MANCHESTER 1824
The University of Manchester

Study title:	**Phase II trial of Interleukin-1 receptor antagonist in intracerebral haemorrhage: BLOcking the Cytokine IL-1 in ICH**
Short title:	**BLOC-ICH**
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IRAS Project ID:	252065
Trials.gov identifier:	NCT03737344

SIGNATURE PAGE

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: ...../...../.....

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Name (please print):

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Position:

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Chief Investigator:

Signature:  Date: 19/12/2022

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Name: (please print):

Adrian Parry-Jones

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Statistician:

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

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Name: (please print):

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Position:

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KEY TRIAL CONTACTS

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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. Details of the committee members and details of their roles and responsibilities can be found in each committee charter.

SYNOPSIS

Title	Phase II trial of interleukin-1 receptor antagonist in intracerebral haemorrhage: BLOcking the Cytokine IL-1 in ICH
Trial Phase	Phase II
Hypotheses	*Primary:* Does interleukin-1 receptor antagonist (IL-1Ra (Kineret®)) reduce subacute perihaematomal oedema after intracerebral haemorrhage (ICH)? *Secondary:* i. Does IL-1Ra (Kineret®) alter other key parameters associated with inflammation, including blood inflammatory markers, blood-brain barrier breakdown and early haematoma growth? ii. Is IL-1Ra (Kineret®) safe in patients after acute ICH?
Primary Outcome	Oedema extension distance (OED) at 72 $\pm$ 12 hours
Secondary Outcomes	• Early haematoma growth (defined as ≥33% and/or ≥6 ml increase in haematoma volume between baseline and 72 $\pm$ 12 hours) • Early Neurological Decline (END) between baseline and 72 hours (determined by change in Glasgow Coma Scale [GCS] and/or National Institutes of Health Stroke Scale [NIHSS] scores) • Clinical outcomes at 3 months (modified Rankin Scale [mRS], Stroke Impact Scale [SIS], Fatigue Severity Scale [FSS], quality of life [EQ-5D-5L], Hospital Anxiety and Depression Scale [HADS]) • Area under the curve for inflammatory markers (C-reactive protein [CRP], Interleukin-6 [IL-6]) from baseline (day 0) to day 4 • Quantitative blood-brain barrier permeability in the perihaematomal brain at day 2-4
Trial Design	A randomised, double blind, placebo controlled, multi-centre phase II trial of IL-1Ra (Kineret®) in 80 patients with acute spontaneous ICH.
Sample Size	Target total recruitment of 80 patients (66 patients with primary outcome data).
Patient Eligibility Criteria	***Inclusion criteria:*** 1. Patients with spontaneous, non-traumatic, supratentorial ICH with no underlying macrovascular or neoplastic cause admitted to a participating centre within 8 hours of symptom onset. 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. 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. ***Exclusion criteria:*** 1. Severe ICH, unlikely to survive to 72 hours scan, in the opinion of the treating clinician. For example, a GCS score $<$ 6 at time of consent);

2. Confirmed or suspected structural abnormality as cause of ICH (including tumour, vascular malformation);
3. Confirmed or suspected haemorrhagic transformation of an arterial or venous infarct;
4. Acute neurosurgery planned within 72 hours of admission;
5. Known active tuberculosis or active hepatitis;
6. Known active malignancy;
7. Neutropenia (absolute neutrophil count (ANC) <1.5 x 10^9/L);
8. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate [eGFR] < 30 ml/minute) documented in the last 3 months prior to this ICH*
9. Live vaccinations within the last 10 days prior to this ICH;
10. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial;
11. Previous or current treatment with etanercept or any other TNF-α antagonist;
12.Known to have participated in a clinical trial of an investigational agent or device in the 30 days prior to symptom onset;
13.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 symptom onset;
14. 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 7.1.1);
15. Known diagnosis of Still's disease;
16. Clinically significant serious concurrent medical condition, premorbid 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;
17. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC (please section 8.1.4);
18.Known allergy to other products that are produced by DNA technology using the micro-organism E. coli (e.g. *E.coli* derived protein).

* - Due to the narrow time window for study inclusion, it is not always possible to obtain confirmation of normal renal function from clinical Biochemistry sample obtained on admission to the Emergency Department; as the results are often subject to significant delay. This may result in willing patients being denied the chance to participate in the trial. The safety profile for the IMP is good and following consultation with a Renal Physician it was agreed that administration of a single dose of IMP would be sufficiently safe in patients with mild-moderate renal failure. This is also supported by the study Sponsor. The research staff will make every attempt to establish that the patient has an acceptable renal function test result (e.g. eGFR of >30ml/min) in the 3 months prior to stroke by using information from the patient themselves (if available) or either their personal representative, general practitioner and electronic patient record. Providing there is no evidence of significantly impaired renal function, we will request permission to administer the first dose of IMP within 8 hours of stroke, as per protocol. As an additional safeguard, no further doses of IMP will be administered until normal renal function has been confirmed from the clinical Biochemistry sample taken on the day of admission to hospital.

	In cases where renal function was not confirmed as acceptable at admission, the clinical Biochemistry results will be reviewed by a medically qualified member of the stroke team before the second dose is prescribed/administered.
Investigational Product Dosage and Administration	Masked recombinant human IL-1Ra (Kineret®) (manufactured as Kineret® from Swedish Orphan Biovitrum Ab (Sobi), Sweden). An initial 100 mg dose will be given subcutaneously (SC) within 8 hours of symptom onset, followed by 5 subcutaneous injections of 100mg Kineret, 12 hourly, for 72 hours.
Control groups	Matched placebo will be used as control trial intervention.
Procedures	*Clinical assessments:* Will be performed at baseline (0-8 hours post symptom onset) and on a daily basis during study treatment by research staff. Assessments for adverse event monitoring will be performed during the study treatment period. Further clinical assessments for safety monitoring will take place at baseline, before the 2nd Investigational Medicinal Product (IMP) administration, on Day 4 and on Day 30 post randomisation. An end of study assessment at 3 months will be performed and will include collection of the mRS, SIS, FSS, EQ-5D-5L and HADS. *Blood sampling:* Blood for research will be taken at baseline (pre-randomisation) and at 09:00am (± 2 h) on a daily basis until the next 09:00am (± 2 h) after the study treatment has completed. Full blood count, urea and electrolytes (U&E), C-Reactive Protein (CRP) and IL-6 will be measured. *Imaging:* A research CT brain scan will be performed 72 ± 12 hours after symptom onset and will be used to measure the volumes of the haematoma and perihaematomal oedema. Unless a patient is deemed too unwell to proceed, an MR scan will also be performed on Day 2 – Day 4 to provide quantitative assessment of blood-brain barrier integrity and aid determination of the likely aetiology of the ICH. *Reporting brain CT/MR*: All brain imaging will be reported by the clinical radiology staff, in accordance with local policy. The brain CT/MR reports will therefore be available to the treating clinical teams to inform clinical management. The brain CT and MR studies will also be anonymised and transferred electronically to a secure imaging archive platform to the University of Manchester and Johns Hopkins University, Baltimore, USA for detailed analysis
Statistical considerations	Primary analysis will be conducted by intention to treat. No imputation of CT scan analysis will be undertaken. Patients who die will be imputed to have poor clinical outcomes. Secondary and sensitivity analyses will consider those who did not receive allocated intervention. For the primary outcome, analysis of covariance will adjust for stratification criteria (GCS 6-13; 14 or 15 and by the centre) in the allocation routine and for baseline value of OED.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
National Institute for Health Research	Funding of research costs
Swedish Orphan Biovitrum	Supply of study drug (IL-1Ra (Kineret®) and placebo) and shipping costs
NIHR CRN	Nurse support for screening and approach
Central / local commissioning	None

LIST of CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
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
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	Intracerebral Haemorrhage
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
NIHSS	National Institutes of Health Stroke Scale
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Patient Information Sheet
QA	Quality Assurance

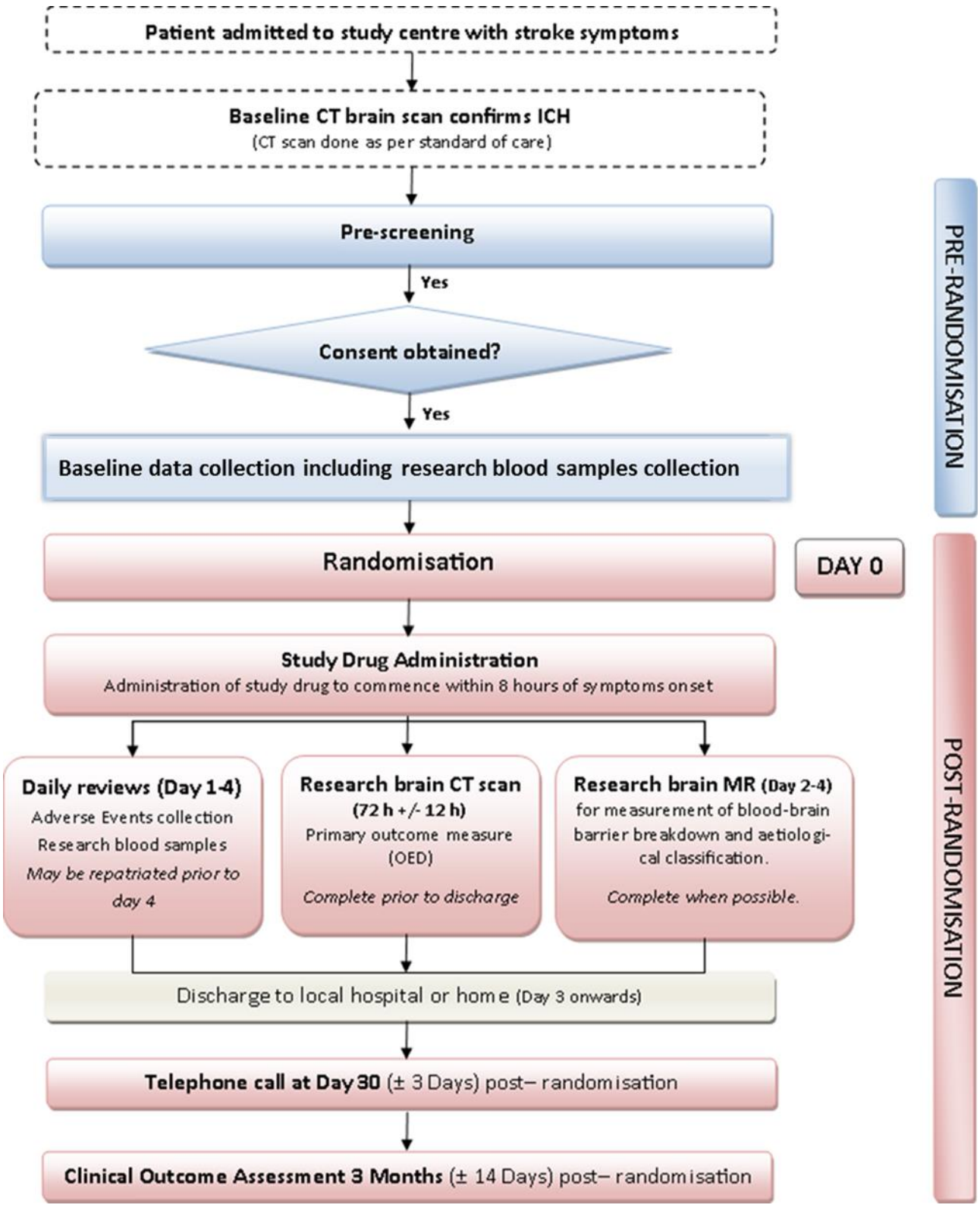
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAH	Subarachnoid Haemorrhage
SAR	Serious Adverse Reaction
SC	Subcutaneous
SDV	Source Data Verification
SIS	Stroke Impact Scale
SOP	Standard Operating Procedure
SmPC	Summary of Product 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 DEFINITIONS

