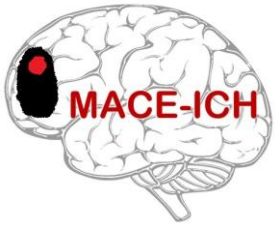
EudraCT number: 2022-000283-22

IRAS number:1004870

SHORT TITLE/ACRONYM: MACE-ICH



FULL/LONG TITLE OF THE TRIAL

MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial

ACRONYM: MACE-ICH

PROTOCOL VERSION NUMBER AND DATE: V.2.0-, 27Jul2023

R&I REFERENCE NUMBER: 22SR001

IRAS NUMBER: 1004870

EudraCT NUMBER: 2022-000283-22

REC REFERENCE NUMBER: 22/EM/0242

TRIAL REGISTRY NUMBER AND DATE: ISRCTN15383301 18 May 2023

SPONSOR: NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST

FUNDER: NIHR-Research for Patient Benefit (RfPB) Programme [203080]

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

For and on behalf of the Study Sponsor:

Signature: DocuSigned by: 5EED0CCAE527413... Date: ...../...../.....

28-Mar-2024 | 12:00:15 PM GMT

Name (please print): Tom Smith

Position: Acting Divisional General Manager

Chief Investigator:

Signature: Date: 27/07/2023

Name: (please print):

Kaliash Krishnan

EudraCT number: 2022-000283-22

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SHORT TITLE/ACRONYM: MACE-ICH

Statistician:

Signature: 

Date:

27/07/2023

Name: (please print):

Lisa Woodhouse

Position:

Trial Statistician and Research Fellow

EudraCT number: 2022-000283-22

IRAS number:1004870

SHORT TITLE/ACRONYM: MACE-ICH

KEY TRIAL CONTACTS

Chief Investigator	Dr Kailash Krishnan Consultant Stroke Physician Queen's Medical Centre, Nottingham University Hospitals NHS Trust Nottingham Tel: 01159249924 email: kailash.krishnan@nuh.nhs.uk
Deputy Chief Investigator	Prof Philip M Bath Stroke, Mental Health and Neuroscience University of Nottingham D floor South Block Queen's Medical Centre Nottingham NG7 2UH UK Tel: 0115 823 1765 email: philip.bath@nottingham.ac.uk
Trial Manager	Dr Jennifer Craig Stroke Trials Unit Stroke, Mental Health and Neuroscience D Floor South Block Queen's Medical Centre Nottingham NG7 2UH Phone: 0115 823 1770 email: Jennifer.craig@nottingham.ac.uk
Sponsor	Nottingham University Hospitals NHS Trust Research & Innovation, Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Derby Road Nottingham NG7 2UH email: ResearchSponsor@nuh.nhs.uk
Funder(s)	National Institute for Health Research Research for Patient Benefit (RfPB) Programme Grange House, 15 Church Street Twickenham, TW1 3NL Tel. 020 8843 8000 www.nihr.ac.uk/ccf
Clinical Trials Unit	Stroke Trials Unit Mental Health and Neuroscience D Floor South Block

	Queen's Medical Centre Nottingham NG7 2UH Phone: 01158231775 email: diane.havard@nottingham.ac.uk
Key Protocol Contributors	Dr Kailash Krishnan Consultant Stroke Physician Queen's Medical Centre, Nottingham University Hospitals NHS Trust Nottingham Tel: 01159249924 email: kailash.krishnan@nuh.nhs.uk Professor Philip M Bath Stroke, Mental Health and Neuroscience University of Nottingham D floor South Block Queen's Medical Centre Nottingham NG7 2UH UK Tel: 0115 823 1765 email: philip.bath@nottingham.ac.uk Professor Nikola Sprigg Professor of Stroke Medicine Stroke, Mental Health and Neuroscience University of Nottingham D floor South Block Queen's Medical Centre Nottingham NG7 2UH UK Tel: 0115 823 1765 email: nikola.sprigg@nottingham.ac.uk Professor Christine Roffe Professor of Stroke Medicine Keele University Stoke-on-Trent ST4 7QB Tel: 01782671655 email: Christine.roffe@uhnm.nhs.uk Professor Jesse Dawson Professor of Stroke Medicine and Hon Consultant Physician

	Queen Elizabeth University Hospital University of Glasgow Glasgow G51 4TF Tel: 01414515868 email: jesse.dawson@glasgow.ac.uk Professor Timothy England Professor of Stroke Medicine and Honorary Consultant Physician University of Nottingham Royal Derby Hospital Uttoxeter Road Derby DE22 3DT Tel: 01332724668 Dr David Hewson Consultant Anaesthetist & Honorary Assistant Professor Department of Anaesthesia & Critical Care C Floor, East Block, Queen's Medical Centre Nottingham University Hospitals NHS Trust NG7 2UH Tel: 01159249924 email: david.hewson@nuh.nhs.uk Professor Rob A Dineen Professor in Neuroradiology Radiological Sciences, Precision Imaging Beacon, University of Nottingham and NIHR Biomedical Research Centre Queen's Medical Centre Nottingham University Hospitals NHS Trust Nottingham NG7 2UH Tel: 01159249924 email: rob.dineen@nottingham.ac.uk Dr Mary Joan Macleod Senior Lecturer in Clinical Pharmacology Department of Medicine and Therapeutics Polwarth Building The Institute of Medical Sciences University of Aberdeen Aberdeen Tel: 01224437842

