14. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC (please section 8.1.4).
15. Known allergy to other products that are produced by DNA technology using the micro-organism E. coli (i.e. *E.coli* derived protein).

# 7. TRIAL PROCEDURES

## 7.1 Schedule of Assessments

Table 1 Schedule of Assessments

| Reason | Action | Time point of assessment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Screening Visit [d]** | **Entry (consent visit) [d]** | **Prior to each administration of study drug** | **From randomisation until final day of study treatment** | **Day 3-5 post randomisation** | **Day 10-12 post randomisation** | **Final day of treatment [e] (≤21 days post ictus)** | **Day 30 post randomisation [a] (+/- 3days)** | **Month 6 (post randomisation [b] (+/- 28 days)** |
| Eligibility | Eligibility screen | X | | | | | | | | |
| | Pregnancy test | X | | | | | | | | |
| | **Consent** | | X | | | | | | | |
| Baseline characteristics | * Demographics | | X | | | | | | | |
| | # Past clinical history | | X | | | | | | | |
| Mechanism | Research blood (IL-6) | | X | | | X | | | | |
| | **Randomisation** | | X | | | | | | | |
| Treatment | Twice daily administration of study drug | | | | X | | | | | |
| Treatment fidelity | Research blood (IL-1Ra) | | | | | X | | | | |
| Safety | Review of clinical blood results by research staff | X | | | | X | X | X | X | |
| | Ongoing review of clinical condition by clinical staff | | | X | X | | | | | |
| | Research staff review of clinical data for adverse events | | | | | X | X | X | X | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Telephone AE check | | | | | | | | X | |
| Data for collection | Survival check | | | | | X | | X | X | |
| | ^ Target aneurysm details | | | | | X | | | X | |
| Efficacy | Outcome Assessments: HADS | | | | | | | | | X |
| | Outcome Assessments: Fatigue (GM-SAT fatigue | | | | | | | | | X |
| | Outcome Assessments: EQ-5D-5L | | | | | | | | | X |
| | Outcome assessment: mRS | | | | | | | | | X |
| | Outcome assessment: Survival check [c] | | | | | | | | | X |

Assessment logistics:

a) Day 30 safety assessment will be performed by the local research team for any participants still an in-patient. Patients who have been discharged to their own home will be contacted directly by telephone by local research team.

b) The 6 month outcome assessments will be performed by telephone, where possible, and will be coordinated centrally.

c) A survival check will be performed by contacting the participant's general practitioner to avoid any distress to next of kin.

d) Clinical CT angiography will be performed in accordance with local clinical practice. This may occur before or after randomisation

e) Additional clinical data including aneurysm location and treatment will be recorded on final day of treatment

Data to be recorded (full details available in section 7.7):

* Demographics – date of birth, sex, treating centre

# Past clinical history – Date and time of ictus, World Federation of Neurological Society grade (WFNS) at first presentation, pre-morbid mRS, pre-morbid risk factors (smoking, hypertension, diabetes, ischaemic heart disease), pre-morbid anxiety, depression and fatigue

^ Target aneurysm details – confirmation, position and treatment at day 3-5 and details of rebleed, cerebrospinal fluid (CSF) diversion, delayed cerebral ischaemia (DCI) and CSF infection by day 30.

## 7.2 Recruitment

Adults admitted to a participating neurosurgical centre with a clinical diagnosis of SAH will be considered for trial participation.

### 7.2.1 Patient Identification and Screening

The clinical team looking after the patient will make the initial approach to the potential participants or their personal legal representatives (if the patient lacks capacity) and ask if they would consider participation in a research trial. Any potential participant or their personal legal representative who expresses an interest and who is thought to be eligible (see 2.1) to participate will be referred to the research team. Basic demographic, clinical and radiological data will be checked against the eligibility criteria in section 6 to determine whether the potential participant may be eligible for entry into the trial. An anonymous record will be kept within the site file of all those screened which will include, age, sex, date of screening and reason for non-inclusion.

A member of the research team will visit the potential participant or their personal legal representative in the clinical areas to discuss what participation in the trial involves. Once this has been discussed, the researcher will again confirm eligibility before proceeding further. Those who are considered to be eligible to participate and who express an interest in participation will also be given written information containing full details of the trial which they must read before giving their consent.

It will be assumed that all women under the age of 55 are of child-bearing potential unless evidence contrary to this can be established from a reliable source. It will be necessary to exclude pregnancy in any woman of child-bearing potential (WOCBP, see list of definitions) prior to entry into the trial. If this cannot be excluded by the potential participant, verbal consent will be sought from the patient or their personal representative and noted in the patient's medical notes for a pregnancy test to be performed prior to consent. If no personal representative is available a professional representative will be asked to give verbal consent for a pregnancy test to be performed to enable determination of the patient's eligibility for the study. During study participation standard practice in regards to the administration of contraception should be followed. Participants enrolled in the study will only be administered IL-1Ra while being an in-patient and the half-life of SC IL-1Ra is 4-6 hours. It is therefore very unlikely that participants who are WOCBP will become pregnant while being exposed to the study drug. Nevertheless the investigator must ensure that all participants are made aware of the potential dangers of being pregnant during their participation in the study. All potential participants will be advised of the need to comply with highly effective contraceptive methods, once permitted to restart contraceptive treatment, for the remaining of the duration of study drug and up to 30 hours from the last administered dose (5 half-lives). Highly effective contraceptive methods are as follows; intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner* or sexual abstinence**. Combined or progesterone only hormonal contraception associated with inhibition of ovulation have not been classed as highly effective contraception because it is unknown whether Kineret may interact with hormonal contraceptives and reduce their efficacy. Additionally, any pregnancies reported during the trial will be reported by the Investigator to Manchester CTU as detailed in section 9.6.

* Provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

** Refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, which is in line with the preferred and usual lifestyle of the participant. For this trial, the period of risk means from first IMP administration until 30 hours after last IMP administration,

## 7.3 Consent

The researcher will ask the potential participant (and/or their personal legal representative) to read the written information sheet in order to reach their decision about participation. The researcher practitioner will be present to answer any questions they may have. If, for any reason it is not convenient for the potential participant/personal representative to read the written information sheet immediately, the research practitioner will arrange to return to at an agreed time point. Potential participants/personal representatives will always be given as long as necessary, to consider study participation. However it will be made clear to potential participants/ personal representatives that, whilst inclusion must be within a maximum of 72 hours from symptom onset, in order to increase the potential benefit from the new treatment, the trial drug should be administered as early as possible. If they unable to decide on study participation within 72 hours of symptom-onset, they will become ineligible. If the potential participant/their representative decide that they wish to take part in the trial they will be asked to sign a consent form confirming their willingness to participate.

**Capacity to consent may be an issue within this patient group**. A formal assessment of capacity will be carried out by an appropriately trained member of the research team where appropriate. Where it is not possible to obtain consent from the potential participant due to lack of capacity, we will seek consent from their personal legal representative. If the patient lacks capacity to consent to participation and no personal legal representative exists, the decision to include the potential participant will be made by a senior member of the clinical team who is independent of the research team (professional legal representative).

In the event that a potential participant has the capacity to consent to participation, but is unable to complete and sign the relevant consent form due to physical difficulties resulting from their clinical condition or pre-existing physical impairments (e.g. visual difficulties or limb weaknesses), witnessed , verbal consent will be obtained. The potential participant will be asked to orally confirm their willingness to participate in each stage of the trial to the professional legal representative (most likely a member of the clinical team independent of the research group) who will then be asked to confirm this consent in writing. In the event that the physical difficulties resolve during the participant's inclusion in the trial, a further consent form will be completed.

Where consent is obtained from the participant's personal legal representative or the professional legal representative in the first instance, the capacity of the participant to consent for themselves will be reassessed before each research assessment/intervention. If the participant regains capacity, they will be given information about the trial and asked to confirm willingness to continue trial participation. Where consent is given by the participant in the first instance, it will be made clear that they will remain in the trial should capacity be lost unless the decision to withdraw them is made by their representative, the research team, or by their clinical team.

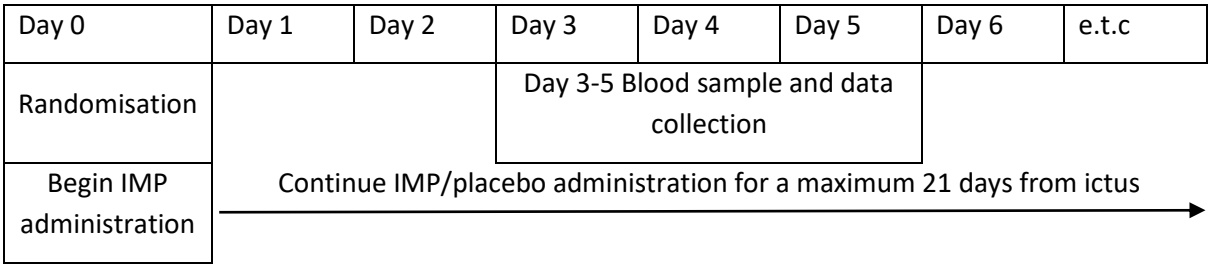
Patients entered into the trial will be randomised and assigned a unique trial participant code, which will be used to identify subsequent samples, for communications and for data collection purposes.

Consent to trial participation will include sharing of personal contact data with the trial centre in order to conduct follow-up assessment and the optional consent to storage of blood samples for use in other ethically-approved research.

## 7.4 Randomisation

Following consent by the patient or their legal representative and the baseline assessment (including baseline blood sample), the patient will be immediately randomised using an independent, bespoke, online randomisation service to ensure third-party concealment of allocation. This randomisation service will be provided by Glasgow Clinical Trials Unit who will design, programme and maintain the online service for the duration of study. 1:1 randomisation will be stratified by site (because of the potential for differences in surgical and post -operative practices), grade of SAH using WFNS (Grades 1&2 vs 3 to 5) and known aneurysmal status (aneurysm confirmed vs aneurysmal status unknown).

Randomisation takes place on Day 0. The first IMP administration should be given as soon as possible after randomisation and within 72 h of ictus. IMP administration will then continue according to the schedule in section 8.4 for a maximum 21 days from ictus or until discharge from neurosurgical care (whichever is earlier). The following diagram illustrates the day of randomisation in relation to IMP administration and data collection.




### 7.4.1 Method for participant randomisation and the implementing the allocation sequence

The randomisation system will be set up to allow storage of study drug kits in out-of-pharmacy fridges in each recruiting centre (see below for full details of contain of each study drug kit). A small supply of "unallocated" kits will be stored in these fridges to allow recruitment outside of standard working hours. The randomisation system will ensure participants are only randomised to kits in this fridge at the time of randomisation.

Research staff undertaking randomisation will access the online system using their own unique log-in details following participant consent and collection of baseline blood sample. Details of the recruiting centre code, WFNS grade, date and time (if not known a close approximation should be entered) of ictus and aneurysmal status will be entered onto the system. The system will request confirmation of eligibility before allowing randomisation to be performed. The researcher will be again asked to confirm their password before the randomisation process is complete. Following randomisation, a confirmatory email will be sent to all staff at the recruiting site and to the coordinating centre detailing kit number, participant ID and date and time of randomisation. A printed copy of the randomisation confirmation email will be stored in the Investigator Site File (ISF).

### 7.4.2 Management of kits at site

The randomisation system will also allow management of kits at the recruiting site. In order to minimise wastage of kits at recruiting sites and to facilitate continued inclusion of participants recruited who move between recruiting sites, an agreed procedure will be followed, which will be detailed in the pharmacy manual.

## 7.5 Blinding

Blinding will be maintained by use of identically packaged and labelled placebo so that participants (the patient, their personal legal representatives) and all trial staff (including the research team and outcome assessors, but excluding the laboratory staff and the statistician preparing reports for the IDMC) are unaware of treatment allocation throughout the period of the trial.

## 7.6 Unblinding

Details of the emergency unblinding procedure will be detailed in the Pharmacy Manual and will be available at all times in the Pharmacy Departments at each recruiting site and in the investigator site file.

If the investigator feels unblinding may be necessary then the participant's study drug should be stopped immediately. In the event an unblinding is required, the responsibility at the local sites resides with the PI. When possible the PI should only make the decision to unblind after consultation/discussion with the CI. If the person requiring the unblinding is not the CI/PI then the attending clinician will follow local procedure to unblind. This would be: where possible the treating clinician should request to unblind with the local PI. Where it is not possible to contact the PI/CI for whatever reason, a back-up unblinding procedure will be held in the local Pharmacy sites with specific instructions to follow.

If a decision is made to unblind, the allocation details will be obtained from the online randomisation site using an unblinding login account. This procedure will make sure the safety of the participant is not compromised and that the participants and research staff are not unblinded unnecessarily. Pharmacy might have a second attempt to contact the CI. This will also apply for out of hours.

On receipt of the treatment allocation details the CI/PI will continue to deal with the patient's medical emergency as appropriate.

The study code will only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team will remain blinded.

The CI/PI will document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report. The CI/Investigating team will notify the Manchester CTU in writing as soon as possible following the code break detailing the necessity of the code break. The Manchester CTU will then notify the Sponsor and the relevant authorities as required. The decision to code break will be included on the Development Safety Update Report (DSUR). The written information will be disseminated to the Independent Data Safety Monitoring Committee (IDMC) for review in accordance with the IDMC Charter.

As part of the terms of the Investigator Sponsored Study (ISS) agreement, Swedish Orphan Biovitrum (Sobi) will also be informed of the decision to code break.

As the investigator is responsible for the medical care of the individual trial subject (Declaration of Helsinki 3§ and ICH 4.3) the coding system in this blinded trial includes a mechanism that permits rapid un-blinding (ICH GCP 5.13.4). While discussion with the PI/CI should be sought, the investigator will not be required to discuss un-blinding if he or she feels that emergent unblinding is necessary.