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 (Kineret®) or placebo.
Women of childbearing potential (WOCBP)	A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

TRIAL FLOW CHART

Figure 1: Trial Flow Chart (dashed lines indicate non-research intervention or process)



TRIAL PROTOCOL

Phase II trial of Interleukin-1 receptor antagonist in intracerebral haemorrhage: BLOcking the Cytokine IL-1 in ICH

1. BACKGROUND

1.1 Intracerebral haemorrhage

Intracerebral haemorrhage (ICH) accounts for at least 10% of strokes in the United Kingdom (UK)[1] and has an incidence of 25 new cases per 100,000 per year[2]. Around 30-40% of ICH patients die before one month and over half of survivors remain dependent on others for day-to-day care[2]. Compared to ischaemic stroke, ICH leads to a greater loss of quality adjusted life years[3] and whilst the incidence of ischaemic stroke has fallen[4], the incidence and case fatality of ICH has not changed in the last 30 years[1,2]. Despite the considerable and persistent health, social and economic burden of ICH, it has received little attention in comparison to ischaemic stroke[5], and has no proven acute therapy, aside from modest benefits from intensive blood pressure lowering[6] and stroke unit care[7]. ICH thus represents a considerable unmet health need, both in the UK and worldwide.

Regardless of the cause, extravasation of blood in to the brain parenchyma leads to rapid physical tissue injury and may lead to mass effect, brain herniation syndromes and early death[8]. ICH can be further complicated by early haematoma expansion (in up to a third of patients within 4 hours of onset) which worsens prognosis[9]. For survivors of the hyperacute phase, secondary brain injury contributes to tissue damage over the subsequent hours to days and is driven by a cascade of cellular and molecular events including the toxic effects of blood components (thrombin, haem, iron) and inflammation[8]. Partly driven by these processes, cerebral oedema increases rapidly over 3 days with a further slow increase up to 1-2 weeks after onset[10,11].

1.1.1 Inflammation in ICH

Preclinical studies have demonstrated that local inflammation occurs in response to diverse acute brain injuries (including ICH), exacerbating early damage and playing an important role in later repair and recovery[14–17]. Within hours of an acute brain injury, a sterile inflammatory response is initiated where activated microglia take on a pro-inflammatory phenotype, releasing cytokines and chemokines that activate astrocytes and endothelial cells and lead to recruitment of neutrophils to the site of injury. This early inflammatory response profoundly exacerbates tissue injury but over subsequent days, factors released by circulating blood monocytes recruited to the site of injury limit damage by switching the resident microglia to an anti-inflammatory phenotype[12].

1.1.2 Interleukin-1 in ICH

The prototypical, proinflammatory cytokine IL-1 plays a key role in the early damaging inflammatory response in the brain and inhibiting IL-1 leads to a reduction in damage in diverse experimental acute brain injuries including ischaemic stroke, excitotoxicity, traumatic brain injury, and ICH[13,14]. We have recently shown that IL-1 alpha (IL-1α), IL-1 beta (IL-1β) and IL-1Ra are all present in high concentrations in serial haematoma fluid collected from acute ICH patients taking part in the Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III (MISTIE III; NCT01827046) trial (Figure 2). IL-1 is also rapidly upregulated in

perihaematomal brain tissue from animal models of ICH[15] and from ICH patients[16]. The naturally occurring IL-1 blocker, IL-1Ra (Kineret®), is expressed at almost undetectable levels in healthy brain[13]. IL-1Ra (Kineret®) is already a licensed treatment for rheumatoid arthritis and has been given to many other patients groups, without significant safety concerns[17]. IL-1Ra is a competitive and highly-selective antagonist that blocks all known actions of IL-1α and 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]. In the haematoma fluid of MISTIE III patients, IL-1Ra is rapidly upregulated and detectable at high concentrations from days 1-5 post randomisation. We have shown that concentrations of IL-1Ra in haematoma fluid at baseline is inversely associated with perihaematomal oedema volume at end of treatment (p=0.018). One possible explanation for this would be that naturally occurring IL-1Ra significantly reduces subacute perihaematomal oedema.

Figure 2: **Concentrations of IL-1α, IL-1β and IL-1Ra in cerebral haematoma**

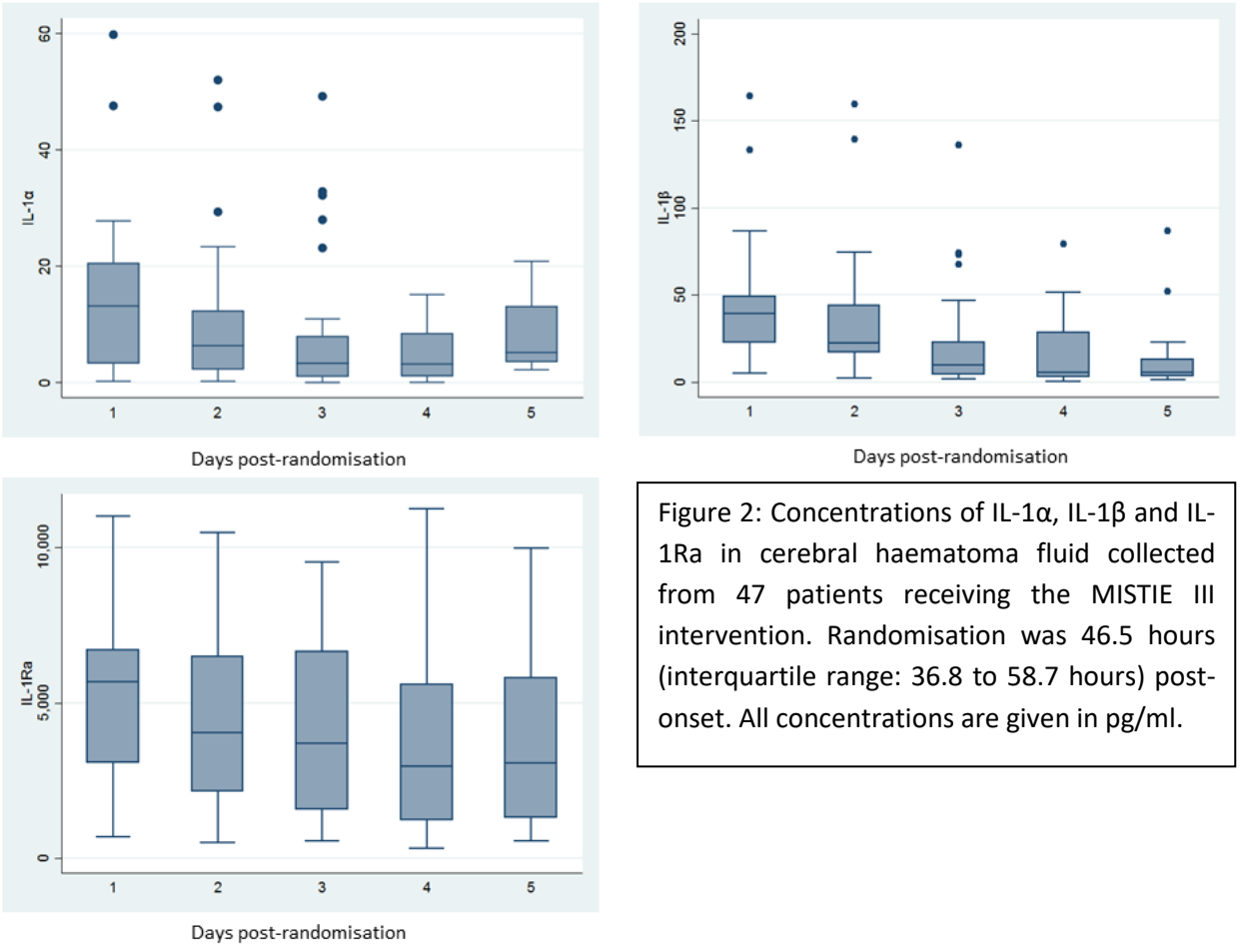


Figure 2: Concentrations of IL-1α, IL-1β and IL-1Ra in cerebral haematoma fluid collected from 47 patients receiving the MISTIE III intervention. Randomisation was 46.5 hours (interquartile range: 36.8 to 58.7 hours) post-onset. All concentrations are given in pg/ml.

1.2 Clinical studies of IL-1Ra in stroke and head injury

A randomised, controlled, phase 2 trial of an intravenous (IV) infusion of IL-1Ra in acute stroke undertaken at Salford Royal NHS Foundation Trust (SRFT), demonstrated a significant reduction in inflammatory markers[18] as well as reversal of stroke-related peripheral immunosuppression[19]. More recently, it has become apparent that IL-1 has detrimental actions in both the brain and systemically in animal models of cerebral ischaemia[20], suggesting that IL-1 blocking treatments may not need to cross the blood-brain

barrier to confer benefit in ischaemic stroke and prompting the use of much lower subcutaneous (SC) doses of IL-1Ra. A further randomised controlled phase 2 trial of SC IL-1Ra (100 mg BD for 3 days) tested this approach in 80 ischaemic stroke patients at SRFT has also demonstrated a significant reduction in plasma IL-6 and CRP[21].

Our group recently completed a Medical Research Council (MRC)-funded phase II study (G1001252/1 ISRCTN25048895) in 3 neurosurgical centres where SC IL-1Ra was administered to people with aneurysmal subarachnoid haemorrhage (SAH)[22]. 136 patients with aSAH within 72 hours of symptom onset were randomised to receive IL-1Ra and standard care or standard care alone in an open label study. Patients continued treatment until discharge from the neurosurgical unit or day 21 (whichever was earlier). Primary outcome was plasma IL-6 concentrations. We showed a 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.

A single-centre, randomised, controlled phase 2 trial of SC IL-1Ra (100 mg OD for 5 days) in 20 patients with severe traumatic brain injury has shown IL-1Ra to be safe in this pathology, and penetrated in to plasma and brain extracellular fluid. A reduction in macrophage-derived chemoattractant within the brain of IL-1Ra treated patients was detected by microdialysis[23].

1.2.1 Safety and tolerability of IL-1Ra (Kineret®)

IL-1Ra has been evaluated in many 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 patients 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 *in vitro* to reverse the immune suppression associated with ischaemic stroke[28].

The Development Safety Update Report (DSUR) for IL-1Ra trials in stroke and aSAH has been compiled 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-1Ra in phase II stroke and aSAH trials.

1.2.2 Brief Trial Outline

This phase II trial will establish whether IL-1Ra (Kineret®), administered over 72 hours post-ICH, reduces perihaematomal oedema, as measured by oedema extension distance (OED) at 72 hours. Patients with ICH admitted to a trial centre will be identified and approached for study participation. Following consent, patients will be randomised to receive either IL-1Ra or placebo for 72 hours. Blood will be taken at presentation (day 0, pre-randomisation) and at 09:00 (± 2 h) on a daily basis until the next 09:00 (± 2 h) after the study treatment has completed (day 3 or 4). A research CT brain scan will be obtained at 72 hours

± 12 hours for measurement of the primary outcome (OED). A research MR brain scan will be obtained at day 2-4 for measurement of blood-brain barrier permeability and to aid aetiological classification. Safety will be monitored at baseline, before the 2nd IMP administration, on Day 4 and on Day 30 post randomisation. Exploratory clinical outcome data will be collected at 3 months post-randomisation.

2. RATIONALE

In a meta-analysis of pre-clinical ICH studies, pooled data from anti-inflammatory drugs (corticosteroids, celecoxib, complement inhibitor) demonstrated a significant improvement in structural outcomes and neurobehavioural scores[24]. However, none of these drugs has been adequately tested in clinical ICH[25] and they may have detrimental effects which are more likely in an elderly ICH population, such as immunosupression and peptic ulceration with corticosteroids and increase in cardiovascular risk with celecoxib[26]. Commonly used immunosuppressive drugs (azathioprine, methotrexate, etc.) are slow acting and target adaptive immunity rather than the early innate immune response which leads to damage in the early stages of acute brain injury. Minocycline has had mixed results in animal models, worsened outcomes in clinical trials in amyotrophic lateral sclerosis, and may lead to neurotoxicity[27]. Inhibiting tumour necrosis factor alpha (TNFα) in experimental models has had contradictory results, suggesting that it has a more complex role and may be important in both early inflammation and regeneration and repair[28].

Previous observational clinical studies in ICH have largely focused on peripheral inflammatory markers and shown associations between fever, elevated white blood cell count, IL-6, CRP, fibrinogen, and c-fibronectin on admission and worse short term outcomes (haematoma expansion and neurological decline at 48 h)[29–32]. Elevated CRP, fibrinogen and matrix metalloproteinases (MMPs) on admission are associated with poor functional outcomes and survival at 1-3 months[32–35]. These clinical studies demonstrate the importance of the systemic inflammatory response but provide no information on the inflammatory response within the brain, where inflammation contributes directly to secondary injury. Animal models have taught us much about the central nervous system (CNS) inflammatory response to ICH[36], but current ICH models have limited relevance to the clinical disease[37] and research in ischaemic stroke has been blighted by the failure to translate promising preclinical findings to effective therapies[38].

As IL-1Ra (Kineret®) is a drug already in clinical use with a good safety profile and there is abundant evidence suggesting an important detrimental role for IL-1 in acute brain injury, it is a promising drug in which to test the therapeutic potential of blocking the acute innate inflammatory response to clinical ICH. Currently, there are no effective treatments for ICH apart from good supportive care on stroke units[39] and a modest reduction in disability from intensive blood pressure lowering[6]. The evidence for surgery to evacuate the intracerebral or intraventricular haematoma is equivocal[40,41]. Ongoing trials of minimally invasive surgery may provide an effective intervention for larger, more severe haemorrhages and targeting secondary injury is likely to provide an adjunct to surgery in these patients, minimising injury to the brain from the residual haematoma and thus enhancing the recovery. For patients with smaller haemorrhages, targeting secondary inflammation may be an effective monotherapy. We have chosen to use placebo in this study to minimise bias in the collection and interpretation of safety and clinical outcomes.

Patients and carers were consulted during the preparation of applications for this trial and an ICH patient and public involvement (PPI) group has met regularly at SRFT since 2017. The group has repeatedly stated that they greatly welcome efforts to develop new treatments for this major cause of death and disability after stroke.

2.1 Rationale for IL-1Ra dose and regimen

Under physiological conditions, <1% of a peripherally administered dose of IL-1Ra is expected to cross the intact blood-brain barrier[42], but increased blood-brain barrier permeability is well recognised after acute brain injury. In experimental focal ischaemia in rodents, IL-1Ra readily entered the brain parenchyma in areas of blood-brain barrier disruption, but not elsewhere[43]. Based on current knowledge, IL-1Ra will be given as an initial dose of 100mg IL-1Ra (Kineret®)/placebo subcutaneously (SC) followed by 5 doses of subcutaneous (SC) 100mg IL-1Ra (Kineret®)/placebo every 12 hours for 72 hours. The regime for the drug, 100 mg of IL-1Ra (Kineret®)/placebo twice daily administered SC has been derived from computer simulation using published pharmacokinetic parameters for SC IL-1Ra[44] and was previously used in our phase II stroke clinical trial[21]. A higher IV dose has been previously used in acute stroke patients, including 5 patients with ICH, without any safety concerns[18]. We are currently completing analysis for an ongoing study, Intracerebral haemorrhage: Imaging microglial activation and blood-brain barrier leakage (IMAGE-ICH; ISRCTN52682983), funded by the CI's NIHR Clinician Scientist Award. This study has recruited 44 patients of whom 42 have undergone quantitative measurement of blood-brain barrier breakdown at day 1-3 post symptom onset. Preliminary results suggest consistent, marked blood-brain barrier breakdown in the perihaematomal region. The pilot of ICH-IMAGE also demonstrated significant blood-brain barrier breakdown around the haematoma in subacute ICH in 5 patients [56]. Therefore, we expect more IL-1Ra to enter the brain parenchyma surrounding the haematoma than expected in healthy, intact brain, supporting the use of a lower, subcutaneous dose of IL-1Ra.

The investigational product will be commenced as soon as possible after recruitment and no later than 8 hours after symptom onset for two reasons. First, it is clear from experimental ICH studies that IL-1 mediated inflammation evolves rapidly during the first 8 hours after onset and thus early inhibition is likely to be important. In rodents, brain IL-1 protein levels rise 30-fold by 6 hours after onset, with levels falling up to 7 days,[48,44,45] and early signs of microglial activation and initial neutrophil infiltration are observed by 1-4 hours from onset[49,50,45,46,46,47]. Secondly, most haematoma expansion occurs within 4 hours of onset and is independently associated with higher CRP and IL-6[30]. It is not known whether inflammation plays a causal role in haematoma expansion, but haematoma expansion will be a secondary outcome. If IL-1Ra can modify the risk of haematoma expansion occurring, it must be commenced as soon as possible.

We expect an IL-1 driven damaging innate immune response to be present in all cases of intracerebral haemorrhage. Many patients with ICH will not have the capacity to consent for themselves when they first present to hospital. Though some will regain capacity later in their admission, IL-1Ra will need to be given acutely as we know that levels of IL-1 begin to rise in the brain within a few hours of onset. In order to maximise the potential benefit of IL-1Ra it will thus need to be given as quickly as possible. Capacity will be monitored throughout the study and patients who regain the capacity to consent to the study will be approached to provide consent to remain in the study.

2.2 Assessment and Management of Risk

IL-1Ra has been evaluated in many 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 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 10^9L). Blood will be taken and results medically reviewed prior to inclusion in the trial. Injection site reactions may occur with IL-1Ra administered subcutaneously (SC) but we have found that by administering the injections in different anatomical sites each time these are generally well tolerated; just two patients (from 68 receiving IL-1Ra) withdrew from our phase II studies because of injection site reactions. All adverse events will be reported.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Aim

a) To determine whether there is evidence of biological effect of IL-1Ra following ICH

3.2 Primary Objective

a) To test whether IL-1Ra reduces subacute perihaematomal oedema after ICH.