## 7.7 Trial Assessments

### 7.7.1 Pre-randomisation evaluation

At screening, research staff will review patient health records to confirm eligibility according to the eligibility criteria in section 6. This will include basic demographics (age), past clinical history and radiological data. No identifiable participant data will be recorded. An anonymised screening log will be maintained. Following consent, participants will undergo a baseline assessment which will include transcription of source data including baseline research blood sampling, demographics (date of birth, sex, treating centre), and past clinical & medical history (date and time of ictus; World Federation of Neurological Societies (WFNS) grade at first presentation; pre-morbid mRS; pre-morbid risk factors (including smoking, hypertension, diabetes, ischaemic heart disease); existence of pre-morbid anxiety, depression or fatigue). A 10ml baseline blood sample will be taken immediately following consent and before randomisation for measurement of plasma IL-6. Sampling will be undertaken to ensure the minimal inconvenience to the patient and wherever possible blood will be sampled from an established central venous or arterial line. Where possible, research bloods will be taken at the same time as clinical bloods. Clinical reports of renal function and full blood count will be checked by an appropriate member of the PI team prior to randomisation (see exclusion criteria). Additional tests of full blood count, renal function, and liver function will be performed at the discretion of the clinical team as part of the direct clinical care and will be reviewed at the pre-specified post-randomisation evaluations as detailed below.

### 7.7.2 Post-randomisation evaluations

Adverse event (AE) reporting checks will be made by a delegated member of the research team at the day 3-5 assessment, between day 10-12, on the final day of study treatment and at day 30 post randomisation. Patients enrolled into the study will also be under continuous clinical observation as part of their routine direct clinical care. The site PI or delegate will liaise with the clinical team on a daily basis and a telephone number will be provided as a direct point of contact with the research team for discussion of any concerns relating to the study or administration of the study drug. Any adverse events noted outside the pre-specified reporting checks will be processed.

Details of each administration of study drug will be recorded in the case report form (CRF) and the clinical drug administration record. This will include details of administration site, date and time of administration.

A second research blood sample will be taken at 3-5 days post randomisation for measurement of plasma inflammatory markers (IL-6) (putative mediator) and IL-1Ra concentration (treatment fidelity and validation of randomisation). Further clinical data (survival check; detail of target aneurysm, including confirmation, position and treatment) will be collected at the day 3-5 post randomisation assessment.

On the final day of study treatment another survival check will be performed. As part of the end of treatment assessment the participants will be asked to confirm their willingness to be contacted at 30 days and 6 months of the date of randomisation and contact details of the participants (or next of kin) will be confirmed.

A final AE check and survival check will be performed at 30 days post randomisation on all patients who have received at least one dose of study drug and will be completed by local research staff. To avoid

distress to the next of kin, the survival check will be performed by contacting the participant's general practitioner. Patients who have been discharged to their own home will be contacted directly by telephone. If the patient is unable to provide this information it will be obtained from the patient representative. In cases where a patient has been transferred to another in-patient care setting, e.g. rehabilitation centre or local district hospital, this information will be sought from the local healthcare provider (usually local treating physician or nursing staff). This final AE check will be completed for all participants, including those with non-aSAH who received a small amount of study drug prior to withdrawal. Full details of AE collection procedure can be found in section 9.1.1. The patient's own general practitioner (GP) will be informed of study participation by letter (including a copy of the participant information sheet and informed consent form) upon discharge from the treating centre sent by a delegated member of the research team.

As part of the assessment at 30 days post randomisation research staff should also ensure details of rebleed, cerebrospinal fluid (CSF) diversion, delayed cerebral ischaemia (DCI) and CSF infection have been completed in the CRF. DCI is defined as the occurrence of focal neurological impairment or decrease in the Glasgow Coma Scale (GCS) by at least 2 points as long as this was not apparent immediately after aneurysm occlusion, and that the deficit could not be attributed to other causes such as hydrocephalus or electrolyte disturbance. CSF infection is defined as definite if it's microbiologically proven or probable if clinical signs and symptoms of CSF sepsis leads to a clinician starting anti-microbial treatment. Length of stay within the neurosurgical service should also be recorded through recording of discharge date from neurosurgical service and discharge destination (or continued status as neurosurgical service patient).

The final outcome assessment will be performed at 6 months (+/- 28 days) from randomisation and will record mortality and primary and secondary outcomes. This will be coordinated centrally. A survival check will be performed by contacting the participant's general practitioner to avoid any distress to next of kin. The assessment will be performed by telephone where possible. This is our first preference for data collection and has influenced our choice of measures. However, if people need more support we can offer a face-to-face interview at any routinely scheduled out-patient appointment in which to complete the outcome assessments. Furthermore, if the participant is unable to answer the questionnaires due to problems with capacity, or ongoing problems with communication or cognition, the researcher may ask a relative or friend, general practitioner or another healthcare provider to assist the patient in completing the questionnaire.

These options will be outlined on the information for participants, personal legal representative and professional legal representative sheets provided as part of the consent process.

The final outcome assessment will record mRS which includes mortality and in survivors, additional outcome assessments relating to anxiety, depression (Hospital Anxiety and Depression scale; HADS), fatigue (Greater Manchester Stroke Assessment Tool; GM-SAT fatigue question)[38] and Fatigue Severity Score[41] and quality of life (EQ-5D-5L). Where the final assessment is performed by the coordinating centre, a standard letter will be sent to the recruiting PI informing him/her of the modified Rankin Score.

## 7.8 Withdrawal Criteria

Participants without confirmation of aneurysm within 72 hours of randomisation and those patients found to be non-aneurysmal post randomisation will be withdrawn from treatment. If participants are withdrawn for this reason they will continue to be followed up until their safety (30 days post randomisation) assessment. While baseline plasma samples collected from these participants will not be analysed for this trial, the samples will be shipped to the trial centre (see section 7.9) for potential use in future research (provided consent was given for this). If consent was not given for use of samples in future research, the sample must be destroyed at the participating site as per local procedure

In the event of death between randomisation and the diagnosis of aneurysm (usually by CTA), these participants will be excluded as 'Failed To Confirmed Aneurysm' and this event should be reported as detailed in notification of death (section 9.5).

Participants have the right to withdraw from the trial treatment or trial participation at any time, without having to give a reason and without any effects on their clinical care. The withdrawal process will be explained prior to consent.

If a participant is withdrawn from trial treatment, study drug will be stopped immediately and no further blood samples will be obtained. Subsequent assessments of patient safety and an end of study outcome will be completed as planned. All data and samples will be retained and included in analyses. Trial treatment should be stopped for the circumstances listed below.

- Uncontrolled AE/SAE that is related to, or potentially related to, study drug;
- Participant or personal legal representative decision, or at the PI discretion;
- If a severe allergic reaction occurs administration of IL-1Ra should be discontinued and appropriate treatment initiated;
- If participants become neutropenic (ANC $<1.5 \times 10^9$/l), IL-1Ra treatment should be discontinued;
- Pregnancy;
- Symptomatic deterioration where the investigator feels the participant's receipt of study drug is no longer clinically appropriate;
- Study suspended or stopped for any reason.

Subarachnoid haemorrhage patients may suffer uncontrolled AEs or SAEs due to the nature of the condition. Therefore only uncontrolled AEs or SAEs that are related to, or potentially related to, study drug should be a direct reason for withdrawal from trial treatment. If a participant suffers any uncontrolled AE or SAE that is not related to study drug, but that in the investigator's opinion it would be in the participant's best interest to end trial treatment, the participant can be withdrawn from trial treatment based on the penultimate point listed above.

If the participant withdraws from trial participation, no further assessments will be performed. The information required for the final 30 day safety information will be gathered from secondary sources including clinical records. Study data and samples will be retained and included in analyses unless the participant requests it be destroyed. It is the responsibility of the participating site research teams to ensure the participant's wishes are met. Samples stored at the participating site must be destroyed as per local procedure and the central laboratory and Manchester CTU must be notified of the participant's request for their data and samples to be destroyed.

Participants and their representatives do not have to give a reason for their withdrawal. However, where available, the research team will record reason for withdrawal or lack of this in the medical notes and the CRF.

## 7.9 Storage and Analysis of Samples

Blood samples obtained for measurement of plasma IL-6 and IL-1Ra will be collected by research staff at the recruiting site. All equipment required for the collection of the research blood samples including the EDTA tubes will be provided to sites by the research team. Recruiting research staff at study sites will receive training in the laboratory manual for preparation of the samples for analysis, including centrifugation, labelling and storage. Blood pellets left over after centrifugation will be retained for use in future genetic analysis if participants and/or representative have given consent to sub-study participation. Prior to shipping on dry-ice to the Biomedical Research Facility laboratories at the trial centre, samples will be stored in -70$^{o}$C freezers. Samples will be received at trial centre in bulk from sites at time points approximately 18 months from recruitment of first participant and following completion of recruitment. Samples will be transferred by courier services arranged by the Coordinating Centre. For full details of sample collection, preparation, storage and shipment please see the laboratory manual.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the Data Protection Act.

Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

Clinical samples will be analysed in accordance with the procedures and methods in place within the study centres. Reference ranges and details of analysis methodology will be obtained.

All research samples will be stored in accordance with an agreed protocol at the research laboratories in the Clinical Science Building at Salford Royal NHS Foundation Trust for analysis following receipt from study site. Concentrations of plasma IL-6 and IL-1Ra will be determined by immunoassay under the supervision of Dr Margaret Hoadley or her designee. Permission will be sought from study participants to retain anonymised samples for use in other ethically-approved research, including future genetic analysis. Samples will be disposed in accordance with the Human Tissue Authority's Code of Practice when they are of no further use.

## 7.10 End of Trial

The definition of the end of the trial will be the final outcome assessment for the last recruited participant.

On the Sponsor behalf, the Manchester CTU will notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion.

# 8. TRIAL MEDICATION

The study drugs are:

- 100mg interleukin-1 receptor antagonist (IL-1Ra), marketed as Kineret®® in 0.67mL prefilled syringe for single use
- Matching placebo, manufactured by Sobi AB

The intervention will consist of twice daily, SC administration of 100mg interleukin-1 receptor antagonist (IL-1Ra), marketed as Kineret®, or matched placebo. Administration of study drug will start as soon as possible after randomisation and will continue consistent, twice daily administration times with a minimum of 8h and a maximum of 16h between each dose for a maximum 21 days from ictus or until discharge from the treating centre (whichever is sooner). All patients will continue to receive all elements of standard care.

## 8.1 Investigational product

### 8.1.1 Interleukin-1 receptor antagonist (IL-1Ra)

Kineret® is indicated in adults for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.

Kineret is also indicated in adults, adolescents, children and infants aged 8 months and older for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including:

- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)
- Muckle-Wells Syndrome (MWS)
- Familial Cold Auto-inflammatory Syndrome (FCAS)

The drug is legally classed as a Biological Response Modifier (BRM). The current version of the Summary of Product Characteristics (SmPC) will be used as the reference safety information for this study. Sobi will be responsible for the annual updates to the SmPc and informing the Sponsor if there is any change. The annual update to the SmPC will be reviewed by the CI for any changes to the safety information. Any emerging safety information will be incorporated into the trial protocol and supporting documents followed by the submission of an amendment where deemed necessary by the CI.

This is a randomised, double-blind, placebo controlled study. The study drug (IL-1Ra / placebo) produced by Swedish Orphan Biovitrum AB, Sweden will be presented as a labelled pre-filled syringe containing 0.67 ml of IL-1Ra /placebo equating to 100 mg of the drug. Study drug will be stored in a secure facility, physically separated from any other medicinal products, with a calibrated temperature monitoring device in a pharmacy-standard refrigerator at 2-8°C at all times. For full details of study drug storage and shipment please see the pharmacy manual.

### 8.1.2 Access to Treatment Assignments

The study is double-blind, randomised, placebo-controlled. Randomisation will be performed by a third-party randomisation service that is independent of the study group. Details of the randomisation code on the allocated pack will be recorded in the participant's clinical and research records. Participants enrolled in the study will be assigned to receive 100 mg of IL-1Ra or placebo subcutaneously (SC) twice daily from within 72 hours of ictus for a maximum of 21 days from ictus. Measures will be in place to enable the

Principal Investigator to access individual subject treatment assignments in exceptional circumstances (e.g. suspected unexpected serious adverse reaction: SUSARs). Please see section 7.6 for details of the unblinding procedure.

### 8.1.3 Compliance in Investigational Product Administration

Given the short duration (maximum 21 days) of the administration of the study intervention and only during in-patient stay, the established safety profile for its use in other disease states and its administration route (SC), it is not anticipated that there will be many problems associated with patient compliance and concordance. However, it is recognised that some patients may develop a self-limiting injection site reaction (ISR) and/or be/become needle-phobic or uncooperative, making it difficult to administer the drug for the prescribed duration. Information will be recorded on any omissions of administration of the drug, any deviations from the expected time of administration and the reasons for such events. The estimated delivered dose will be calculated and recorded for each SC administration.

Interruption of study drug should be avoided. If an injection(s) is missed participants should be given the next one at the stipulated (pre-planned) time. The reason for any missed dose should be recorded on the CRF. The decision to restart study drug, after any interruption as long as this is not after 21 days from ictus, is at the PI discretion.

Administration of the study drug will be performed twice daily by delegated research staff or appropriately trained ward nurses and will continue until the participant is considered fit enough for discharge from the treating centre. Some attrition is expected due to the high mortality associated with aSAH (9% overall in 6 months but mortality is included in the primary outcome mRS). Patients with aSAH are routinely followed up by the neurosurgical team for at least 6 months and tend to remain in contact with their treating team throughout this period.

### 8.1.4 Concomitant medication

Concomitant medications may be given as medically indicated. Concomitant medications will be checked at screening, through daily liaison between the site PI or delegate and the direct clinical care team and at the pre-specified adverse event (AE) reporting checks at the day 3-5 assessment, between day 10-12 and on the final day of study treatment. Treatment with TNF-α inhibitors (e.g. etanercept or other TNF antagonists) is not permitted during the period of the study intervention and for 48 hours following its discontinuation. Live vaccines should not be given concurrently with study drug. Therefore if a participant is required to take any of the above medications as part of clinical care they would be withdrawn from study treatment (see section 7.8).

Any other medications that are known or subsequently reported as having, or potentially having, interactions with study drug and are not recommended to be used concurrently with study drug will be restricted from this time period. If the medication is part of clinical care the participant will be withdrawn from study treatment (section 7.8).

Patients who are currently in receipt of IL-1Ra will not be eligible to participate for patient safety reasons.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus, it may be expected that for an IL-1 receptor antagonist, such as Kineret, the formation of CYP450 enzymes could be normalized during treatment. This would be clinically relevant for CYP450 substrates with a narrow therapeutic index (e.g. warfarin and phenytoin). Upon start or end of Kineret treatment in patients on these types of medicinal products, it may be relevant to consider therapeutic

monitoring of the effect or concentration of these products and the individual dose of the medicinal product may need to be adjusted.

All standard care and medications will continue unaffected by study participation.

### 8.1.5 Special warning and precautions for use

Please see current approved version of the SmPC for full details of these events below.

**Allergic reactions:**

Allergic reactions, including anaphylactic reactions and angioedema have been reported uncommonly. The majority of these reactions were maculopapular or urticarial rashes.

If a severe allergic reaction occurs, administration of study drug should be discontinued and appropriate treatment initiated.

**Hepatic events:**

Investigators should exercise caution when administering study drug to patients with a history of severe hepatic impairment or liver dysfunction, defined as total bilirubin above the ULN (excluding patients with Gilbert's syndrome), AST or ALT >3 times the ULN or alkaline phosphatase >2.5 times the ULN.

**Renal impairment:**

Study drug should be used with caution in patients with moderate renal impairment (creatinine clearance or eGFR 30 to 59 ml/minute).

**Serious infections:**

Investigators should exercise caution when administering study drug to patients with a history of recurring infections or with underlying condition which may predispose them to infections (e.g. Asthma).

When diagnosing infection in a patient in the study, investigators should not rely solely on the CRP level as reduction in plasma CRP has been seen in patients receiving IL-1Ra. However, the reduction is modest and therefore unlikely to impact on clinical decision making.

Consideration should be given to the higher risk of infection in all grades of aSAH patients compared to the normal population (e.g. the RA patient referenced in the SmPC). It is important to note that there is no evidence in the SmPC or from our previous trials (see section 0 for more detail) to support withdrawal of study drug in the event of a serious infection in this population. The decision to interruption or stop IL-1Ra is at the discretion of the local investigator.

**Neutropenia:**

Events of neutropenia have been observed in previously RA studies when administered long-term. Therefore precaution is recommended in patient with a history of neutropenia.

If a participant becomes neutropenic (ANC < 1.5 x $10_9$/l) the ANC should be monitored closely and study drug should be discontinued.

### 8.1.6 Labelling of study drug (IL-1Ra / placebo)

The study drug will be labelled by the drug company (Sobi) and both active drug and placebo will arrive at third-party cold-chain distribution company identical in packaging, schedule of administration and appearance. This will ensure that site staff remain blinded to the identity of study treatment unless

emergency unblinding is required. Each treatment study drug kit will contain 7 syringes. The outer kit packaging and each syringe will be flagged with an individual label. There will also be loose labels inside the outer kit packaging for use on source documentation. When a kit is dispensed, the outer packaging and each syringe label will be labelled with the participant ID number and the syringe labels and loose labels will be labelled with the kit number shown on the outer packaging. When a syringe is removed from the kit and taken to the participant for administration, the batch number, participant ID and expiry date will be checked by the researcher and a member of the clinical staff.

The loose label will be applied to the Proof of Administration record. Once administered, the syringe will be destroyed in a sharps bin and a member of clinical staff will be asked to sign a Proof of Destruction sheet. Original copies of the Proof of Administration and Proof of Destruction sheets will be stored in the pharmacy site file. The researcher will also confirm administration in the clinical prescription record. This procedure will aid reconciliation of study drug and monitoring.

#### 8.1.7 Supply of Study Drug (IL-1Ra / placebo)

The study drug will be shipped from Swedish Orphan Biovitrum AB, Sweden to a third-party cold-chain distribution company in staged shipments, as required. Upon receipt of drug, a designated member of staff will check the delivery and acknowledge receipt. Study drug will be stored securely at 2-8°C until it is shipped to recruiting sites.

A supply of study drug will be shipped to sites one month before initiation of recruitment with QP release certificate for each batch. To minimise wastage, the volume of study drug supplied to sites will be based on expected recruitment. Kit usage at sites will be monitored by the cold-chain distributor through the randomisation system and resupply will be initiated as necessary. Study drug will not be transferred between recruiting sites.

#### 8.1.8 Ordering and Storage of Study Drug (IL-1Ra / placebo)

On arrival at recruiting sites, the bulk of the study drug will then be stored in the clinical trials area of the pharmacy department. The study drug will therefore be in a secure area, with limited access and separate from non-clinical trial medication. The temperature of the fridges used for storage in a temperature controlled fridge in the main pharmacy department will be monitored on a daily basis

A small supply of study drug will be stored in designated secure pharmacy-standard, temperature-monitored fridges at recruiting sites. This is to allow commencement of treatment to participants outside of pharmacy opening hours.

The fridges will be supplied to recruiting sites where necessary by the Coordinating Centre but it will be the responsibility of the sites to monitor and record the temperature on a daily basis. Pharmacy staff at recruiting sites will be responsible for ensuring, on a weekly basis, that this is being done. It will be the responsibility of the researcher dispensing out of hours medication to check that no temperature deviations have occurred immediately prior to dispensing and this check will form part of the dispensing procedure.

### 8.2 Prescribing and allocation of study drug kit

Study drug (IL-1Ra or placebo) will be prescribed on the clinical prescription form following randomisation and allocation of first treatment pack (7 syringes). Study drug will be prescribed by medically-qualified member of the research team who have been delegated the responsibility by the PI. In addition, a paper

copy of a clinical trial prescription will be completed by the prescriber following each randomisation or resupply. This will be placed in the Pharmacy file following dispensing. Where available at recruiting sites, study drug may also be prescribed on an electronic prescribing record.

The randomisation system will generate the anticipated date and time of last dose of study drug. If the participant is discharged from the recruiting site before this date study treatment will cease. It is the responsibility of the PI to ensure that study drug is prescribed and administered correctly. For details of study drug kit allocation and resupply please see section 7.4.

## 8.3 Dispensing of Study Drug (IL-1Ra / placebo)

The first kit (7 syringes) of study drug will be dispensed from the supply of unallocated kits stored in out-of-pharmacy fridges within the recruiting site. This will be on the authority of a clinical trial prescription written by a medically-qualified member of the research team authorised to do so on the delegation log. Where appropriate, the prescriber must also ensure that the prescription is cross-referenced on the hospital's electronic prescribing system. The dispenser must ensure that the correct treatment kit assigned to the participant is dispensed and all required labelling has been completed and that accountability logs have been completed appropriately.

Dispensing of the first kit must be performed by two members of delegated research staff following a dedicated dispensing procedure.

A dispensing procedure will be put in place with a training log for all other members of staff that have not signed the delegation log. On the next working day after recruitment of a new participant, the research team should ensure the paper copy clinical trial prescription, together with a request for a replacement unallocated kit of the out-of-pharmacy fridge are sent to Pharmacy.

Re-supply of study drug kits to participants will be performed by research staff using the facility within the randomisation system (see section 5.4). A paper clinical trials prescription should be completed as above. Resupplied kits will be dispensed by Clinical Trials Pharmacy staff and allocated kits will be stored in out-of-pharmacy fridge until administration. The date and time will be recorded in the prescription. It will be the responsibility of the PI at the recruiting site to ensure accountability of reconciliation of study drug.

## 8.4 Administration of Study Drug (IL-1Ra / placebo)

Administration of study drug will be limited to research staff or appropriately trained ward nurses. The maximum duration of study treatment is 21 days from ictus.

The choice of dose and frequency of administration was originally informed by a phase II trial[42] that demonstrated the pharmacokinetics of IL-1Ra following subcutaneous administration of a 100mg dose. Subsequent research detailed in section 2.1.1 of this protocol has provided justification for the 100mg dose given twice daily by subcutaneous administration for a maximum of 21 days. Administration times should be standardised after the first injection to twice daily injections given at consistent times that are convenient and practical for the patients and research/nursing staff providing there is a minimum 8 hours and maximum 16 hours between administrations. It is the responsibility of the PI at the recruiting site to ensure the efficient resupply of kits to ensure there are no gaps in administration of study drug. The injection site will be recorded in the CRF and research staff will be instructed to rotate administration sites to reduce the risk of injection site reaction and bruising.

### 8.5 Post-trial Access to Study Drug (IL-1Ra)

There will be no post-trial access to study drug.

## 9. PHARMACOVIGILANCE

### 9.1 Definitions

The trial will adhere to recognised definitions of adverse events.

**Table 2:** Definitions of Adverse Events

| Term | Definition |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.<br><br>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.<br><br>All cases judged by the reporting medically qualified professional as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:<br>•results in death<br>•is life-threatening<br>•requires inpatient hospitalisation or prolongation of existing hospitalisation<br>•results in persistent or significant disability/incapacity<br>•consists of a congenital anomaly or birth defect<br>•Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences (please see section 9.2 for a list of 'important medical events'.<br><br>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at 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 one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:<br>•in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product |

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

### 9.1.1 Operational definitions for (S)AEs

The safety reporting period will commence from the time of consent, and will continue up to 30 days from date of randomisation.

Given the nature of aSAH these participants will have experienced a number of AEs which are disease related. A list of expected events related to normal disease progress is detailed in **Table** 4. However this does not mean that these events should always be attributed to SAH. All events should be assessed for causality by the investigator. There is no requirement to capture disease-related AEs that occur during the trial in the CRF but all disease-related AEs should be recorded in the patient's medical notes. AEs that are un-related to SAH should be recorded in the CRF. Pre-existing conditions (i.e. those that already appear in the medical notes) do not qualify as adverse events unless they worsen. If the PIs suspect this worsening is related to study drug then this event should be treated as an AR.

AEs will be classified as detailed in **Table 3**.

All AR's occurring during the trial whether observed by the investigator or reported by the participant will be captured in the patient's medical notes and CRF.

All SAEs which occur within the safety reporting period will be captured in the patient's medical notes, CRF and expediently reported as detailed in section 9.2.

Any new ARs, SAEs or AEs that are unrelated to SAH occurring after discharge but within 30 days from date of randomisation will be recorded in the patient's CRF and will be considered as potentially related to study drug.

Any ARs, SAEs or AEs unrelated to SAH that are still on-going at the time of the final AE check (30 days post randomisation), the participant may be followed up for a longer period of time until the event has resolved, stabilised or has been fully investigated to the satisfaction of the PI and the study Sponsor. To capture the outcome of these on-going AEs, this may require contact with the participant's general practitioner and other health care practitioners involved in the participant's on-going clinical care following discharge from the recruiting site. The GP/other healthcare providers will have been informed of the patient's study participation and they will be provided with a copy of the participant's consent which details this clause of contact to be made.

Any new AEs, ARs or SAEs which occur after 30 days from randomisation will not be sought or recorded in the CRF. They will be recorded in the patient's medical records if considered necessary for clinical care. If an investigator becomes aware of any drug-related SARs that occur after the end of safety reporting period (30 days post randomisation) these must also be reported to the Manchester CTU within the expedited timelines (please see section 9.2).

Reporting of any AE will be performed in line with MHRA guidelines and the Sponsor's requirements. The following attributes will be assigned where known: description, dates of onset and resolution; severity; assessment of relatedness to study drug administration; meets criteria of serious (Y/N); action taken and treatment required. If treatment for the event was administered it will be recorded in the medical record.

The PI or medical delegate at the recruiting centre will be responsible for assessing any AE on the following characteristics: seriousness, relationship to the study drug, expectedness and severity. AEs severity will be reported to the definitions detailed in table 3 below. Assessment of expectedness will be made against the current approved version of the SmPC.

**Table 3:** Assessment of Severity

| SCALE | SEVERITY | DEFINITION |
|---|---|---|
| **1** | *Mild* | Aware of sign / symptom but easily tolerated |
| **2** | *Moderate* | Discomfort enough to cause interference with usual activity |
| **3** | *Severe* | Incapacitating, unable to work or perform usual tasks |
| **4** | *Life-threatening* | Risk of death at time of event |
| **5** | *Fatal* | Death ensues |

The PI or delegate will determine whether there is a **reasonable possibility** that the study drug has caused or contributed to an event, based on clinical judgment and available information on the study drug from the SmPC. Factors taken into account will include, but not be limited to, the following:

- A temporal relationship between the event and administration of the study drug
- A plausible biological mechanism for the study drug to cause the event
- Previous report of similar AEs associated with the study drug, in accordance with the SmPC
- Recurrence of the AE after re-challenge or resolution after discontinuation of study drug

Sponsor & IDMC will continue to monitor SAEs for trends and possible signal detection associated with study drug.

Any serious adverse event, that is deemed study drug related, that is considered unexpected by the PI/CI should be reported as a SUSAR as detailed in section 9.2. In the event of a SUSAR unblinding procedure should be followed as detailed in section 7.6.

In addition, AEs related to study drug (ARs) that are critical to the safety evaluation of the participant must be reported to the Sponsor as if they were SAEs (please see section 8.1.5 for precaution of use for examples); these may be volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation.

In addition to the protocol, the SmPC will be used for pharmacovigilance purposes to assess the expectedness of events. This will be checked by the CI for changes on the anniversary of the CTA or if an update of the SmPC occurs within the reporting period.