3.3 Secondary Objectives

a) To test whether IL-1Ra alters other key parameters associated with inflammation, including blood inflammatory markers, blood-brain barrier breakdown and early haematoma growth.
b) To determine whether IL-1Ra is safe in acute ICH.

3.4 Outcome Measures/Endpoints

Primary outcome:

- Oedema extension distance (OED) at 72 hours

Secondary outcomes:

- Early haematoma growth (defined as ≥33% or ≥6 ml increase in haematoma volume between baseline and 72 hours)
- Early Neurological Decline (END) between baseline and 72 hours. END defined as a decrease of ≥2 in the Glasgow Coma Scale (GCS) score or an increase in the National Institutes of Health Stroke Scale (NIHSS) score ≥ 4, lasting longer than 8 h, requiring surgical intervention, or resulting in death.
- Clinical outcomes at 3 months (mRS, SIS, FSS, EQ-5D-5L, HADS)
- Area under the curve for inflammatory markers (CRP, IL-6) from baseline to day 4
- Quantitative blood-brain barrier permeability in the perihaematomal brain at day 2-4

3.4.1 Primary outcome

The primary outcome for the trial will be perihaematomal oedema on CT scan at 72 hours as measured by the 'oedema extension distance' (OED)[51,47,48], which equates to the average distance that oedema extends beyond the haematoma border. After deriving the volume of perihaematomal oedema (PHO vol) and of the haematoma (ICH vol), the OED will be calculated using the formula in Figure 3. This measure is biologically meaningful and is consistent across a range of haematoma volumes, unlike the absolute and relative perihaematomal oedema volumes (Figure 3).

Figure 3: CT Scan demonstrating delineation

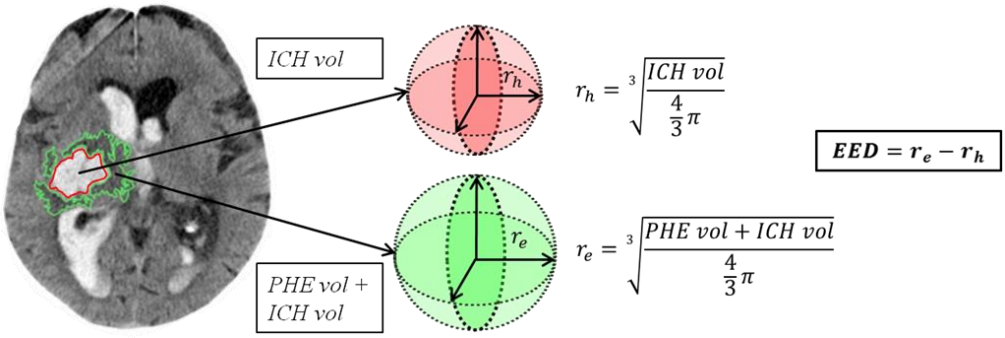


Figure 3: Example of a CT scan demonstrating delineation of the region of perihaematomal edema (PHE) (outlined in green) and ICH (outlined in red). The EED is the difference between the radius (r_e) of a sphere (shown in green) equal to the combined volume of PHE and ICH and the radius of a sphere (shown in red) equal to the volume of the ICH alone (r_h) [10].

3.4.2 Secondary Outcomes

We will measure the following secondary outcomes after ICH:

1. Early haematoma growth: Haematoma volume will be measured by the central study team on the baseline clinical diagnostic CT brain scan and the 72 hours research CT brain scan using standard volumetric methods. Haematoma will be defined by tissue with a Hounsfield Unit (HU) range of 44-100. Significant haematoma expansion will be defined as a ≥33% and/or ≥6 ml increase in haematoma volume between baseline and 72 hours. The chosen definition for haematoma expansion is widely used and has been shown to have a high specificity and moderate sensitivity for a poor long term outcome[52,48,49]
2. Early Neurological Decline (END) between baseline and 72 hours: END defined as a decrease of ≥2 in the Glasgow Coma Scale (GCS) score or an increase in the National Institutes of Health Stroke Scale (NIHSS) score ≥ 4, lasting longer than 8 h, requiring surgical intervention, or resulting in death.
3. Blood-brain barrier breakdown: Using a tracer kinetic model developed and established at the University of Manchester, maps of the blood-brain barrier transfer constant (K^{trans}) will be generated. Mean values for K^{trans} will be derived from within haematoma and perihaematomal oedema volume (as defined by co-registered FLAIR images) and the mean linear distance that increased K^{trans} extends beyond the haematoma border will be derived, using a similar approach to that described for OED.
4. Clinical outcomes: Exploratory clinical outcomes will be measured at 3 months and will include the mRS, SIS, FSS, EQ-5D-5L and HADS. Fatigue, depression and cognitive deficits are key unmet needs in stroke patients[52,48,49] and may be influenced by inflammation via 'cytokine-induced' sickness behaviour[53,54,49,50,51], so will be measured alongside the mRS at 3 months.

5. Area under the curve for inflammatory markers (CRP, IL-6) from baseline to day 4. Measuring inflammatory markers will allow assessment of the impact of IL-1Ra on systemic inflammation.

4. TRIAL DESIGN

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

5. TRIAL SETTING

80 patients with ICH will be recruited from Hyper Acute Stroke Units (HASUs) in the UK. Adults admitted to a participating centre with a clinical diagnosis of acute ICH 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 acute management of anticoagulant reversal, blood pressure lowering, intensive or high dependency care, rehabilitation, and 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 spontaneous, non-traumatic, supratentorial ICH with no underlying macrovascular or neoplastic cause admitted to a participating centre within 8 hours of symptom onset.
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.
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. Severe ICH, unlikely to survive to 72 hours scan, in the opinion of the treating clinician. For example, a Glasgow Coma Scale score $<$ 6 at time of consent);
2. Confirmed or suspected structural abnormality as cause of ICH (including tumour, vascular malformation);
3. Confirmed or suspected haemorrhagic transformation of an arterial or venous infarct;
4. Acute neurosurgery planned within 72 hours of admission;
5. Known active tuberculosis or active hepatitis;
6. Known active malignancy;
7. Neutropenia (neutrophil count (ANC) $<1.5 \times 10^9$/L);
8. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 ml/minute) documented in the last 3 months prior to this ICH*;
9. Live vaccinations within the last 10 days prior to this ICH;
10. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial;
11. Previous or current treatment with etanercept or any other TNF-α antagonist);
12. Known to have participated in a clinical trial of an investigational agent or device in the 30 days prior to symptom onset;

13. 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 symptom onset;
14. 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 7.1.1);
15. Known diagnosis of Still's disease;
16. Clinically significant serious concurrent medical condition, premorbid 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;
17. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC (please section 8.1.4);
18. Known allergy to other products that are produced by DNA technology using the micro-organism E. coli (e.g. *E.coli* derived protein).

* -

Due to the narrow time window for study inclusion, it is not always possible to obtain confirmation of normal renal function from clinical Biochemistry sample obtained on admission to the Emergency Department; as the results are often subject to significant delay. This may result in willing patients being denied the chance to participate in the trial. The safety profile for the IMP is good and following consultation with a Renal Physician it was agreed that administration of a single dose of IMP would be sufficiently safe in patients with mild-moderate renal failure. This is also supported by the study Sponsor. The research staff will make every attempt to establish that the patient has an acceptable renal function test result (e.g. eGFR of >30ml/min) in the 3 months prior to stroke by using information from the patient themselves (if available) or either their personal representative, general practitioner and electronic patient record. Providing there is no evidence of significantly impaired renal function, we will request permission to administer the first dose of IMP within 8 hours of stroke, as per protocol. As an additional safeguard, no further doses of IMP will be administered until normal renal function has been confirmed from the clinical Biochemistry sample taken on the day of admission to hospital.

In cases where renal function was not confirmed as acceptable at admission, the clinical Biochemistry results will be reviewed by a medically qualified member of the stroke team before the second dose is prescribed/administered..

7. TRIAL PROCEDURES

Table 1: Schedule of Assessments

	On Admission	Consent	Screening Assessments	Randomisation	Day 0 [f] first drug administration	Day 1	Day 2	Day 3	Day 4 [c]	Safety Follow up	Final assessment
	SOC assessments		**Baseline**		**Within 8 hours** from symptoms onset	**<24 hours**	**24-48 hours**	**48-72 hours**	**within 24h post last dose**	**Day 30** [h] (±3 days)	**Month 3** [i] (±14 days)
Research blood samples			X [a]			X [b]	X [b]	X [b]	X [b]		
Standard of Care blood samples [l,a]			X								
CT scan [q]	X [d]							X[j] ⟷	X[j]		
Demographics and medical history			X [g]								
GCS			X					X			
Confirmation of Eligibility			X [e]								
Renal function test			X [K]		X [K]	X [K]					
Pregnancy Test			X								
Informed Consent		X									
Randomisation				X							
Drug Administration [f]					⟷	⟷	⟷	⟷			
Clinical outcomes [l]											X [i]
NIHSS [m]	X		X [r]					X			
Screening for END[s]								X[s]			
MR brain scan (optional) [n,q]							⟷	⟷	⟷		
Adverse Event check			X [p]			X [p]			X [p]	X [p]	
ConMeds check			X [p]						X [p]	X [p]	
Confirm willingness to be contacted at D30 and M3									X [o]		
Survival check										X	X

a) Mandatory, baseline bloods to be taken pre-treatment
b) Mandatory daily research blood samples to be taken at 09:00am ± 2 hours from Day 1 to Day 4 or until discharge from the treating centre (whichever is sooner). The final sample will be collected at the next 09:00am (± 2 h) following the final dose of study drug, unless the patient is discharged
c) Patient may be discharged prior to day 4, in which case the treatment and research blood samples stop. End of Treatment assessment
d) Standard of Care (SOC) scan to diagnose intracerebral haemorrhage
e) Full eligibility must be confirmed prior to randomisation.
f) A 100 mg subcutaneous (SC) initial dose will be given after randomisation and within 8 hours of symptom onset, followed by 5 subcutaneous injections of 100mg Kineret®, or matched placebo. Administration of study drug will start as soon as possible after randomisation and will continue twice daily (with a minimum of 8h and a maximum of 16h between doses) for up to 3 days (6 doses) from onset of symptoms or until discharge from the treating centre (whichever is sooner).
g) Date of birth, ethnicity, clinical history, Concomitant medications, presenting features, vital signs, weight and height, physical and neurological assessment. Clinical history to include radiological data, date and time of symptom onset at first presentation. We would also like to collect information on previous standard of care for patients including anticoagulant reversal agents.
h) Day 30 safety assessment will be performed by the local research team for any patients still an in-patient. Patients who have been discharged to their own home or local hospital will be contacted directly by telephone by local research team. A survival check will be performed by contacting the patient's general practitioner prior to phone call to avoid any distress to next of kin.
i) Three month outcome data (+/- 14 days) will be collected centrally by the trial coordinating team as a telephone assessment. Prior to telephone contact, the coordinating team will perform a survival check by contacting patient's GP, where possible to avoid any distress to next of kin. This assessment will record survival, mRS, EQ-5D-5L, SIS, FSS and HADS. If the patient did not recover capacity and was unable to give their own consent to follow-up before the day 4 assessment is completed (or they are discharged from hospital earlier); a pre-notification pack will be sent by the coordinating team. The pre-notification pack will contain a pre-notification letter, retrospective participant information sheet, modified rankin score questionnaire (mRS), reply slip and pre-paid envelope to the participant.