**Table 4:** Events related to normal diseases processes in SAH (Expected events)

| **System Organ Class** | **High Level Group Term** | **High Level Term** (Symptoms) | | **Likely frequency**<br>Very common >= 1/10<br>Common (frequent) •> = 1/100 and < 1/10<br>Uncommon (infrequent) >= 1/1000 and < 1/100 |
|---|---|---|---|---|
| Neurological | Aneurysmal SAH | Headache, photophobia, meningism, confusion | | Very common |
| | New neurological deficit | Deterioration in GCS, confusion | | Common |
| | Raised intracranial pressure (ICP) | Confusion, seizures | | Very common |
| | Hydrocephalus /Ventriculomegaly | Confusion, seizures | | Very common |
| | External CSF Drain malfunction | Blockage, leaking, accidental removal | | Common |
| | Rebleed | Deterioration in GCS, confusion | | Common |
| | Delayed Cerebral ischaemia (DCI) | | | Very common |
| | Cerebral infarction | | | Very common |
| | Radiological vasospasm/clinical DCI | | | Very common |
| | CNS Infection | | | Common |
| Metabolic | Water and electrolyte imbalance | Dehydration | | Very common |
| | Raised white cell count | Infection | | Very common |
| | Low white cell count | | | Uncommon |
| | Increased haemoglobin | | | Common |
| | Decreased haemoglobin | | | Common |

| | | | | |
|---|---|---|---|---|
| | Increased ALT | | | Common |
| | Altered liver function | | | Common |
| Thromboembolic | Deep vein thrombosis | | | Common |
| | Pulmonary embolism | | | Uncommon |
| | Post-operative bleeding | | | Common |
| | Distal embolism | | | Common |
| Renal | Renal failure | Low Mg, high Cl | | Common |
| | Acidosis | | | Very common |
| | Alkalosis | | | Very common |
| Genitourinary | Lower urinary tract infection | | | Very common |
| | Urinary retention | | | Very common |
| | Urinary incontinence | | | Very common |
| Gastrointestinal | Clostridium deficile | Diarrhoea, vomiting, nausea | | Common |
| | Candida Albicans (Thrush) | | | Common |
| | Constipation | Abdominal pain, nausea | | Very common |
| Respiratory | Lower Respiratory Tract infection (including aspiration pneumonia, VAP or HAP) | | | Very common |
| | Upper Respiratory Tract Infection | | | Common |
| | Empyema | | | Uncommon |
| | Pulmonary oedema | | | Common |
| Skin | Ecchymosis (Bruising) | | | Very common |
| | Tracheotomy site infection | Redness, skin breakdown, pain, oozing | | Common |

| | | | | |
|---|---|---|---|---|
| | MRSA | | | Uncommon |
| | Pressure sore | | | Uncommon |
| | Infection | thrush | | Common |
| Cardiac | Cardiac arrhythmia | | | Common |
| | Hypertension / hypotension | | | Common |
| | Endocarditis | | | Uncommon |
| | Myocardial infarction | | | Common |
| Miscellaneous | Failure to progress | | | Common |
| | Pyrexia of unknown origin | | | Common |
| | Coincidental findings on brain imaging | Meningioma, tumour | | Common |
| | Falls | | | Common |
| | Pain | | | Common |
| | Anxiety | | | Very common |
| | Depression | | | Very common |
| | Fatigue | | | Very common |
| | Blindness | | | Uncommon |
| | Visual disturbance | | | Common |
| | Vitreous haemorrhage | | | Common |
| | Post-operative/procedural complications | Haematoma (wound, groin, pelvis, arterial line) thrombosis, thrombectomy, wound infection (cerebral, groin), INTRA-procedural rupture | | Common |

## 9.2 Recording and Reporting of SAEs, SARs AND SUSARs

All SAEs, SARs and SUSARs occurring from the time of written informed consent until 30 days from date of randomisation must be recorded on the Serious Adverse Event/Reaction Form and emailed to the Manchester CTU immediately but no later than 24 hours of the research staff becoming aware of the event. The research staff should also report any SAE occurring after this time period which they believe to be related to the study drug.

***All SAEs must be reported by email immediately but no later than 24 hours of being aware to the SCIL trial manager at the Manchester CTU.***

***Email: SAEreport_manctu@manchester.ac.uk***

In addition to events that meet the SAE criteria detailed in section 9.1, the following 'important medical events' should be reported as SAEs:

- A diagnosis of new or recurrent Tuberculosis
- A diagnosis of new cancer
- Any suspected transmission of an infectious agent via study drug shall also be considered serious.

Exceptions that will not be subject to expedited reporting include:

- Extended hospitalisation for treatment of underlying condition
- Routine treatment or monitoring of SAH not associated with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition including SAH provided that the SAH is not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications or insertion of shunt.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission
- Admission to hospital or institution for another life circumstance that has no bearing on health status e.g. lack of housing, caregiver respite, family circumstances.

For each SAE, SAR & SUSAR 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 (i.e. relatedness to study drugs), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

All SAEs that occur within safety reporting period (consent until 30 days from date of randomisation) should be considered for their potentially relatedness to study drug.

Any change of condition or other follow-up information should be emailed to the Manchester CTU using the Follow-up Form as soon as it is available but no later than 24 hours of the information becoming available. All serious adverse events will be followed up until the event resolves, stabilises or a final outcome has been reached.

Initial assessment of seriousness, causality and expectedness will be made by the PI or delegated doctor at the recruiting centre. If an authorised doctor from the reporting site is unavailable, initial reports without causality will be submitted to the Manchester CTU by a healthcare professional immediately but no later than 24 hours after of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Assessment of seriousness, causality and expectedness will be reviewed by the CI against the current approved version of the SmPC. If a difference of opinion exists between the investigator and CI regarding causality, the event cannot be downgraded by the CI as the investigator is more familiar with the participant's history, clinical signs and symptoms, lab findings and other investigations. The CI may, however, upgrade the investigator's assessment of causality.

All SAEs assigned by the CI or delegate (or following central review) as both **suspected** to be related to study drugs **and unexpected** will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Manchester CTU will inform the MHRA, the REC and the Sponsor of SUSARs within the required expedited reporting timescales.

### 9.3 Responsibilities

The Trial Steering Committee (TSC) will be responsible for overseeing the management of the study and its conduct. They will be responsible, in conjunction with the Chief Investigator for determining whether the study should stop. However, the overall responsibility for the decision to continue or stop will remain with the Sponsor.

The constitution, responsibilities and remit of the TSC and IDMC for the study will be in keeping with the recommendations and guidance of the NIHR & Sponsor (full details of the TSC can be found in section 10.2.2). The role, functions and operating practices of the TSC and the IDMC will be agreed with the NIHR & Sponsor before the commencement of recruitment.

The IDMC will undertake clinical review of a line listing of all life threatening or SAEs resulting in death each month and a cumulative review of all unblinded safety information on a 12 monthly basis. The total numbers of SAEs per month will be sent to the IDMC Chair – in order to expedite a safety review if more SAEs are being seen than would be expected.

**Table 5:** Responsibilities relating to AE reporting

| | **PI / recruiting centre** | **CI** | **Manchester CTU** |
|---|---|---|---|
| Adverse event | • Identification of adverse event<br>• Assessment of seriousness<br>• Assess if appropriate for expedited reporting<br>• Complete AR log in the CRF and send to the Manchester CTU within 30 days of safety assessment visit<br>• Follow-up until resolution or stabilisation | • Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.<br>• Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.<br>• Using the approved SmPC in assigning expectedness.<br>• Immediate review of all SUSARs.<br>• Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.<br>• Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.<br>• Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR). | • Central data collection and processing of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.<br>• Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit.<br>• Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.<br>• Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.<br>• Notifying Investigators of SUSARs that occur within the trial.<br>• A summary report of all SAEs, regardless of causality, will be sent to Sobi on a quarterly basis. |
| Serious adverse event / SARs | • Ensure all necessary care and including immediate support necessitated by the event has been implemented<br>• Complete SAE form<br>• Assessment of seriousness, expectedness, & causality<br>• Submit SAE/SAR form to the Manchester CTU immediately but no later than 24 hours of the research staff becoming aware of the event<br>• Follow-up until resolution or stabilisation | | |
| SUSARs | • Ensure all necessary care and including immediate support necessitated by the event has been implemented.<br>• Complete SAE form<br>• Assessment of seriousness & causality.<br>• Submit SAE/SAR form to the Manchester CTU immediately but no later than 24 hours of the research staff becoming aware of the event.<br>• Confirm with CI drug reaction and unexpected.<br>• Follow-up until resolution or stabilisation. | | • Record details of event.<br>• Request further information if needed.<br>• Generate a detailed adverse event monthly report.<br>• Ensure follow up information is completed to outcome.<br>• Ensure information passed on to DMC, MHRA, Sobi within regulatory timescales. |

| | IDMC | TSC | |
|---|---|---|---|
| | • Monthly clinical review of safety reports.<br>• In accordance with the Trial Terms of Reference for the IDMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.<br>• Recommend continuation or suspension of trial to TSC | • In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the IDMC regarding safety issues. | |
| | • Discuss with TSC if recruitment should be suspended | • Confirm continuation of recruitment | |

Safety monitoring will be undertaken by the IDMC. They may recommend suspending or terminating recruitment on the grounds of safety, but will not extend the study. The decision to suspend or terminate the study remains the responsibility of the CI and the study sponsor.

## 9.4 Criteria for Intervention and Discontinuation

The administration of study drug may be discontinued by the PI or designee if they no longer consider it in the participant's best interest to continue in the study, for example, SAE, clinical reasons, or if a patient is entered onto the palliative care pathway. The study intervention will also be discontinued if the participant or their representative requests it. Should the study drug be discontinued, the participant will continue to be followed for safety purposes (up to 30 days of date of randomisation) and participants will remain in the study for follow-up purposes unless they decline follow-up. If the study treatment is discontinued and the participant is willing to undergo follow-up, these will be performed as outlined previously.

Where patients do not wish to undergo further assessments, information relating to safety will be obtained from the participant's clinical records. We will retain and analyse all information obtained up to the point of withdrawal on an intention to treat basis. This will be explained in the participant information sheet and outlined at study entry.

The study will be discontinued in the event that new information comes to light that would make the findings of the study obsolete, if there are changes to the study infrastructure which mean that the study can no longer feasibly be completed or if there are serious safety concerns. Otherwise, it is anticipated that the study will continue until completion.

## 9.5 Notification of Deaths

All deaths that occur within 30 days of the date of randomisation will be reported as SAE as per pharmacovigilance section to the Manchester CTU. This report will be within 24h of the research team becoming aware. In addition, all deaths will be recorded in the CRF up to 6 months post randomisation.

## 9.6 Pregnancy Reporting

The demographic profile of aSAH is such that the incidence is double in females than in males. For this reason, women of child-bearing potential (WOCBP) will be included in the trial. There are limited data from the use of IL-1Ra in WOCBP. However, reproductive studies have been conducted with IL-1Ra on rats and rabbits at doses up to 100 times the human RA dose and have revealed no evidence of impaired fertility or harm to the foetus. IL-1Ra is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether IL-1Ra/metabolites are excreted in human milk. A risk to the newborns / infants cannot be excluded so breast-feeding should be discontinued during treatment with IL-1Ra. Great effort will be made to ensure that female participants who are pregnant or breast feeding will be identified at screening and excluded from study participation.

The Investigator must ensure that all participants are fully aware at the start of a clinical trial of the importance of reporting all pregnancies that occur whilst being treated with the study drug and occurring up to 30 days post randomisation. This should be done as part of the consent process by explaining clearly to the participants or the participant representative of the potential dangers of being or becoming pregnant.

WOCBP enrolled in the study will only be administered IL-1Ra while being an in-patient. Moreover the half-life of SC IL-1Ra is 4-6 hours. It is therefore very unlikely that such participants will become pregnant while being exposed to the study drug. Nevertheless WOCBP will be informed of the lack of safety data on the use of IL-1Ra in pregnancy and strongly advised to avoid becoming pregnant during their in-patient participation.

No safety concerns on the use of IL-1Ra in male RA or CAPS patients with partners of childbearing potential have arisen since its introduction for clinical use, therefore no contraceptive requirements will be put in place for male participants.

Any pregnancy occurring in a participant during treatment or within 30 days of randomisation must be reported to the ***Manchester CTU by*** **email (SAEreport_manctu@manchester.ac.uk) immediately but no later than 24 hours** of the site staff becoming aware of it using a Pregnancy Notification Form. Study drug will be stopped immediately. It is the Investigator's responsibility to obtain consent for follow-up from the participant.

The Manchester CTU will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Outcome Form. The Manchester CTU will then inform the sponsor and manufacturer within one working day of receipt. The Manchester CTU will work with the investigator to ensure that all relevant information is provided to the sponsor and manufacturer. Should a pregnancy occur during the trial, the Investigator should offer counselling to the participant, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the participant and the baby should continue until the conclusion of the pregnancy. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

## 9.7 Overdose Reporting

Administration of study drug is restricted to research staff delegated the responsibility by the PI or appropriately trained ward nurses. Participants will receive two injections of 100mg study drug / placebo via a subcutaneous syringe each day. Injections must be a minimum of 8 hours and maximum of 16 hours

apart. Participants are allocated treatment kits and the procedure to show proof of administration and drug reconciliation make accidental overdose highly unlikely.

Accidental overdose will be reported to the Manchester CTU by the completion of the Overdose CRF page. The completed Overdose CRF page should be reported to the ***Manchester CTU by*** **email (SAEreport_manctu@manchester.ac.uk) immediately, but no later than 24 hours** of the investigator or site staff becoming aware. The Manchester CTU will then inform the sponsor and manufacturer within one working day of receipt. The Manchester CTU will work with the investigator to ensure that all relevant information is provided to the sponsor and manufacturer.

Participants will continue study participation. No adverse effects are anticipated for an accidental overdose.