   Approximately 2 weeks prior to 3m assessment, the coordinating centre will contact the recruiting site to seek;

   1. confirmation of survival
   2. details of consent obtained
   3. request contact/GP details for the participant.

   If the participant had not recovered capacity and/or given their own consent before they were discharged from hospital (or earlier); the trial coordinating centre will confirm survival with the participant's GP before sending a pre-notification pack to the participant. The participant will be asked to return the reply slip if they do not wish to undergo 3 month follow-up interview. However, if no reply slip is received by the date the 3m assessment is due, a telephone approach will be made and the participant will be asked to verbally confirm willingness to complete the 3m outcome assessment.

   If the patient has ongoing health or cognitive difficulties which would make it impossible for them to participate in the telephone assessment, the personal consultee will be asked to provide this information on their behalf. This option will be made clear on the information for Personal consultee given at initial approach. Completion of 3 month assessment will complete study participation unless the patient has given their consent to re-contact.
j) To be performed at 72 hours after randomisation (±12 h) or prior to discharge. The research CT scan should be carefully assessed for signs of Haematoma Expansion (HE).
k) Due to the tight window for study inclusion, it may not always possible to obtain confirmation of normal renal function prior to randomisation. The research staff should make every attempt to establish that the patient has normal renal function (eGFR >30ml) in the 3 months prior to this ICH by using information from the patient themselves (if able) or either their personal representative, general practitioner and electronic patient record. Providing there is no evidence of significantly impaired renal function, the first dose of

IMP can be administered, however no further doses of IMP will be administered until normal renal function has been confirmed from the clinical Biochemistry sample taken on the day of admission to hospital.

In cases where renal function was not confirmed as normal at admission, the clinical Biochemistry results will be reviewed by a medically qualified member of the stroke team before the second dose is prescribed/administered.

l) If bloods are collected for clinical purposes, results will be collected for review of safety, but these are not mandatory except at baseline where full blood count and eGFR are needed to determine eligibility.

m) National Institute of Health Stroke Scale (NIHSS for Early Neurological Decline (END). To be collected at screening if not done as SOC on admission and again at 72h or Day 4 if not done at 72 hours.

n) Optional; complete where possible. For measurement of blood-brain barrier breakdown and aetiological classification.

o) To be completed on the day of discharge if prior to Day 4

p) Mandatory

q) All anonymised scans, including standard of care and unscheduled standard of care scans to be transferred electronically or hard copy send via post to a secure imaging archive platform to the University of Manchester and Johns Hopkins University, Baltimore, USA for detailed blinded analysis including measurement of oedema and haematoma volume which will be used to determine the primary outcome (OED) and a secondary outcome (haematoma expansion).

r) If not done as per SOC on admission

s) Confirmation of occurence of END (Sustained change in GCS or NIHSS for > 8 h) including date and time.

7.1 Recruitment

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

7.1.1 Patient Identification and Screening

The clinical team looking after the patient will make the initial approach to the patient or their personal legal representatives (if the patient lacks capacity) and ask if they would consider participation in a research trial. Any patient 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 to determine whether the patient 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 patient 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 be given written information containing full details of the trial.

It will be assumed that all women under the age of 55 are of childbearing potential unless evidence contrary to this can be established from a reliable source. It will be necessary to exclude pregnancy in any woman of childbearing potential (WOCBP, see list of definitions) prior to entry into the trial. If this cannot be excluded by the patient, verbal consent will be sought and noted in the patient's medical notes for a pregnancy test to be performed prior to consent. During study participation standard practice in regards to the administration of contraception should be followed. WOCBP enrolled in the study will only be administered IL-1Ra whilst an in-patient and the half-life of subcutaneous IL-1Ra is 4-6 hours. It is therefore very unlikely that these patients will become pregnant while being exposed to the study drug. Nevertheless, the investigator must ensure that all patients are made aware of the potential dangers of being pregnant during their participation in the study. All patients will be advised of the need to comply with highly effective contraceptive methods, once permitted to restart contraceptive treatment, for the remaining 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 0.

* Provided that partner is the sole sexual partner of the WOCBP trial patient 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 patient. For this trial, the period of risk means from first IMP administration until 30 hours after last IMP administration.

7.2 Consent

The researcher will then allow the patient (and/or their personal legal representative) time to reach their decision about participation and will return to discuss the trial again at an agreed time point. Patients will be given as long as necessary to consider study participation but it will be made clear to patients or their representatives that inclusion must be within 8 hours of symptom onset or they will become ineligible. If the patient or their representative decides 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. An appropriately trained member of the research team will carry out a formal assessment of capacity, where appropriate. Where it is not possible to obtain consent from the patient 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 patient 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 patient 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 patient 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 patient's inclusion in the trial, a further consent form will be completed.

Where initial consent is obtained from the patient's personal legal representative or the professional legal representative, the capacity of the patient to consent will be reassessed before each research assessment/intervention. If the patient regains capacity, they will be given information about the trial and asked to confirm willingness to continue trial participation. If the patient regains capacity before being discharged from hospital, their willingness to continue in the study will be assessed using the Retrospective Participant Information Sheet and Ongoing participation Informed Consent Form. If the patient does not regain capacity before being discharged, a pre-notification letter will be sent approximately 2 weeks before the assessment is due to be completed (for full details, refer to part i of section 7, Schedule of Assessments)Where initial consent is given by the patient, 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 patient 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.

7.3 Randomisation

Following consent by the patient or their personal legal representative, the patient will be randomised using an independent, bespoke, online randomisation service to ensure third-party concealment of allocation. 1:1 randomisation will occur as soon as possible after the completion of baseline assessment. Randomisation will be stratified by centre and Glasgow Coma Scale (GCS) score at time of consent (6-13; 14 or 15).

7.3.1 Method for patient 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 contents 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 patients 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 patient consent and collection of baseline blood sample.

7.3.2 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. See current version of the pharmacy manual for additional details.

The trial is double-blind, placebo controlled and the study drug will be prescribed by a delegated prescriber. The dosage given (initial dose 100 mg of IL-1Ra (Kineret®) or matching placebo followed by 5 doses of 100 mg of IL-1Ra (Kineret®) or matching placebo SC at 12 hourly intervals (minimum of 8 hours and maximum of 16 hours between doses) for total of 72 hours (6 doses)) will be noted in the patient's medical notes as well as their research records.

7.4 Blinding

Blinding will be maintained by use of identically packaged and labelled placebo so that patients (the patient, their personal legal representatives) and all trial staff (including the research team and outcome assessors) are unaware of treatment allocation throughout the period of the trial.

7.5 Unblinding

Details of the emergency unblinding procedure will be detailed in the Investigator Site Files and Pharmacy File / Manual and will be available at all times in the Pharmacy Departments and at each recruiting site.

If the Investigator or Research Team feels unblinding may be necessary then the patient's study drug must 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 PI is unable to contact the CI, the PI will be able to unblind if required. 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 Investigator Site Files and/ or Pharmacy File with specific instructions to follow. If a decision is made

to unblind, the allocation details will be obtained from the randomisation site using an unblinding login account. This procedure will make sure the safety of the patient is not compromised and that the patients 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 patient 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 Investigator 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 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 unblinding if he or she feels that emergency unblinding is necessary.

7.6 Trial Assessments

7.6.1 Pre-randomisation evaluation

At screening and baseline, research staff will review patient health records to confirm eligibility including basic demographics (age), past clinical history and radiological data. No identifiable patient data will be recorded. An anonymised screening log will be maintained.

Following consent, patients will undergo a baseline assessment which will include:

- transcription of source data including demographics (date of birth, sex, ethnicity), and CT Scan time and date,
- premorbid mRS (modified Rankin Scale) score,
- key event times (date and time of symptom onset and arrival in hospital),
- vital signs (blood pressure[BP], temperature),
- neurological assessment (GCS, National Institutes of Health Stroke Scale [NIHSS]),
- past medical history (chronic hypertension, diabetes, previous ischaemic stroke, previous ICH),

- premorbid medication (anticoagulants, antiplatelets, antihypertensives)
- adverse event check
- and baseline research bloods.

A 10ml baseline blood sample will be taken immediately following consent (and before randomisation) for measurement of plasma CRP and IL-6. Clinical reports of renal function and full blood count will be checked prior to randomisation (see exclusion criteria). It is expected that patients will undergo at least one further full blood count, renal function and liver function test as part of routine clinical care within the first week of admission (see withdrawal criteria).

7.6.2 Post-randomisation evaluations

Adverse event (AE) reporting checks will be made by a delegated member of the research team at baseline, before the 2nd IMP administration, on Day 4 and on 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.

Daily blood samples will be taken at 09:00am (± 2 h), with the final sample being collected at the next 09:00am (± 2 h) following the final dose of study drug. Blood is collected for measurement of plasma inflammatory markers (CRP, IL-6). At 72 hours (± 12 h), a research CT brain scan will be performed. Depending on scanner availability and fitness of the patient to undergo MR imaging, a research MR scan will be performed at day 2-4. Further clinical data will be collected at the day 3 post-randomisation and on the final day (day 4) of study treatment (AE check, NIHSS, GCS, BP). As part of the end of treatment assessment the patients will be asked to confirm their willingness to be contacted at 30 days and 3 months of the date of randomisation and contact details of the patients (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, a survival check will be performed by contacting the patient'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 patients. Full details of AE collection procedure can be found in section 0. The patient's own general practitioner (GP) will be informed of study participation by letter upon discharge from the treating centre sent by a delegated member of the research team.

The final outcome assessment will be performed at 3 months (+/- 14 days) from randomisation and will record mortality and clinical outcomes in survivors. This will be coordinated and performed centrally by telephone. If the participant does not recover capacity to consent before being discharged from hospital, a

pre-notification letter will be sent approximately 2 weeks before the assessment is due to be completed (for full details, refer to part i of section 7, Schedule of Assessments). A survival check will be performed by contacting the patient's general practitioner to avoid any distress to next of kin. This will be outlined on the information for patients, personal legal representative and professional legal representative sheets provided as part of the consent process.

The final outcome assessment at 3 months will record mRS which includes mortality and survivors and additional outcome assessments relating to:

- quality of life (EQ-5D-5L),
- stroke impact (Stroke Impact Scale),
- fatigue (Fatigue Severity Score),
- anxiety and depression (Hospital Anxiety and Depression scale; HADS).

7.7 Withdrawal Criteria

Patients 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 patient 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:

- AE/SAE that is related to, or potentially related to study drug and in Investigator's opinion is uncontrolled, prolonged or intolerable toxicity;
- Patient's decision or their personal legal representative if the patient is not able to make the decision;
- At the PI discretion or treating physician discretion following discussion with CI where possible;
- If a severe allergic reaction occurs, administration of study drug should be discontinued and appropriate treatment initiated;
- If patients become neutropenic (ANC $<1.5 \times 10^9/l$), study drug should be discontinued;
- Pregnancy;
- Symptomatic deterioration where the investigator feels the patient is no longer receiving clinical benefit;
- Study suspended or stopped for any reason.

Intracerebral Haemorrhage (ICH) 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 patient 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 patient's best interest to end trial treatment, the patient can be withdrawn from trial treatment based on the penultimate point listed above.

If the patient 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 patient requests it be destroyed. It is the responsibility of the participating site research teams to ensure the patient'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 patient's request for their data and samples to be destroyed.

Patients will be withdrawn from study participation and further follow up only in the event of:

- Patient's withdrawal from trial participation,
- Death,
- End of trial.

Patients and their representatives do not have to give a reason for their withdrawal. However, where available, the research team will record information on the reason for withdrawal in the patient's medical notes if one is offered.

7.8 Storage and Analysis of Samples

Plasma samples obtained for measurement of CRP and IL-6 will be collected by research staff at the recruiting site. All equipment required for the collection of the research plasma samples including the EDTA tubes will be provided by the Biomedical Research Facility Laboratory at Salford Royal Foundation Trust. 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. Prior to shipping on dry-ice to the Biomedical Research Facility laboratories at the coordinating centre, samples will be stored in -70^{o}C freezers. Samples will be received at the Coordinating Centre in bulk from sites 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 (2018) and General Data Protection Regulation (GDPR). Biological samples collected from patients as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage.

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 CRP will be determined by immunoassay under the supervision of Dr Margaret Hoadley or her designee. Permission will be sought from study patients to retain anonymised samples for use in other ethically-approved research. Samples will be disposed in accordance with the Human Tissue Authority's Code of Practice when they are of no further use.

7.9 End of Trial

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

On the Sponsor's 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 twice daily (with a minimum of 8h and a maximum of 16h between doses) for up to 3 days (6 doses) from onset of symptoms or until discharge from the treating centre (whichever is sooner). These times are convenient and practical for the patients and their attending medical and nursing staff. All patients will continue to receive all elements of standard care. This dose and regimen was used in our recent phase 2 trial in ischaemic stroke and provide to be safe whilst significantly reducing systemic inflammation[21]. It is practical and easy to administer for research teams.

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 Summary of Product Characteristics (SmPC) provided for the investigator site file will be used as the reference safety information for this study. The SmPC will be reviewed annually for any changes that might affect the safety or integrity of the study. 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 patient's clinical and research records. Patients enrolled in the study will be assigned to receive an initial dose of 100 mg of IL-1Ra or placebo subcutaneously (SC), followed by further 5 maintenance doses of 100 mg IL-Ra or matching placebo, subcutaneously, every 12 hours for 72 hours will complete the trial treatment. Study drug must be started within 8 hours of symptom onset. Measures will be in place to enable the PI to access individual subject treatment assignments in exceptional circumstances (e.g. suspected unexpected serious adverse reaction: SUSARs). Please see section 0 for details of the unblinding procedure.

8.1.3 Compliance in Investigational Product Administration

Given the short duration (72 hours) of the administration of the study intervention and only during in-patient stay, and the established safety profile for its use in other disease states, it is not anticipated that 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 subcutaneous (SC) administration.

Interruption of study drug should be avoided. If an injection(s) is missed patients 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 3 days (72 hours) post-onset, is at the PI's discretion.

Administration of the study drug will be performed twice daily by appropriately trained and delegated research staff only and will continue for 3 days (72 hours) or until the patient is considered fit enough for discharge from the treating centre, whichever is first. Some attrition is expected due to the high mortality associated with ICH (33% overall by 30 days, though patients not expected to survive to 72 hours are excluded).

8.1.4 Concomitant medication

Concomitant medications may be given as medically indicated. Details (inducing dose, frequency, route and start and stop dates) of the concomitant medication given must be recorded in the patient's medical notes

and CRF. Recording of concomitant medication should continue, wherever possible, until 30 days after the date of randomisation.

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.

Any other medications that are known or subsequently reported as having, or potentially having, interactions with study drug will be restricted from this time period, or if the medication is part of clinical care the patient will be withdrawn from study treatment.

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® (anakinra), 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 provided to the sites in the investigator site file 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 ICH 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 interrupt 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 patient becomes neutropenic (ANC < 1.5 x 10^9/L) the ANC should be monitored closely and study drug should be discontinued.

Blood cholesterol increase:

Increases in blood cholesterol have been seen in RA patients very commonly in previous clinical trials. Therefore caution is recommended in patient with a history of high cholesterol.

Thrombocytopenia:

Thrombocytopenia has been observed in patients with RA in long-term use studies. Therefore caution is recommended in patients with a history of thrombocytopenia.

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

The study drug will be labelled as per annex 13 to comply with current clinical trials regulation. Kineret and placebo will be labelled identical in packaging, schedule of administration and appearance. This will ensure that site staff remain blinded to the study treatment arm unless emergency unblinding is required.

Each treatment study drug kit will contain 6 syringes. When a kit is dispensed, the outer packaging and each syringe label must be labelled with the patient ID number. When a syringe is removed from the kit and taken to the patient for administration, the kit number, batch number, patient ID and expiry date will be checked against the kit allocation details provided by the randomisation system by the researcher and a member of the clinical staff.

Inside each kit a set of 6 loose labels will be provided. These loose labels will contain information of the kit syringe numbers. At the time of IMP administration, one of these labels will be applied to the Proof of Administration record. Once administered, the syringe will be disposed in a sharps bin and a member of clinical staff will be asked to sign a Proof of Disposal/Destruction sheet. Original copies of the Proof of Administration and Proof of Destruction sheets will be stored in the out of 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 labelled, packaged and stored securely at 2-8°C until it is shipped to recruiting sites.

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. Study drug will be prescribed as per local procedures by the PI or a medically qualified member of the research team who has 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 patient 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.

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

For details on dispensing the study drug, please refer to the current version of the pharmacy manual.

Administration of study drug will be limited to research staff and or ward nurses who have received specific training in study drug administration, completion of syringe reconciliation documentation and AE awareness. The maximum duration of study treatment is 72 hours from date and time of randomisation.

8.4 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 patient 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 patient to an investigational medicinal product which is related to any dose administered to that patient. 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. 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: •results in death •is life-threatening •requires inpatient hospitalisation or prolongation of existing hospitalisation •results in persistent or significant disability/incapacity •consists of a congenital anomaly or birth defect •Other 'important medical events' may also be considered serious if they jeopardise the patient or require an intervention to prevent one of the above consequences (please see section 0 for a list of 'important medical events'. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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: •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 ICH these patients will experience a number of AEs which are disease related. There is no requirement to capture disease-related AEs that occur during the trial in the CRF but all AEs should be recorded in the patient's medical notes. Pre-existing conditions 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 AEs that are unrelated to ICH and all ARs occurring during the safety reporting period, whether observed by the investigator or reported by the patient, 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 0

If the adverse event is still on-going at the time of the final AE check (30 days post randomisation), the patient 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 patient's general practitioner and other health care practitioners involved in the patient'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.

All new AEs and SAEs occurring after discharge but within 30 days from date of randomisation will be recorded in the patient's CRF and will be assessed for causality related to study drug (Kineret®, IL-1Ra).

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 0). Any ARs, SAEs or AEs unrelated to ICH that are still on-going at the time of the final AE check (30 days post randomisation), the patient 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 patient's general practitioner and other health care practitioners involved in the patient'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 patient's consent which details this clause of contact to be made.

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 (Kineret®, IL-1Ra) 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

Given the nature of the disease, most patients with intracerebral haemorrhage (ICH) will experience 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 contributed to ICH. All events should be assessed for causality by the investigator.

Sponsor & IDMC will continue to monitor SAEs for trends and possible signal detection associated with study drug (Kineret® (IL-1Ra)).

Any serious adverse event, that is deemed study drug (Kineret®) related, that is considered unexpected by the CI or a delegated deputy should be reported as a SUSAR as detailed in section 0. In the event of a SUSAR unblinding procedure should be followed as detailed in section 0.