## 9.8 Urgent Safety Measures

If any urgent safety measures are required the CI/Sponsor will contact the MHRA's Clinical Trial Unit to discuss the issue with a safety scientist. Ideally within 24 hours but no later than 3 days from the date the measures are taken, the Sponsor will send written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures. Written notification in the form of a substantial amendment will also be submitted to MHRA within 7 days. If an urgent safety measure is implemented at site the Manchester CTU should be notified immediately by emailing saereport_manctu@manchester.ac.uk. The Manchester CTU will also notify all recruiting centres within 24 hours of the measures being imposed.

## 9.9 New Safety Findings

If a new safety finding emerges from sources such as study drug manufacturers, data analysis or IDMC findings, the CI will review the finding for its impact on the subjects participating in the relevant trial(s). If there is a potential impact on trial participants' safety, the Manchester CTU will take appropriate action in conjunction with the Sponsor, CI and research team. Appropriate reporting mechanisms are followed in the event of actions being taken.

## 9.10 The type and duration of the follow-up of subjects after adverse events

All study participants who experience an adverse event will be followed-up until resolution or stabilisation. If an event is identified as potentially related to study drug at day 30 assessment, further contact will be made with the participant until the event is resolved. Resolution reports will be sent to the Manchester CTU within 7 days of the recruiting centre becoming aware. Should an Investigator become aware of any drug-related SAEs after the patient's 30 day assessment, these must also be reported to the Manchester CTU within the expedited timelines stated above.

## 9.11 Periodic Safety Reports

### 9.11.1 Development safety update reports (DSUR)

The Manchester CTU will submit a development safety update report (DSUR) to the MHRA within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended by the Manchester CTU on behalf of the Sponsor.

### 9.11.2 Annual progress reports (APR)

The Manchester CTU will submit an annual progress report (APR) 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.

# 10. TRIAL MANAGEMENT AND OVERSIGHT ARRANGMENTS

## 10.1 Roles and Responsibilities

### 10.1.1 Trial sponsor

The trial will be Sponsored by the University of Manchester. The responsibilities of the Sponsor are as defined in 9.10 of the UK Policy Framework for Health and Social Care Research, V3.3. In line with this requirement, the Chief Investigator will ensure that all involved in the research project understand and discharge their responsibilities in accordance with the agreed protocol and any relevant management, ethical and regulatory approvals.

Responsibilities of the Sponsor are detailed in University of Manchester Policy for Compliance with The Medicines for Human use (Clinical Trials) Regulations 2004 and subsequent amendments (Investigational Medicinal Products) UM/10/POL/CT003. The University of Manchester as the Sponsor has delegated a number of these responsibilities as detailed in the Delegation of Responsibilities section of the research agreement signed between the Sponsor and Manchester CTU. The Sponsor has legal responsibilities that cannot be delegated.

### 10.1.2 Manchester CTU

Full details of the role and responsibilities of the Manchester CTU are outlined in the Delegation of Responsibilities section of the research agreement signed between the Sponsor and Manchester CTU.

**Trial Management:**

Provision of trial management activities, including but not limited to, provision of expert advice on the Study Protocol design, development of protocol and other study documentation, preparation of regulatory submissions and reporting, co-ordination with sponsor, study lifecycle project management, management of safety reporting, preparation and maintenance of essential documents (including amendments) in accordance with GCP, management of study monitoring activities and co-ordinate study close-out.

**Data management:**

Provision of data management activities, including but not limited to, provision of expert advice on the Study Protocol design, study risk assessments, design of CRF and study database and CRF completion guidelines, study database testing, production of data validation guidelines and attendance at relevant Chief Investigator meetings.

Data review and validation of data, raising data queries for resolution, liaison with Study Sites with regard to clinical trials data and data queries, provision of relevant data for IDMC meetings and reports, data QC if required and provision of data for statistical analysis. Provision of expert advice on any Study Protocol amendments relating to data aspects.

**Quality Assurance & Pharmacovigilance:**

Provision of QA/QC activities in connection with data capture, verification and relevant supporting documentation. Maintenance of relevant Manchester CTU standard operating procedures.

Review of relevant clinical trial documentation, including relevant GCP essential documents (source document verification).

**Contractual Arrangements:**

To put in place the necessary Study Site agreements with the relevant organisations as set out in the Protocol or otherwise agreed.

#### 10.1.3 Funder

The trial is funded by the National Institute for Health Research. The roles and responsibilities of the funder are defined in the investigator-sponsor study (ISS) agreement.

### 10.2 Oversight Committees

#### 10.2.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and will include those individuals responsible for the day-to-day management of the trial including the Chief Investigator, co-investigators and identified collaborators, Principal Investigators, sponsor pharmacist, the trial statistician and Manchester CTU trial manager(s), data manager(s) and monitor(s). Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial including monitoring overall progress to ensure the protocol is adhered to and to take appropriate action to safeguard the participants and the quality of the trial.

The TMG will meet to discuss progress at least quarterly once the trial is actively recruiting. Minutes will be taken at TMG meetings and copies of the minutes will be filed in the Trial Master File. The trial manager and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites. Minutes of all TMG meetings are available on request.

#### 10.2.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established and will include an independent Chair (not involved directly in the trial other than as a member of the TSC), not less than two other independent members, a representative from a consumer group, plus the CI, and a statistician. The role of the TSC is to take responsibility for the scientific integrity of the trial, the scientific validity of the trial protocol, assessment of the trial quality and conduct (to ensure that the trial is being conducted in accordance with the principles of GCP and the relevant regulations) as well as for the scientific quality of the final study report. Decisions about the continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

The TSC will meet once ethics approval has been given and before the trial begins recruitment. Once the trial has started the TSC should meet at least every 6 months annually to monitor the progress of the trial although there may be periods when more frequent meetings are necessary. Meetings should be organised by the CI via the CTPM. Minutes will be taken at TSC meetings and copies of the minutes will be filed in the Trial Master File and made available to the Sponsor. The trial manager and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites. Minutes of all TSC meetings are available on request. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by the Manchester CTU.

### 10.2.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be instituted to review accruing trial safety data and to assess whether there are any safety issues that should be brought to the participants' attention, whether any safety amendments should be made or if there are any reasons for the trial to discontinue. The IDMC will be independent of the investigators, funder and sponsor. The CI and TMG with the support of the Manchester CTU will be responsible for nominating IDMC members.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by Manchester CTU. This charter will outline any stopping rules and the frequency of analysis and IDMC meetings during the trial. The IDMC will receive a monthly report detailing all life threatening or SAEs resulting in death and the IDMC Chair will also receive the total numbers of SAEs in order to expedite a safety review if more SAEs are being seen than would be expected. A cumulative review of all unblinded safety information will occur on a 12 monthly basis.

Reports to the IDMC will be prepared and presented by the trial statistician and CTPM prior to the IDMC meeting. In these reports all infections will be grouped together rather than assigned to body systems. The IDMC Chair will then report their recommendations to the Chair of the TMG and may request additional reports or information if required. This report will be submitted to the TMG, and if required, the HRA and the MHRA and the CI and CTPM will ensure that all actions and recommendations are followed up.

Prior to scheduled review of safety data, the unblinded allocation list will be supplied to the members of the Data Monitoring Committee by the randomiser using confidential email.

For statistical analysis purposes, the confidential section of reports to the IDMC will be unblinded by merging the participant database with the randomisation schedule. Only the statistician undertaking the analyses and the IDMC members will have sight of these reports. At the end of data collection the validated participant data will be merged with the randomisation schedule to create a locked analysis dataset. Validation of the allocation by comparison with IL1-Ra at day 3-5 will be undertaken at this stage.

## 11. STATISTICS AND DATA ANALYSIS

### 11.1 Sample Size Calculation

The target total recruitment is 1000 patients (800 participants with confirmed aSAH). We have based our calculation on the distribution of the modified Rankin Scale (mRS) at 6 months reported in the control group of the STASH trial[14] using the Whitehead formula[43,44]. A sample size of 360 participants per group contributing data to the primary analysis will give 90% power at the 5% significance level to detect a common odds ratio of 0.65. This is equivalent to increasing the proportion of those with 'good' outcome (mRS higher than 2) from 72% to 80%. Allowing for up to 10% attrition the target total recruitment is 1000 patients (800 participants with confirmed aSAH). This is conservative given the loss to follow up in STASH and our own phase II study in this population. The TSC will monitor both the proportion of non-aSAH participants and the attrition rate.

Using the classical approach of dichotomising the mRS for primary analysis, such a difference would require approximately 600 participants per group. Our use of the ordinal analysis therefore represents an approximate 40% efficiency saving. The target effect size matches that which was deemed clinically significant in planning the STASH trial.

This is lower than our estimate from phase II (although well within confidence intervals) but the latter used the GOS-E with less discrimination at the "good recovery" end of the scale; over 50% of outcomes in this population were deemed "good recovery". Further exploratory analysis using the sliding dichotomy approach[45] to define success according to baseline prognosis estimated an odds ratio very similar to our current target.

## 11.2 Planned Recruitment Rate

The trial will recruit 1000 participants over 42 months. We have based our calculations on the recruitment rate into our own phase II study (3 centres), recruitment into the STASH trial[14], and numbers recorded in national audit data (https://www.hope-academic.org.uk/uksah).

Our calculations distinguish 8 'category A' sites each anticipated to recruit two participants per month, 6 'category C' sites each recruiting one participant per month, and 6 intermediate, 'Category B', sites. We have allowed a two-month 'run-in' phase at each site with 50% of target recruitment and assumed opening of one new site per month.

## 11.3 Statistical Analysis Plan

A detailed statistical analysis plan will be confirmed with the Trial Steering Committee prior to the study's end and pre-tested using a randomly generated indicator variable in place of "allocation". A summary of the approach is presented below.

### 11.3.1 Summary of baseline data and flow of patients

The following variables will be presented to demonstrate the extent of comparability between the randomised groups:

Age

Sex

WFNS grade

Time since ictus (completed days)

A CONSORT flow chart *(http://www.consort-statement.org/)* will be used to show the participant flow with reasons (where known) for discontinuation.

### 11.3.2 Primary outcome analysis

Primary analysis will apply proportional odds regression to the mRS at 6 months with adjustment for the stratification criteria. The adjusted odds ratio will be presented with 95% confidence interval.

### 11.3.3 Secondary outcome analysis

Secondary outcomes will be assessed for the same population using logistic and linear regression methods with similar adjustment. Safety analyses up to 30 days will be undertaken in both the aSAH population and the full randomised cohort.

#### 11.3.4 Mechanistic analysis

As mechanistic mediation analysis is not currently developed for ordinal outcomes we will apply the sliding dichotomy approach to our primary outcome[45]. We will then adopt the parametric modelling approach of counter-factual direct and indirect effects [STATA 'paramed' command] to assess the causal relationship between IL-6 and clinical outcome.

### 11.4 Subgroup Analyses

A limited number of participant subgroups thought likely to differentially benefit from IL-1RA will be defined by the TSC within the detailed SAP. Analysis will be by assessment of treatment by subgroup interactions for the primary outcome.

### 11.5 Adjusted Analysis

All inferential analyses will adjust for the stratification factors used in the allocation routine. Plasma IL-6 and IL-1Ra levels will be log-transformed prior to analysis and presentation.

### 11.6 Interim Analysis and Criteria for the Premature Termination of the Trial

We will monitor recruitment closely and 12 months after first site initiation we estimate we will have recruited at least 100 participants. This will inform the need for additional sites. Our Trial Management team will monitor monthly recruitment rates, both overall and per site, against target. Twelve months after the first site initiates recruitment, all eight 'Category A' sites should be running at full capacity and 20 participants should be recruited in the month. The Trial Steering Committee will formally evaluate recruitment to date at each meeting and recommend according to the following.

1) Overall recruitment at or near target.
2) Site initiation on target but total participant recruitment below 75% of target.
3) Site initiation below target but site-specific recruitment at or near target.
4) Site initiation below target and site-specific recruitment below 75% of target.

In all cases administrative adjustments will be considered to expedite recruitment, learning from the best performing centres. If not 'at or near target' at this review, recruitment will be formally reassessed six months following review. If the current rate of site-specific recruitment remains below target at this stage the recruitment phase will end, participants will complete follow up and the trial will then close. If the site-specific recruitment exceeds this threshold, the trial recruitment will continue and the Trial Steering Committee will consider approaches to achieve 'catch-up'.
At month 22 after the first site initiates recruitment, the trial should be recruiting at full capacity. During month 26, recruitment is scheduled to reach the half-way mark of 500. At or around month 32 therefore, the Data Monitoring Committee will be asked to view a formal analysis of primary outcome data for the first 400 participants with confirmed aneurysmal diagnosis. If the analysis crosses the Haybittle-Peto threshold the recruitment phase will end, participants will complete follow up and the trial will then close, saving approximately 10 months from the recruitment period. We suspect that early stopping with fewer participants would be unlikely to convince clinical opinion as it would require an implausible effect size to achieve the threshold.

## 11.7 Subject Population

We will seek outcomes for all randomised participants with confirmed aSAH regardless of protocol adherence and include them in analyses under the allocated group. That is, the analyses will be by intention to treat for all randomised participants whose confirmed diagnosis is aSAH. The anticipated 20% of randomised patients who are confirmed with alternative diagnoses will be excluded from all efficacy and mechanism analyses. This post-randomisation exclusion will not cause statistical bias because neither the treatment itself nor knowledge of the allocation (achieved by concealment and blinding) can affect the diagnosis. Patients excluded post-randomisation due to absence of confirmed aSAH will be analysed separately for adverse events.

Given the study population it is anticipated that all participants will receive at least one dose of their allocated study drug. It will be reported if an SAE occurred in a participant who did not receive their allocated study drug and an additional, separate "treatment received" population will be defined in this instance.

### 11.7.1 Procedure(s) to account for missing or spurious data

All reasonable efforts will be made to obtain outcome data for randomised participants with confirmed aSAH. This will include requesting follow-up for those who decline treatment at any stage, and repeated and flexible approaches as permitted by ethical review (e.g. options for data collection by telephone, or in person). Where participants are willing to give a reason for withdrawal of consent to follow-up these reasons will be recorded and tabulated.

The primary analysis will use a 'complete case' approach with multiple imputation reserved for sensitivity analysis. Details will be confirmed in the SAP when attrition rates are known.

# 12. DATA HANDLING

## 12.1 Data Collection Tools and Source Document Identification

All clinical outcome questionnaires used at the final assessment (6 months (+/- 28 days) from randomisation) are validated. No non-standard tools will be used. The final assessment will record mRS which includes mortality, and in survivors, additional outcome assessments relating to anxiety, depression (Hospital Anxiety and Depression scale; HADS), fatigue (Greater Manchester Stroke Assessment too; GM-SAT fatigue question) and Fatigue Severity Score and quality of life (EQ-5D-5L).

Final assessment will be coordinated centrally and will be performed by telephone, where possible, with the participant. However, if people need more support a face-to-face interview at any routinely scheduled out-patient appointment will be completed. Options will be made clear on the information for personal-legal representative. In the event of the participant being unable or unwilling to complete the final assessment then the patients relatives will be contacted or their medical records accessed via their GP or other healthcare providers

Case report forms (CRFs) will be used to collect the data. The PI is responsible for ensuring the accuracy, completeness, and timely provision of the data recorded in the CRFs. Only the Investigator and those personnel who have signed the Delegation Log provided by the Manchester CTU and have been authorised by the Investigator should enter or change data in the CRFs.

The Investigators must retain all original reports, traces and images from these investigations for future reference. At the end of the trial all CRFs will be retained and preparation for archiving will be coordinated by the Manchester CTU on behalf of the Sponsor.

#### 12.1.1 CRFs as Source Documents

If the protocol requires data to be entered directly onto the case report forms (CRF), these portions of the CRF would then be considered a source document. Sites will retain copies of all CRFs submitted to the CTU/Sponsor to ensure that the principal investigator or research team can provide access to the source documents to a monitor, auditor, or regulatory agency.

It is possible that in some circumstances, data recorded in the CRF will be source data that will not be verifiable from other sources e.g. recording of mRS will be performed centrally by the research team as part of the 6 month outcome assessment. Permission will be sought from REC to record source data in the CRF only. The PI is responsible for maintaining a comprehensive and centralised filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consent forms, and supporting copies of source documentation (if applicable)
- Study files containing the protocol with all amendments, copies of pre-study documentation and all correspondence to and from Research Ethics Committees
- All original source documents supporting entries in the CRF must be maintained and be readily available (except above).

### 12.2 Data Handling and Record Keeping

#### 12.2.1 Data Handling at Manchester CTU

Completed electronic CRFs will constitute the database and will be reviewed by the designated data manager. The database will be secured via appropriate access control and password protection. Any paper records will be stored securely with access limited to authorised personnel.

Data provided to the Manchester CTU will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the Manchester CTU will request that the data be clarified. Pre-defined checking routines will be applied to all batches of data to ensure complete, accurate data are provided for statistical analysis and reporting. All aspects of data collection and handling throughout the life cycle of the trial will be described in trial specific documents.

### 12.3 Access to Data

By participating in the SCIL trial, the Principal Investigators are confirming agreement with the University of Manchester to ensure that:

- Sufficient data are recorded for all participants to enable accurate linkage between hospital records and CRFs
- Source data and all trial-related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- Trial-related monitoring, audits and IRB/IEC are permitted and direct access to source data/documents is provided as required

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

### 12.3.1 Trial performance and monitoring

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. Manchester CTU must be informed immediately of any change in the personnel involved in the conduct of the trial. On-site monitoring will be based on a risk-based strategy and will be detailed in the project delivery plan. The Investigator will receive reasonable notification before each monitoring visit.

Unused drug must be destroyed at each participating site once authorised by Manchester CTU and accountability completed by the site pharmacist.

It is the responsibility of the Sponsor to inform the HRA within 90 days of the 'end of the trial' that the trial has closed.

### 12.3.2 Clinical study report

The Manchester CTU and CI will prepare a clinical study report based on the final data set. The report will be submitted to Sobi for review. A summary of the final clinical report will be submitted to the MHRA and to the Research Ethics Committee.

## 12.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected.

Each recruiting centre will be responsible for archiving trial documents at their sites. All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for 25 years from the end of the trial. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the minimum/maximum period of time permitted by the hospital, institution or private practice. The participating sites will be required to submit documentation to the Manchester CTU confirming the archiving arrangement.

All other essential documents and trial study data set will be archived by the University of Manchester for 25 years from the date of the final publication in a way that will facilitate any audit and inspection. Documents should be securely stored and access restricted to authorised personnel. Destruction of essential documents will require authorisation from the Sponsor.

# 13. MONITORING, AUDIT & INSPECTION

A detailed risk assessment will be completed by the Sponsor and the Manchester CTU as part of the study set-up process to ascertain the frequency and intensity of monitoring visits required (although additional monitoring may be conducted if necessary). The sponsor and Manchester CTU's risk assessments will be used to ensure that all risks pertinent to the study are incorporated into the associated project delivery plan. The project delivery plan will be agreed by the sponsor. A copy of the Manchester CTU and sponsor's risk assessment and the project delivery plan will be stored in the TMF.

On-site monitoring will be performed by the Manchester CTU based on this detailed risk assessment. Authorised representatives of Sponsor, regulatory authority, or an Ethics Committee may perform audits or inspections at the recruiting centres, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

## 14. ETHICAL AND REGULATORY CONSIDERATIONS

### 14.1 Research Ethics Committee (REC) Review & Reports

Before the start of the trial, application will be submitted to Health Research Authority (HRA) for approval. Approval will also be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters

Substantial amendments will be submitted with the oversight of the study Sponsor. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study, confirmation of No Objection is received from MHRA and local R&D department approval.

In addition:

- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- 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
- The Chief Investigator, Manchester CTU and Sponsor will notify the REC of the end of the study. If the study is ended prematurely or temporarily halted, the Chief Investigator, Manchester CTU and Sponsor will notify the REC, including the reasons for the premature termination within 15 days of the decision.
- The Chief Investigator, Manchester CTU and Sponsor will submit a final report with the results, including any publications/abstracts to the REC within 12 months of the declaration of end of the trial.

### 14.2 Regulatory Compliance

Before the trial commences a Clinical Trial Authorisation (CTA) will be obtained from the Medicine and Healthcare products Regulatory Agency (MHRA). The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

In addition:

- All correspondence with the MHRA will be retained in the Trial Master File/Investigator Site File
- An annual development safety update report (DSUR) will be submitted to the MHRA within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.
- The Chief Investigator, Manchester CTU and Sponsor will notify the MHRA of the end of the study. If the study is ended prematurely or temporarily halted, the Chief Investigator will notify the MHRA within 15 days of the decision, including the reasons for the premature termination or halt.

- The Chief Investigator, Manchester CTU and Sponsor will submit a final report with the results, including any publications/abstracts to the MHRA within 12 months of the declaration of end of the trial.

#### 14.2.1 Local capability and capacity review

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for confirmation of local capability and capacity from the site's Research & Development (R&D) department.

It is the Principal Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the trial. The Principal Investigator must ensure this is documented in the patient's medical notes and the participant is re-consented. It is the responsibility of the PI to ensure that the trial has local R&D approval and the sponsor and Manchester CTU will verify this, plus the presence of all other essential documentation (and potentially an initiation meeting), before giving the "green light" to open the trial to recruitment. The PI is also responsible for ensuring that any subsequent amendments gain the necessary approvals.

### 14.3 Peer Review

As part of the grant application through NIHR EME, the project was reviewed by four independent, anonymous peer reviewers and by the funding board. The applicants responded to all feedback received and changes were made to the project plan as required.

The clinical study protocol will be reviewed and approved by the funder, the Sponsor and the independent chair(s) of the TSC prior to the submission to the ethical and regulatory committees.

### 14.4 Public and Patient Involvement (PPI)

Patients and the public have always been involved in our research through our contact with local patient groups who have been treated in our hospital and through the Brain and Spinal Injury Charity (BASIC) where we meet with aSAH survivors and their families. We work closely with the Stroke Association locally and service users (including some with aSAH) have attended our research meetings (www.mhs.manchester.ac.uk/strokeresearch/events). We have worked with service users on the preparation of this application, with support from a RDS PPI bursary. We met on three occasions with groups of service users (aSAH patients and their carers) to discuss the application. They have offered advice on the research questions and the clinical outcome measures. They have been particularly interested in the secondary clinical outcome measures and have advised which measures best reflect their experiences at around 6 months post aSAH. They have advised on the feasibility of collecting clinical outcome data, including whether some people would prefer to submit their responses on-line or in person. They have reviewed this application and made changes for clarity to the lay summary.

The PPI group involved in the preparation of the application have expressed an interest in continuing involvement throughout the study. A service-user is a co-applicant and will join the trial management group. Two service-users are willing to join the Trial Steering Committee (TSC) and we will endeavour to ensure PPI representation at every meeting. All PPI members will be offered appropriate training and mentorship prior to study start. They will be provided with written meeting papers in advance of all meetings and have contact with the trial manager prior to all meetings to discuss the agenda, and will have a debriefing call following the meeting to deal with any queries.

We will have continued PPI involvement throughout the trial and our panel of service-users will continue to assist in the development of study materials (e.g. patient information sheet) and strategies to improve the collection of clinical outcome data, to foster recruitment by providing written and verbal explanations of the study for patients and relatives considering participation on our trial website. The PPI panel will help with dissemination, both by contributing to lay summaries, and presenting results to service users at meetings and through social media.

### 14.5 Protocol Compliance

The UK Regulations on Clinical Trials state that no deviation must be made from an approved trial protocol, unless it is an urgent safety measure taken to protect a participant from immediate harm. Deviations from the protocol may be taken by an investigator without prior approval from the Sponsor or regulatory bodies to eliminate an immediate hazard to a participant. The rationale must be submitted to the Manchester CTU and the appropriate regulatory bodies as soon as possible after the deviation for urgent safety measures.

Accidental protocol deviations can happen at any time. The participating sites are encouraged to contact the Manchester CTU if a potential protocol deviation has occurred (or if an event has occurred and it is unclear whether it should be classified as a deviation). The Manchester CTU will advise the site what information and actions are required. All notified protocol deviations will be compared to the protocol deviation assessment document by the Manchester CTU to assess their severity (Minor/Major/Serious breach) and whether immediate action is required. The Manchester CTU will maintain a protocol deviation log to aid the monitoring of frequently recurring protocol deviations. Any participating sites with evidence of continuous non-compliance will be escalated to the sponsor for immediate action and could potentially be classified as a serious breach.

### 14.6 Notification of Serious Breaches to GCP and/or the protocol

For Clinical Trials of Investigational Medicinal Products (CTIMPs), there is a legal requirement to report serious breaches of GCP or the trial protocol to the MHRA and appropriate REC within a defined timeframe. If a major deviation on a CTIMP meets the criteria for a serious breach, it is notified immediately to the Sponsor and reported to the HRA and the MHRA within 7 days of confirmation by the Manchester CTU.

Complete investigations of breaches will be fully documented, filed in the TMF and a copy sent to the sponsor.

### 14.7 Data Protection and Patient Confidentiality

Participants will be assigned a unique Trial ID via the Glasgow Clinical Trials Unit's Randomisation system that will be used throughout their participation in the trial. Any personal data recorded will be regarded as confidential, and any information that would allow individual participants to be identified will not be released into the public domain.

Investigators and trial site staff must not provide any participant- identifying data (e.g. name, address, hospital, reference number) to the Manchester CTU during the course of the trial, unless with prior approval by the Research Ethics Committee. Any participant identifying data received by Manchester CTU will be redacted or destroyed, and the sender notified.

Each participating centre should keep a separate Trial ID and screening log of all participants consented and screen status. The investigator must maintain this screening log and all other trial documents (including participant's written consent forms) which are to be held at the participating centre, in strictest confidence.

The investigator must ensure the participants' confidentiality is maintained. As part of this study, participants (or next of kin) contact details will be shared with the trial centre to enable the 6 month telephone follow-up assessment to be performed centrally. Data sharing will be performed via encrypted NHS to NHS emails or verbally by telephone. All information shared with the trial centre will be stored securely by the trial centre staff. Full details of this process are detailed a separate procedure document.

The Manchester CTU will maintain the confidentiality of all participants and will not reproduce or disclose any information by which participants could be identified. The Investigator and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.

Representatives of the Manchester CTU and the regulatory authorities will be required to have access to participants' notes for quality assurance purposes but participants should be assured that their confidentiality will be respected at all times. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

All Investigators and trial site staff involved with the trial must comply with the requirements of the Data Protection Act with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The sponsor will be the data custodian.

Participant notes and trial files at site must be kept in a secure storage area with limited access. Computers used to collate the data will have access restrictions via user names, passwords, and the use of encrypted digital files and storage media. Published results will not contain any personal data that could allow identification of individual participants.

### 14.8 Financial and Other Competing Interests

None of the research team, investigator teams, and the sponsor has any financial or other conflict of interest. All members of the oversight committees will declare any potential conflicts of interest as part of their membership agreement. If any financial or other completing interests come to light during the course of the trial, a declaration of these conflicts of interest will be sorted in the agreement & finance section of the TMF.

An investigator-sponsor study (ISS) agreement will be in place before the study opens to recruitment to clarify the financial position of Sobi. This ISS agreement will comply with NIHR requirements.

### 14.9 Indemnity

The University of Manchester will act as the sponsor for this study. Delegated responsibilities will be assigned to the Chief Investigator & Manchester CTU to manage the trial on behalf of the sponsor and to the participating sites recruiting participants into this trial. The sponsor will ensure that adequate insurance and indemnity are in place before the start of patient recruitment.