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 ICH (Expected events)**

System Organ Class	**High Level Group Term**	**High Level Term** (Symptoms)		**Likely frequency** Very common >= 1/10 Common (frequent) •> = 1/100 and < 1/10 Uncommon (infrequent) >= 1/1000 and < 1/100
Neurological	Spontaneous ICH	Headache, weakness, speech problems, visual disturbance		Very common
	Haematoma growth and/or ventricular extension	Deterioration in GCS, worsening neurological deficit		Very common
	Perihaemtomal oedema	Deterioration in GCS, worsening neurological deficit		Very common
	Hydrocephalus	Deterioration in GCS		Very common
	Epileptic seizures	Deterioration in GCS		Common
	Spasticity or contractures	Pain, immobility		Common
Metabolic	Water and electrolyte imbalance	Dehydration		Very common
	Raised white cell count	Infection		Very common
	Hyperglycaemia	Drowsiness		Uncommon
	Altered liver function			Common
Thromboembolic	Deep vein thrombosis			Common
	Pulmonary embolism	Breathlessness, chest pain		Uncommon
Genitourinary	Lower urinary tract infection			Very common
	Urinary retention			Very common
	Urinary incontinence			Very common
Gastrointestinal	Clostridium difficile	Diarrhoea, vomiting, nausea		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
	Pulmonary oedema			Common
Skin	Ecchymosis (Bruising)			Very common
	Pressure sore			Uncommon
Cardiac	Cardiac arrhythmia			Common
	Hypertension / hypotension			Common
	Myocardial infarction			Common
Miscellaneous	Pyrexia of unknown origin			Common
	Coincidental findings on brain imaging	Meningioma, tumour		Common
	Pain			Common
	Anxiety			Very common
	Depression			Very common
	Fatigue			Very common
	Visual disturbance			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 (Kineret® (IL-1Ra)).

All SAEs must be reported by email immediately within 24 hours of being aware to the BLOC-ICH trial manager at the Manchester CTU.

Email: saereport_manctu@manchester.ac.uk

In addition to events that meet the SAE criteria detailed in section 0, the following 'Notable 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 (Kineret®) 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 ICH not associated with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition including ICH provided that the ICH 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 (Kineret®).

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 Principal Investigator (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 or a deputy 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 patient'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 drug (Kineret® (IL-1Ra)) **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) and Trial Management Group (TMG) 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, TMG and Independent Data Monitoring Committee (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 0). The role, functions and operating practices of the TSC, TMG and 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 SAEs or SAEs resulting in death each month and a cumulative review of all unblinded safety information on a regular basis specified in the IDMC charter. 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 • Assessment of seriousness • Assess if appropriate for expedited reporting • Complete Adverse Events Log in the eCRF system within 30 days of safety assessment visit • 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. • Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment. • For SAEs: Confirmation of causality and final expectedness assessment as per the approved SmPC • Immediate review of all SUSARs. • Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol. • Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs. • Preparing the clinical sections and final sign off of the	• Central data collection and processing of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol. • Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit. • 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. • Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines. • Notifying Investigators of SUSARs that occur within the trial. • 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 • Complete SAE form • Assessment of seriousness, causality and initial assessment of expectedness (to be confirmed by the CI) • Submit SAE/SAR form to the MANCHESTER-CTU immediately but no later than 24 hours of the research staff becoming aware of the event • Follow-up until resolution or stabilisation		
SUSARs	• Ensure all necessary care and including immediate support necessitated by the event has been implemented. • Complete SAE form • Assessment of seriousness & causality. • Submit SAE/SAR form to the MANCHESTER-CTU immediately but no later than 24 hours of the research staff becoming aware of the event. • Confirm with CI drug reaction and unexpected. • Follow-up until resolution or stabilisation.		• Record details of event. • Request further information if needed. • Generate a detailed adverse event monthly report. • Ensure follow up information is completed to outcome. • Ensure information passed on to DMC, MHRA, and Sobi within regulatory timescales.

		Development Safety Update Report (DSUR).	
	IDMC	**TSC**	
	• Monthly clinical review of safety reports. • 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. • 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 patient'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 patient or their representative requests it. Should the study drug be discontinued, the patient will continue to be followed for safety purposes (up to 30 days of date of randomisation) and patients will remain in the study for follow-up purposes unless they decline follow-up. If the study treatment is discontinued and the patient 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 patient'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 patient 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 on SAE form as per pharmacovigilance section (Section 9) to the MANCHESTER-CTU. This report will be submitted within 24h of the research team becoming aware. In addition, all deaths will be recorded in the CRF up to 3 months post randomisation.

9.6 Pregnancy Reporting

ICH has a similar incidence in both men and women. At SRFT, the median age of unselected ICH patients from Jun 2016 – Jun 2017 was 71.5 (interquartile range 59.6 – 80.9). Although most women will thus be post-menopausal, a significant minority will not be. 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 patients who are pregnant or breast feeding will be identified at screening and excluded from study participation.

The Investigator must ensure that all patients 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 patient or the patient 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 patients 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.

There is good safety data on the use of IL-1Ra for male RA subjects with partners of childbearing potential and therefore no contraceptive requirements will be put in place for male patients.

Any pregnancy occurring in a patient 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 patient.

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 patient, and discuss the risks of continuing with the

pregnancy and the possible effects on the foetus. Monitoring of the patient 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 the study drug is restricted to members of the research team delegated the responsibility by the PI and staff who have received specific training in study drug administration, completion of syringe reconciliation documentation and AE awareness. Patients will receive two injections of 100mg study drug / placebo via a subcutaneous syringe each day with a minimum of 8h and a maximum of 16h between doses . Patients are allocated treatment kits and the procedure to show proof of administration and drug reconciliation make overdose highly unlikely.

An overdose will be reported to the MANCHESTER-CTU by the completion of the Overdose CRF form. The completed Overdose CRF form 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.

Patients 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. 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 patients' 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 patients 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 patient until the event is resolved. Resolution reports will be completed in the eCRF 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.

9.11.1 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 3.8 of the Research Governance Framework for Health and Social Care (2005). 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, design of CRF and CRF completion guidelines, study database design and testing, production of data validation guidelines, study risk assessments and attendance at relevant Chief Investigator meetings.

CRF collection, data entry, electronic data review and validation , 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, PIs, sponsor pharmacist, funder representative, the trial statistician, the trial manager(s), trial monitors and data managers. 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 patients 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, one or two PIs, sponsor representative, funder representative the Trial Manager and 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 patients' 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 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 independent statistician from the MANCHESTER-CTU 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 TSC 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 patient 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 patient data will be merged with the randomisation schedule to create a locked analysis dataset.

11. STATISTICS AND DATA ANALYSIS

11.1 Sample Size Calculation

The primary outcome for the trial will be perihaematomal oedema on CT scan at day 3-4 as measured by the 'oedema extension distance' (OED), which equates to the average distance that oedema extends beyond the haematoma border. After deriving the volume of perihaematomal oedema (PHO vol) and of the haematoma (ICH vol), the OED will be calculated using the formula in Figure 3.This measure is biologically meaningful and is consistent across a range of haematoma volumes, unlike the absolute and relative perihaematomal oedema volumes.

In previous work in rats, the water content of the ipsilateral striatum at day 3 after 100 µl injection of autologous blood is increased by 5.2% (measured using wet/dry weights) relative to the contralateral striatum[14]. Animals overexpressing IL-1Ra had only a 3.3% increase in water content, representing a 36.5% treatment effect of IL-1Ra. If the absolute PHO volume is reduced to a similar extent, this equates to a 30% reduction in OED for a haematoma of around 30 ml. This magnitude of treatment effect is supported by the MISTIE II study, in that despite very similar baseline ICH volumes (30.3 ml vs. 33.3ml), patients receiving the MISTIE intervention had a reduction in perihaematomal oedema at day 3 (27.7ml vs. 41.7ml), equating to a 14 ml (33%) effect of the treatment[55,53,54,52].

Based on analysis of CT brain scans from day 3 post-onset in conservatively managed (control) patients in the MISTIE II trial (n=39), mean (SD) OED was 0.57 (0.14) cm. We will target a conservative reduction of 0.1 cm, approximately half the effect size previously observed in the animal model, to allow for regression to the mean and over-optimism. For 90% power at the 5% significance level this would require 43 patients per group in a *t*-test comparison. However, adjustment for baseline OED will gain efficiency. We anticipate a correlation of at least 0.5 between baseline and outcome assessments (MISTIE II observed correlation 0.67) so that target sample size can be reduced by 25% to 33 patients per group. We know that 15% of ICH patients with a GCS ≥ 6 on presentation will die by day 4. To allow for this, we will recruit 40 patients per group. For comparison, if absolute perihaematomal oedema volume were the primary outcome, we would need 170 patients to achieve similar power, demonstrating the utility of the OED as the primary outcome.

11.2 Planned Recruitment Rate

All study sites receive over 1000 stroke admissions/year and benefit from HSRC teams who will screen and recruit patients to take part in the trial. We aim to recruit 80 patients over 1 year for this study, thus a recruitment rate of 1.3/month for each centre. All chosen HSRCs have a good record for recruiting to acute ICH intervention studies. They include 3 of the top 4 recruiters to TICH2, a trial of an IV bolus and infusion of tranexamic acid in ICH, initiated within 8 hours of symptom onset. As this is the same patient group, time window and involves an IV bolus and infusion it represents a very good indication of potential recruitment to the proposed IL-1Ra study. Between them, the three study sites have recruited 86 patients/year to TICH-2. TICH2 is scheduled to complete recruitment in October 2017, so will not be competing with BLOC-ICH for patient recruitment.

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
- Premorbid mRS
- NIHSS
- Time since onset
- Glasgow Coma Scale
- Blood pressure
- Haematoma location
- ICH volume
- Intraventricular haemorrhage
- Use of antiplatelet and antithrombotic drugs

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

11.3.2 Primary outcome analysis

Primary analysis will be conducted under the principle of intention to treat and analysis of covariance will adjust for baseline value of OED.