The participating site will be liable for clinical negligence and other negligent harm to participants taking part in the study and covered by the duty of care owed to them by the site concerned. For participating sites that are part of the NHS, the NHS indemnity scheme will also apply.

The manufacturer supplying the study drug has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

### 14.10 Amendments

Any changes in research activity will be reviewed and approved by the Chief Investigator. With the oversight of the sponsor, the subsequent amendment will be categorised as substantial or non-substantial. Any required changes to the CTA or the documents that supported the original application for the CTA and/or ethical approval will be submitted as an amendment to the appropriate ethical and regulatory authorities by the Manchester CTU. Substantial amendments will not be implemented until the HRA grants approval of the study and confirmation of 'No Objection' is received from MHRA is obtained. The Manchester CTU will maintain an amendment history tracker to ensure the most recent version of the protocol and supporting documents are used at all times.

For any amendment that will potentially affect a site's local capability and capacity, the Manchester CTU will confirm with each participating site's R&D department that local capability and capacity is ongoing.

The Manchester CTU will ensure that all relevant stakeholders are informed of substantive changes in appropriate time.

### 14.11 Post-Trial care

Patients will have no further access to the study drug once their study treatment is complete (maximum 21 days from ictus or when fit for discharge from neurosurgical unit). All patients will continue to receive the standard care for subarachnoid haemorrhage and participation in this study will not affect or delay this care.

## 15. DISSEMINATION POLICY

### 15.1 Dissemination Policy

As detailed in section 12.3.2, upon completion of the trial the Manchester CTU and CI will prepare a clinical study report based on the final data set.

A trial website with links to our research group website will be established (http://www.mhs.manchester.ac.uk/strokeresearch/). This will have information for patients and their families and for clinicians and research staff. It will include filmed interviews of aSAH survivors and previous study participants, describing their experiences as aSAH survivors and research participants. This will include people who participated in our recently completed phase II study of IL-1Ra in aSAH. Triallists and service users regularly use social media to share information about research studies and we will tweet study updates and results when available (@UofMStrokeRes). Once the trial has gained ethical and regulatory approval, the approved clinical study protocol will be available on the trial website. We will regularly update Researchfish and international and national trial websites.

In keeping with the guidance for the Research Governance Framework, the information arising from the study will be made available to the study population that it affects, the clinical community who may use the information and also to anyone who may benefit from the study's findings. In order to achieve this, all participants will be asked whether they wish to receive a summary of the study's findings at study entry, regular presentations will be made to clinicians and the study will be submitted for presentation at scientific and clinical meetings and for publication in peer-reviewed periodicals.

The main trial results will be published in the name of the trial in high impact open access journals such as Stroke and Lancet Neurology, on behalf of all collaborators. The trial results will also publish in the EME journal to ensure that the research is publicly available and the abstract freely available via the NIHR Journals Library website and the Europe PubMed website.

Presentations will be submitted at meetings of clinicians and scientists, for example UK Stroke Forum, European Stroke organisation meetings, British Neurovascular Research Group, Society of British Neurosurgeons, World Stroke Organisation meetings or American Association of Neurological Surgeons meeting. Trial results will be presented at meetings of service users (for example, the Stroke Assembly, and the Manchester World Stroke Day Event) and lay summaries of the research will be prepares with our PPI panel for all participants who express a wish to receive them. We will work with national guidelines groups and those who commission and provide services for people with SAH to ensure that any positive results are rapidly taken up into clinical practice.

All presentations and publications relating to the trial must be authorised by the TMG, Sponsor and study drug manufacturer and must knowledge the funders, and supporting bodies (participating sites associated NHS trusts) and the Sponsor. All presentations and publications relating to the trial will be submitted to the NIHR EME Programme at the time of submission.

Post-publication the anonymised dataset generated and analysed during the trial will be made available, upon request, to other research groups wanting to undertake systematic reviews or other secondary analyses.

## 15.2 Authorship Eligibility Guidelines

The manuscript of the primary study publications will be prepared by a writing group, appointed from amongst the Trial Management Group. The participating site(s) and clinicians will be acknowledged in this publication together with staff from the Manchester CTU.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2004), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

- When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

- Each author should have participated sufficiently in the work to take public responsibility for appropriate proportions of the content.

Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator or company may present or attempt to publish data relating to SCIL without prior permission from the TMG and Sponsor.

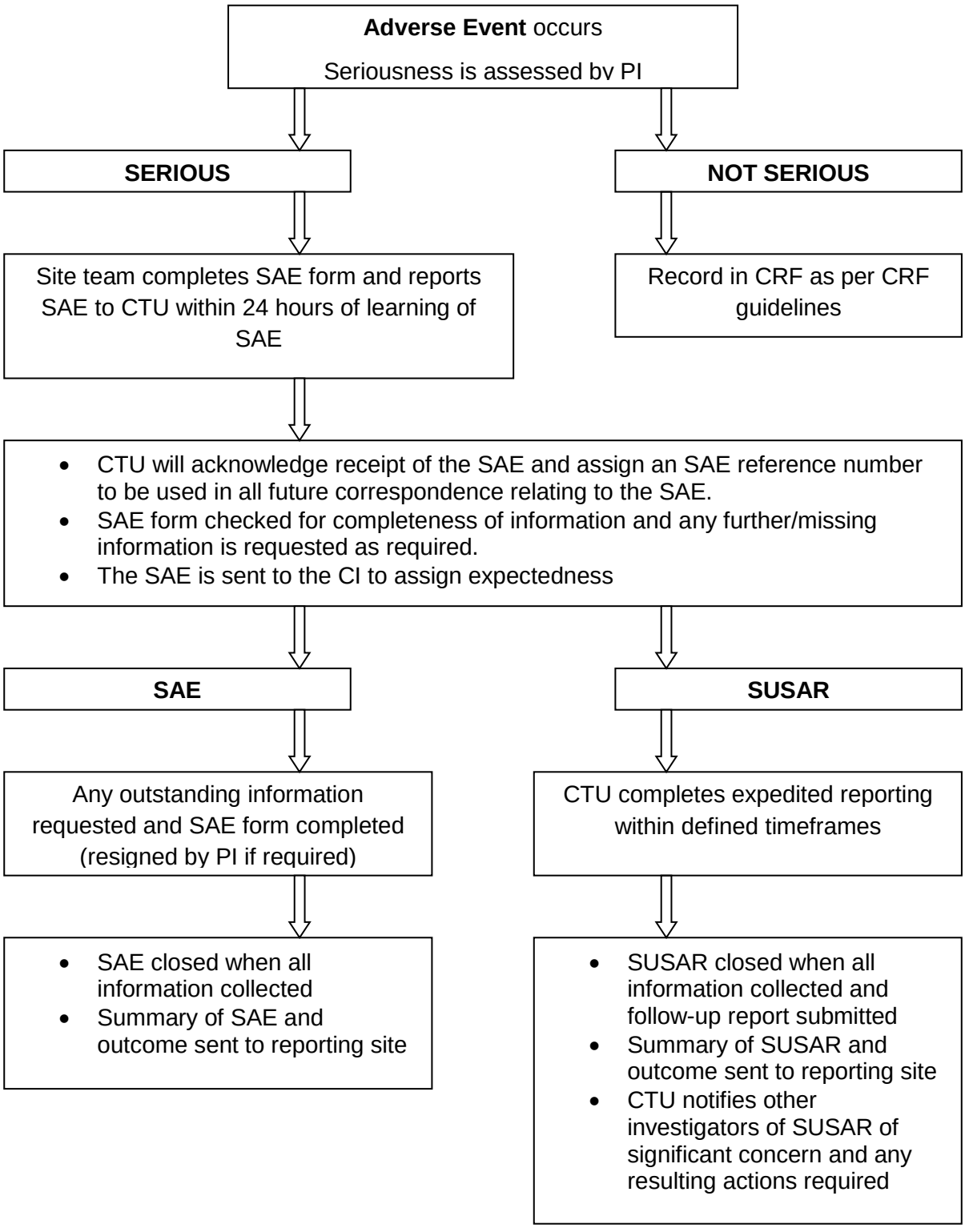
# 16. APPENDICES

## 16.1 Appendix 1: List of live vaccinations commonly used in the UK

| **Bacterial Vaccines** | **Viral Vaccines** |
|---|---|
| Bacillus Calmette Guerin (BCG) vaccination | Measles vaccination |
| Typhoid vaccination (oral) | Mumps vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox; herpes zoster) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |

This is not a definitive list please use PI discretion before including any patient who has received a vaccination within 10 days of SAH in this study.

## 16.2 Appendix 2: Safety Reporting Flow Chart



## 16.3 Appendix 3: Amendment History

| Amendment No. | Protocol version no. | Date issued | Author(s) of changes | Details of changes made |
|---|---|---|---|---|
| n/a | 1.0 | 07-Mar-2017 | n/a | N/A – First Issue |
| 1.0 | 2.0 | 19-Sep-2017 | Helen Bradley | Correction of title of Prof Tyrrell in confidentiality notice on page 1.<br><br>Table and section number formatting changes.<br><br>Wording changes section funding and support in kind, 7.2.1, 7.7.2 and 12.1.1, 14.8.<br><br>This version was submitted for REC review on 19 Sep 2017. |
| 2.0 | 3.0 | 23-Jan-2018 | Helen Bradley | Change of CI details on page 1 and in key trial contacts. Addition of the title Deputy CI for Mr Hiren Patel. Change of contact details for Mr James Galea and Beatriz Duran-JImenez<br><br>Wording changes of: assent to consent in synopsis; & to and in Funding and Support in Kind section and section 13, in vitro moved in sentence in section 1.1.4, login account rather than code to be used for unblinding in section 7.6, AB added to SOBI in section 8<br><br>Addition of secondary outcome into synopsis in line with secondary objective listed in section 3.3.<br><br>Meets inclusion criteria changed to meets eligibility criteria in trial flow chart.<br><br>Addition of secondary outcome into section 3.4 in line with secondary objective listed in section 3.3.<br><br>References to appendices removed in section 3.4.2 due to questionnaire distribution restrictions.<br><br>Schedule of assessments amended to reflect clarifications of data to be collected and safety checking. |

| | | | | |
|---|---|---|---|---|
| | | | | Section 7.2.1 – clarification that demographic, clinical and radiological data will be checked against eligibility criteria and clarification of verbal consent process for pregnancy testing.<br><br>Section 7.4 – Clarification of timings of consent, baseline assessment and randomisation<br><br>Section 7.4.2 – Removal of detail on management of kits at site – to be incorporated into pharmacy manual instead<br><br>Section 7.7.2 – Clarification on data to collect at baseline<br><br>Section 7.7.2 – Clarification on data to collect post randomisation<br><br>Section 7.8 – Wording change of 'withdrawal of content for participant or their personal legal representative' to 'Participant or personal representative decision'. Wording change of 'Uncontrolled AE/SAE' to 'Uncontrolled AE/SAE that is related to, or potentially related to, study drug'. Wording change to clarify symptomatic deterioration withdrawal point. Clarification of rationale why uncontrolled AE/SAE withdrawal point has changed. And clarification of site responsibilities in event of participant withdrawal.<br><br>Section 7.9 – Correction that research team will provide blood sampling tubes to sites<br><br>Section 8.1.4 – Clarification on approach to concomitant medication<br><br>Section 8.1.5 – Removal of requirement for caution in case of high blood cholesterol or thrombocytopenia, because these conditions do not require caution according to SmPC (Jan 2016)<br><br>Section 8.1.6 - Clarification on labelling<br><br>Section 8.1.7 – Removal of specification of two shipments. Shipments will be as |

| | | | | |
|---|---|---|---|---|
| | | | | required.<br><br>Section 8.4 – Clarification that study drug can be administered by senior ward nurses as well as research staff<br><br>Section 9.1.1 – Clarification of approach to AE reporting<br><br>Section 9.2 – Change of SAE reporting email address and addition of fax number.<br><br>Section 9.6 – Change of pregnancy reporting email address<br><br>Section 9.7. Clarification that study drug can be administered by senior ward nurses as well as research staff and change of overdose reporting email address<br><br>Section 10.1.1 – Update to reflect UK policy framework for health and social care research has replaced Research governance framework for health and social care.<br><br>Sections 10.1.2 and 12.2.1 – Clarification of data management responsibilities of CTU<br><br>Section 10.2,1 – Clarification of TMG members<br><br>Section 10.2.2 – Clarification of TSC members<br><br>Section 11.3.1 – Removal of glasgow coma score as only WFNS is needed here<br><br>Section 11.7.1 and 12.1 – removal of an online option to provide 6 month outcome data<br><br>Section 12.4 – clarification of site archiving requirements<br><br>Section 15.1 – statement on future data sharing plans |
| 3.0 | 4.0 | 01-Mar-2018 | Helen Bradley | List of Definitions – A definition of woman of childbearing potential has been added<br><br>Section 2.1.1 – This section has been added |

| | | | | |
|---|---|---|---|---|
| | | | | to provide justification of the IMP dose and administration duration<br><br>Section 7.2.1 – Definitions of highly effective contraceptive methods and abstinence have been added<br><br>Section 8.4 – Wording changes have been made to clarify the content of reference 42 and the reader is referred to section 2.1.1 for further detail on the justification of IMP dose and administration duration.<br><br>Section 9.6 – The wording of the statement that no contraceptive requirements will be put in place for male participants has been changed, to more accurately reflect the evidence available, |
| 4.0 | 5.0 | 27-Jun-2018 | Helen Bradley | Exclusion criteria added due to caution surrounding Still's Disease in Apr2018 SmPC.<br><br>Exclusion criterion number 8 changed to better align with the guidance in SmPC (versions dated Jan2016, Oct2017 and Apr2018).<br><br>To improve clarity of wording, exclusion criteria number 9 has been split into two.<br><br>Exclusion criterion number 13 – correction of use of e.g. to i.e.<br><br>Section 7.4 – Addition of stratification based on known aneurysmal status<br><br>Section 7.4.1 – Removal of text saying participant ID will be selected from a list. This is incorrect, the randomisation system will generate the participant ID.<br><br>Section 7.5 – clarification that the trial statistician will be aware of treatment allocations during the period of the trial.<br><br>Section 7.8 – Clarification that baseline blood samples from non-aneurysmal participants will be sent to central lab for potential use in future research (provided consent was given for this).<br><br>Section 7.9 – Wording corrections as it is |

| | | | | |
|---|---|---|---|---|
| | | | | blood samples, rather than plasma samples, that will be collected.<br><br>Section 8.1.3 – correction of spelling error<br><br>Section 8.1.4 – changes made to better align with the guidance in SmPC (dated Jan2016, Oct2017 and Apr2018).<br><br>Section 8.1.5 – Categorisation of 'Moderate Renal Impairment' changed to 30-59 ml/minute in line with Apr2018 SmPC.<br><br>Section 10.2.2 – clarification of TSC membership<br><br>Section 10.2.3 – clarification that the trial statistician will prepare the IDMC report.<br><br>Section 11.2 – correction of website address through addition of https:// |
| 5.0 | 6.0 | | Marianne Stewart | All references to MAHSC CTU changed to Manchester CTU<br><br>Updates to Key contact details including addition of Dr Ian Galea, Associate Professor in Experimental Neurology, Dr Kayode Ogungbenro, Lecturer in Cancer Pharacometrics, University of Southampton and change in contact details of the Clinical Trials Unit<br><br>Trial flow chart amended to clarify that randomised patients given study drug at day 0 and then subsequently not being confirmed as having an aneurysm will only have AE follow up for 30 days before being withdrawn from the trial<br><br>Synopsis - Addition of sub-study in Trial Design section and addition of blood pellets retention for use in future genetic analysis in the procedures section<br><br>Addition of University of Southampton in Funding and Support in Kind table<br><br>Section 1.1.5 – Addition of sub-study<br><br>Section 7.2.1 – Wording added to ensure PIS is read before consent given<br><br>Section 7.3 – wording amended to remove |

| | | | | |
|---|---|---|---|---|
| | | | | requirement for at least 1 hour wait between patient approach and consent but to clarify that patients/personal representatives will have as much time as required to consider taking part<br><br>Section 7.4 – Clarification that randomisation takes place on day 0<br><br>Section 7.9 – Addition of blood pellet retention for sub-study and inclusion of future genetic analysis permission from participants<br><br>Section 8 – Change in study drug administration from taking place twice daily at 07:00 or 19:00 (± 2 hours) to twice daily minimum 8 hours and maximum 16 hours between administrations<br><br>Section 8.1.3 – Deletion of 'Senior' in relation to ward nurses, and removal of specific training changed to appropriately trained ward nurses<br><br>Section 8.4 - Deletion of 'Senior' in relation to ward nurses, and removal of specific training changed to appropriately trained ward nurses. Change in study drug administration from taking place twice daily at 07:00 or 19:00 (± 2 hours) to twice daily minimum 8 hours and maximum 16 hours between administrations<br><br>Section 9.2 – Update to SAE reporting contact details<br><br>Section 9.7 – Deletion of 'Senior' in relation to ward nurses, and removal of specific training changed to appropriately trained ward nurses. Update to SAE reporting contact details<br><br>Section 9.8 – Addition of urgent safety measures being implemented at site being notified to Manchester CTU |
| 6.0 | 7.0 | 20Sep2019 | Marianne Stewart | Trial Flow chart updated to reflect dosing times implemented in Version 6 |

| | | | | |
|---|---|---|---|---|
| | | | | The wording in all references made to the maximum days trial drug/placebo administration have been changed to standard text of 'maximum 21 days from ictus'<br><br>Section 9.2 – All references to faxes removed as no longer in use<br><br>Section 9.7 – The gap between dosing times corrected to align with change made in Version 6 |

## 17. REFERENCES


1 de Rooij, N. K., Linn, F. H., van der Plas, J. A., Algra, A. & Rinkel, G. J. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *Journal of neurology, neurosurgery, and psychiatry* **78**, 1365-1372, doi:10.1136/jnnp.2007.117655 (2007).

2 Feigin, V. L., Lawes, C. M., Bennett, D. A., Barker-Collo, S. L. & Parag, V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *The Lancet. Neurology* **8**, 355-369, doi:10.1016/S1474-4422(09)70025-0 (2009).

3 Rinkel, G. J. & Algra, A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *The Lancet. Neurology* **10**, 349-356, doi:10.1016/S1474-4422(11)70017-5 (2011).

4 Al-Khindi, T., Macdonald, R. L. & Schweizer, T. A. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke; a journal of cerebral circulation* **41**, e519-536, doi:10.1161/STROKEAHA.110.581975 (2010).

5 Rivero-Arias, O., Gray, A. & Wolstenholme, J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. *Cost effectiveness and resource allocation : C/E* **8**, 6, doi:10.1186/1478-7547-8-6 (2010).

6 Buunk, A. M., Groen, R. J., Veenstra, W. S. & Spikman, J. M. Leisure and social participation in patients 4-10 years after aneurysmal subarachnoid haemorrhage. *Brain injury*, 1-8, doi:10.3109/02699052.2015.1073789 (2015).

7 Dorsch, N. W. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part III: Mechanisms of action of calcium antagonists. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* **1**, 151-160 (1994).

8 Miller, B. A., Turan, N., Chau, M. & Pradilla, G. Inflammation, vasospasm, and brain injury after subarachnoid hemorrhage. *BioMed research international* **2014**, 384342, doi:10.1155/2014/384342 (2014).

9 Macdonald, R. L. Delayed neurological deterioration after subarachnoid haemorrhage. *Nature reviews. Neurology* **10**, 44-58, doi:10.1038/nrneurol.2013.246 (2014).

10 Macdonald, R. L., Pluta, R. M. & Zhang, J. H. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nature clinical practice. Neurology* **3**, 256-263, doi:10.1038/ncpneuro0490 (2007).

11 Lee, K. H., Lukovits, T. & Friedman, J. A. "Triple-H" therapy for cerebral vasospasm following subarachnoid hemorrhage. *Neurocritical care* **4**, 68-76, doi:10.1385/NCC:4:1:068 (2006).

12 Pickard, J. D. *et al.* Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *Bmj* **298**, 636-642 (1989).

13 Brough, D., Rothwell NJ, Allan, SM. Interleukin-1 as a pharmacological target in acute brain injury. *Exp Physiol* **0.0**, 1–6 (2015).

14 Kirkpatrick, P. J. *et al.* Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. *The Lancet. Neurology* **13**, 666-675, doi:10.1016/S1474-4422(14)70084-5 (2014).

15 Turner, C. L. *et al.* Elevated Baseline C-Reactive Protein as a Predictor of Outcome After Aneurysmal Subarachnoid Hemorrhage: Data From the Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) Trial. *Neurosurgery* **77**, 786-793, doi:10.1227/NEU.0000000000000963 (2015).

16 Greenhalgh, A. D. *et al.* Interleukin-1 receptor antagonist is beneficial after subarachnoid haemorrhage in rat by blocking haem-driven inflammatory pathology. *Disease models & mechanisms* **5**, 823-833, doi:10.1242/dmm.008557 (2012).

17 Hollig, A. *et al.* Association of early inflammatory parameters after subarachnoid hemorrhage with functional outcome: A prospective cohort study. *Clinical neurology and neurosurgery* **138**, 177-183, doi:10.1016/j.clineuro.2015.08.030 (2015).

18 Denes, A. *et al.* Central and haematopoietic interleukin-1 both contribute to ischaemic brain injury in mice. *Disease models & mechanisms* **6**, 1043-1048, doi:10.1242/dmm.011601 (2013).

19 Dinarello, C. A. Interleukin-1 and interleukin-1 antagonism. *Blood* **77**, 1627-1652 (1991).

20 Maysami, S., Wong, R, Pradillo, JM, Denes, A, Dhungana, H, Malm, T, Koistinaho, J, Orset, C, Rahman,M, Rubio,M, Schwaninger,M, Vivien, D, Bath,PM, Rothwell,NJ, Allan, SM. . A cross-laboratory preclinical study on the effectiveness of interleukin-1 receptor antagonist in stroke. *Journal of Cerebral Blood Flow and Metabolism* doi:10.1177/0271678X15606714 (2015).

21 Larsen, C. M. *et al.* Interleukin-1-Receptor Antagonist in Type 2 Diabetes Mellitus. *N Engl J Med* **356**, 1517-1526 (2007).

22 Fleischmann, R. M. *et al.* Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis & Rheumatism* **48**, 927-934 (2003).

23 Ilowite, N. *et al.* Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. *Clinical Rheumatology* **28**, 129-137 (2009).

24 Clark, S. R. *et al.* Interleukin-1 receptor antagonist penetrates human brain at experimentally therapeutic concentrations. *J Cereb Blood Flow Metab* **28**, 387-394 (2008).

25 Galea, J. *et al.* Intravenous anakinra can achieve experimentally effective concentrations in the central nervous system within a therapeutic time window: results of a dose-ranging study %L 0000 %U http://dx.doi.org/10.1038/jcbfm.2010.103. *J Cereb Blood Flow Metab* (2010).

26 Singh, N. *et al.* The effect of intravenous interleukin-1 receptor antagonist on inflammatory mediators in cerebrospinal fluid after subarachnoid haemorrhage: a phase II randomised controlled trial. *Journal of neuroinflammation* **11**, 1, doi:10.1186/1742-2094-11-1 (2014).

27 Kirkness, C. J. *et al.* The impact of aneurysmal subarachnoid hemorrhage on functional outcome. *J Neurosci Nurs* **34**, 134-141 (2002).

28 Smith, C. J. *et al.* Interleukin-1 receptor antagonist reverses stroke-associated peripheral immune suppression. *Cytokine* **58**, 384-389, doi:10.1016/j.cyto.2012.02.016 (2012).

29 Molyneux, A. J. *et al.* Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *The Lancet. Neurology* **8**, 427-433, doi:10.1016/S1474-4422(09)70080-8 (2009).

30 Etminan, N., Vergouwen, M. D., Ilodigwe, D. & Macdonald, R. L. Effect of pharmaceutical treatment on vasospasm, delayed cerebral ischemia, and clinical outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Cereb Blood Flow Metab* **31**, 1443-1451, doi:10.1038/jcbfm.2011.7 (2011).

31 Veldeman, M. *et al.* Delayed cerebral ischaemia prevention and treatment after aneurysmal subarachnoid haemorrhage: a systematic review. *British journal of anaesthesia* **117**, 17-40, doi:10.1093/bja/aew095 (2016).

32 Perry, J. J. *et al.* High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study. *Bmj* **341**, c5204, doi:10.1136/bmj.c5204 (2010).

33 Galea, J. *et al.* Reduction of inflammation after administration of interleukin-1 receptor antagonist following aneurysmal subarachnoid hemorrhage: results of the Subcutaneous Interleukin-1Ra in SAH (SCIL-SAH) study. *Journal of neurosurgery* **128**, 515-523, doi:10.3171/2016.9.JNS16615 (2018).

34 Loddick, S. A., Turnbull, A. V. & Rothwell, N. J. Cerebral interleukin-6 is neuroprotective during permanent focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab* **18**, 176-179, doi:10.1097/00004647-199802000-00008 (1998).

35 Pradillo, J. M. *et al.* Delayed administration of interleukin-1 receptor antagonist reduces ischemic brain damage and inflammation in comorbid rats. *J Cereb Blood Flow Metab* **32**, 1810-1819, doi:10.1038/jcbfm.2012.101 (2012).

36 Snaith, R. P. The Hospital Anxiety And Depression Scale. *Health and quality of life outcomes* **1**, 29, doi:10.1186/1477-7525-1-29 (2003).

37 Golicki, D. *et al.* Validity of EQ-5D-5L in stroke. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* **24**, 845-850, doi:10.1007/s11136-014-0834-1 (2015).

38 Rothwell, K., Boaden, R., Bamford, D. & Tyrrell, P. J. Feasibility of assessing the needs of stroke patients after six months using the GM-SAT. *Clinical rehabilitation* **27**, 264-271, doi:10.1177/0269215512457403 (2013).

39 Duncan, F. *et al.* Clinically significant fatigue after stroke: a longitudinal cohort study. *Journal of psychosomatic research* **77**, 368-373, doi:10.1016/j.jpsychores.2014.06.013 (2014).

40 Noble, A. J. *et al.* Posttraumatic stress disorder explains reduced quality of life in subarachnoid hemorrhage patients in both the short and long term. *Neurosurgery* **63**, 1095-1104; discussion 1004-1095, doi:10.1227/01.NEU.0000327580.91345.78 (2008).

41 Friedman, J. H. *et al.* Fatigue rating scales critique and recommendations by the Movement Disorders Society task force on rating scales for Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* **25**, 805-822, doi:10.1002/mds.22989 (2010).

42 Yang, B. B., Baughman, S. & Sullivan, J. T. Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* **74**, 85-94 (2003).

43 Emsley, R., Dunn, G. & White, I. R. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Statistical methods in medical research* **19**, 237-270, doi:10.1177/0962280209105014 (2010).

44 Whitehead, J. Sample sizes calculations for ordered categorical data. *Statistics in medicine* **15**, 1065-1066, doi:10.1002/(SICI)1097-0258(19960530)15:10<1065::AID-SIM288>3.0.CO;2-9 (1996).

45 Ilodigwe, D. *et al.* Sliding dichotomy compared with fixed dichotomization of ordinal outcome scales in subarachnoid hemorrhage trials. *Journal of neurosurgery* **118**, 3-12, doi:10.3171/2012.9.JNS111383 (2013).