Baseline characteristics and the main outcome measures will be described using appropriate summary statistics. Brain CT scans will be reported by the local radiology staff and made available to the stroke team. All MR and CT brain imaging will also be anonymised and transferred off-site for blinded measurements

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 the full randomised cohort.

11.4 Subject Population

11.4.1 Procedure(s) to account for missing or spurious data

All reasonable efforts will be made to obtain outcome data for randomised participants with confirmed ICH. This will include requesting follow-up for those who decline treatment at any stage. 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 statistical analysis plan (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 (3 months (+/- 14 days) from randomisation) are validated. No non-standard tools will be used.

Electronic Case report forms (e-CRFs) will be used to collect the study data. The PI is responsible for ensuring the accuracy, completeness, legibility and timely provision of the data recorded in the e-CRFs. Only the Investigator and those personnel who have signed the Delegation Log provided by Manchester – CTU and have been authorised by the Investigator should access the study database to enter or change data in the e-CRFs. The Investigators must retain all original reports, traces and images from these investigations for future reference. At the end of the trial all e-CRFs will be retained, site access to the study database removed, copy of patient data for the study provided to respective sites and preparation for archiving 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 PI or research team can provide access to the source documents to a monitor, auditor, or regulatory agency.

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 print-outs of completed e-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 eCRFs will be reviewed by the designated data manager at the MANCHESTER-CTU. The database will be secured via appropriate access control and password protection. Paper records will be stored securely with access limited to authorised personnel.

Data 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, data review 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 BLOC-ICH trial, the PIs are confirming agreement with the University of Manchester to ensure that:

- Sufficient data are recorded for all patients to enable accurate linkage between hospital records and eCRFs
- 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, MANCHESTER-CTU, 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 should 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, 25 years. 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 & 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 & 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 CI/PI or designee will apply for confirmation of local capability and capacity from the site's Research & Development (R&D) department.

It is the PI's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The PI must ensure this is documented in the patient's medical notes and the patient 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, the project was reviewed by two 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 we have a PPI group of those affected by ICH that meets regularly at Salford. We have worked with service users on the preparation of this application, with support from PPI funding in the PIs NIHR Clinician Scientist Award. We met on two occasions with groups of service users (ICH patients and their carers) to discuss the application. They have offered advice on the research questions and the clinical outcome measures. 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 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 patient 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 patient. 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 will be assessed by the MANCHESTER CTU for 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

Patients 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 patients to be identified will not be released into the public domain.

Investigators and trial site staff must not provide any patient- 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 patient identifying data received by MANCHESTER-CTU will be returned back to the sender or destroyed, and the sender notified.

Each participating centre should keep a separate Trial ID and screening log of all patients consented and screen status. The investigator must maintain this screening log and all other trial documents (including patient's written consent forms) which are to be held at the participating centre, in strictest confidence. The investigator must ensure the patients' confidentiality is maintained. As part of this study, patients (or next of kin) contact details will be shared with the trial centre to enable the 3 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 patients and will not reproduce or disclose any information by which patients 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 patients' notes for quality assurance purposes but patients 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 2018 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.

Patient 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 patients.

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 to clarify the financial position of Sobi prior to ethical and regulatory submission. This ISS agreement will comply with NIHR requirements.

z14.9 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 patients 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 patients 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 patients 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. All patients will continue to receive the standard care for intracerebral haemorrhage and participation in this study will not affect or delay this care.

15. DISSEMINATION POLICY

15.1 Dissemination Policy

As detailed in section 0, 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 ICH survivors and previous study patients, describing their experiences as ICH survivors and research patients. 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 patients 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. Presentations will be submitted at meetings of clinicians and scientists, for example UK Stroke Forum, European Stroke Organisation meetings. 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 patients who express a wish to receive them. We will work with national guidelines groups and those who commission and provide services for people with ICH 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 at the time of submission.

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.

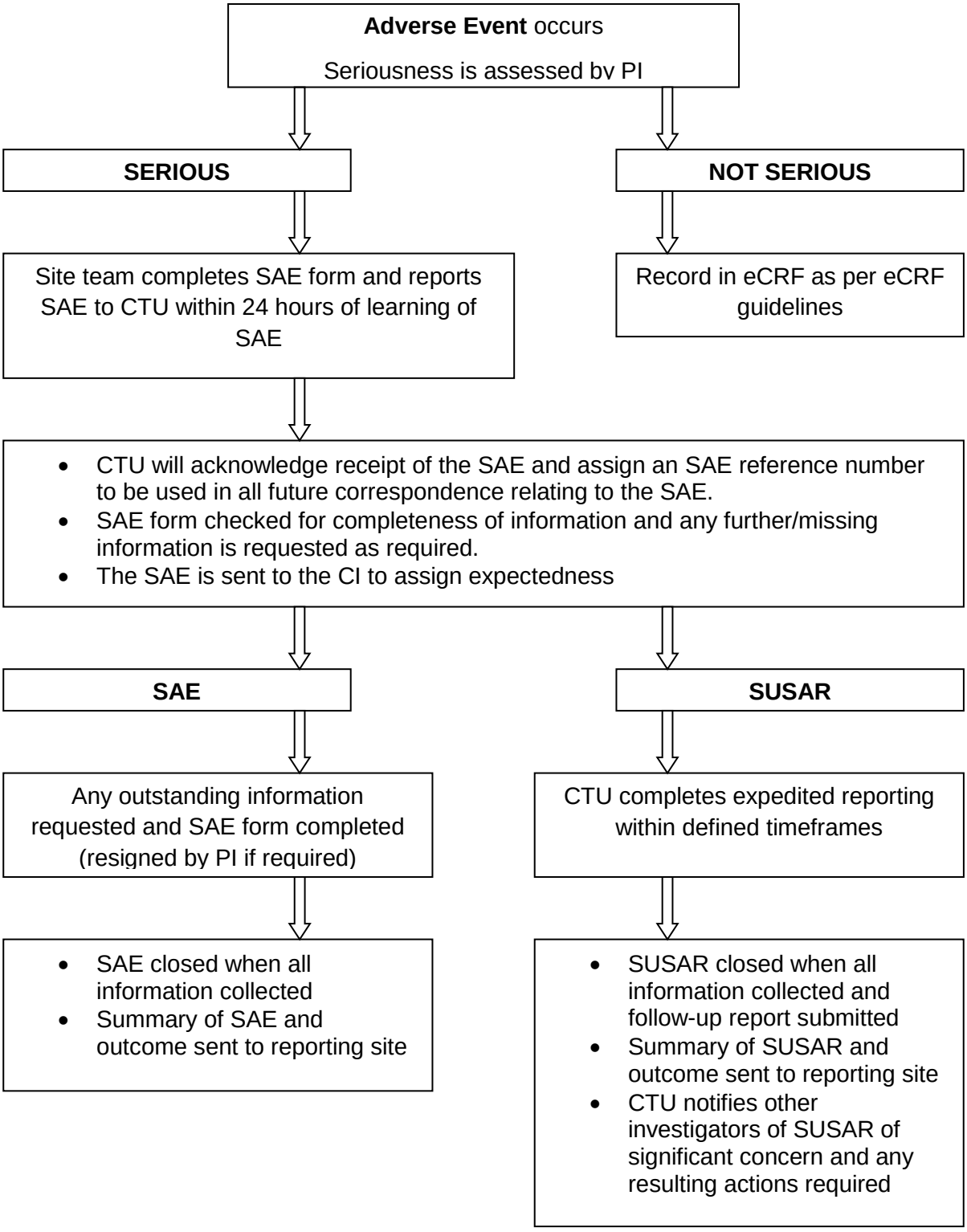
16. APPENDICES

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 ICH 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		N/A	N/A
Substantial Amendment 02	1.1	08July2019	Timothy Lubinda	Minor administration changes Removal of pre-IMP requirement for daily blood samples Addition of pre-notification pack information for 3m assessment Update to SAE reporting details
Substantial Amendment 03	2.0	26Feb2020	April Hoyle	Change to the IMP administration timings Minor administration changes

16.4 Appendix 4: MR Safety questionnaire

This is an example of a clinical MR safety questionnaire but sites will use their own version

Magnetic Resonance Imaging Facility wellcome trust

MR PATIENT DECLARATION –

TO BE COMPLETED BEFORE EXAMINATION COMMENCES

Please answer the following confidential questions by circling YES or NO to each one. Some of items mentioned may interfere with the quality of the pictures obtained during your scan and, in a few cases, can be hazardous to your safety.

If you do not understand any of the questions please ask a member of staff to help you.

1	Do you have a pacemaker or artificial heart valve?	*	YES/NO
2	Do you have a hydrocephalus shunt?	*	YES/NO
	If so, is it a programmable shunt?		YES/NO
3	Have you had any operations on your head?	*	YES/NO
4	Have you had any surgery to you head or body within the last 2 months?		YES/NO
5	Do you have any joint replacements or metal implants?		YES/NO
6	Have you EVER had metal in your eyes or worked with metal at high speed, e.g. in a machine shop?	*	YES/NO
7	Do you have any shrapnel from a war injury?		YES/NO
8	Do you wear a false limb, caliper or brace?		YES/NO
9	Do you have dentures, a dental plate or a hearing aid?		YES/NO
10	Have you suffered from epilepsy or blackouts?		YES/NO
11	Do you have any ear implants, e.g. cochlear?		YES/NO
12	Have you had any history of kidney problems or renal dialysis?		YES/NO

Please note - If you have answered YES to any of the questions marked '*' please telephone the department on 0161 206 5845, prior to your appointment date.

TO BE ANSWERED BY WOMEN OF CHILD BEARING AGE

a	Do you have any intrauterine contraceptive device or coil?		YES/NO
b	Could you be pregnant?	*	YES/NO

I confirm that I have read the above questions and that my answers are correct to the best of my knowledge and belief.

Name: _____ **Weight:** _____

D.O.B. _____

Address _____

_____

_____ **Post Code** _____

Signed: X _____ **Date:** _____

Radiographer witness: _____

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