	email: m.j.macleod@abdn.ac.uk Dr Lisa Woodhouse Stroke, Mental Health and Clinical Neurosciences University of Nottingham Tel: 0115 823 1765 email: L.woodhouse@nottingham.ac.uk Mr Philip Johnson PPI representative
Statistician	Dr Lisa Woodhouse Stroke, Mental Health and Clinical Neurosciences University of Nottingham Tel: 0115 823 1765 email: L.woodhouse@nottingham.ac.uk
Trials pharmacist	Maria Scott Clinical Trial pharmacist Nottingham University Hospitals NHS Trust 0115 9691169 (ext 79414) and 0115 9249924 (ext 88450) email: maria.scott@nuh.nhs.uk
Committees	Membership details for the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) are detailed in separate TSC and DMC charters. The TSC includes members independent of the trial, and all DMC members are independent of the trial.

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TRIAL SUMMARY

Trial Title	MAnnitol for Cerebral oEdema after intracerebral haemorrhage: a feasibility trial
R&I ref. no. (or short title)	MACE-ICH (22SR001)
Objectives	To determine the feasibility of screening, assessing eligibility, approaching potential participants, randomisation, administering mannitol and completing follow-up for acute haemorrhagic stroke patients with cerebral oedema, or at risk of cerebral oedema, to inform a definitive trial. To determine the feasibility and inform the design and conduct of an adequately powered, pragmatic, prospective multi-centre RCT testing mannitol as a treatment for cerebral oedema in spontaneous ICH.
Trial Design	A multicentre, prospective, randomised, open-label, blinded-endpoint trial
Trial Participants	Adults (≥18 years) with spontaneous intracerebral haemorrhage with estimated largest diameter > 2 cm, presenting within 72 hours of onset with, or at risk of cerebral oedema with or without mass effect (limited GCS score <9 (eye opening and motor only) and NIHSS≥8)
Setting	Ten UK, NHS hospitals providing acute stroke services
Eligibility	Inclusion criteria: • Adults (≥18 years) • Spontaneous ICH confirmed by CT scan with estimated largest diameter > 2 cm • ≤ 72 hours of ictus (or from last seen healthy) • Cerebral oedema with or without evidence of mass effect • At risk of developing oedema (limited GCS <9 (eye opening and motor only) and NIHSS≥8) • Signed consent (patient, personal or professional representative or independent physician) Exclusion criteria: • GCS<5 • Premorbid mRS >3

	• Isolated subarachnoid haemorrhage • Haemorrhage known to be from: trauma or venous thrombosis or arteriovenous malformation or brain tumour or transformation of cerebral infarct or cerebral aneurysm or thrombolytic drug • Known hypersensitivity to mannitol • Severe renal failure (e-GFR<30ml/min or dialysis) • Severe pulmonary oedema/ cardiac failure • Hypotension at baseline (SBP <90 mm Hg) • Anuria • Patient unwilling to participate • Geographical or other factors which prohibit follow-up • Pre-existing comorbidity with pre-ictal life expectancy <6 months • Severe dementia • Planned for palliative care • Severe hypernatremia (sodium >160 mmol) • Severe hyponatremia (sodium <125 mmol) • Women of child-bearing potential with a positive pregnancy test at the time of admission, or lactating • Patients in whom peripheral intravenous cannula cannot be placed • Planned neurosurgery
Participant co-enrolment	Co-enrolment between certain trials is allowed at the discretion of the CI; an up-to-date list of trials which MACE-ICH can co-enrol with, and at which time points, will be available on the trial website.
Sample size estimate	This is a feasibility trial so there is no formal sample size calculation. It is likely that a planned target of 45 patients with high rates of adherence to treatment and follow-up data would inform a definitive trial. Lower recruitment would not preclude progression if there is evidence that barriers to recruitment could be overcome.
Number of participants	45
Description of intervention and duration of treatment	Participants will be enrolled to one of three groups as soon as possible after randomisation: • Arm 1: 1 g/kg 10% single dose mannitol infusion at 10ml/min, in addition to standard care • Arm 2: 1 g/kg 10% mannitol at 10 ml/min followed by a second dose 1 g/kg repeated at 24 hours, if the serum osmolality is <320 mOsm/Kg and sodium <160 mEq/L after the first dose, in addition to standard care • Arm 3: Standard care alone Administration of mannitol 1 g/kg as a single dose or a second dose repeated at 24 hours is within the British National Formulary recommendations (0.25-2 g/kg).

	We have chosen 1g/kg as it has been tested in traumatic brain injury but not exceeded in a single dose in previous trials.
Follow up duration	6 months from enrolment
Planned Trial Period	24 months
Randomisation and blinding	Randomisation will be performed by the Stroke Trials Unit (STU), University of Nottingham with computerised minimisation on key prognostic factors: age, limited GCS, time from stroke onset and largest haemorrhage diameter. Outcome assessors will be masked to treatment allocation.

Outcomes	**Feasibility outcomes (Primary Outcomes)**
	• Number of patients: screened and eligible
	• Number of eligible patients recruited and reasons for not recruiting
	• Proportion of eligible patients who received allocated treatment and reasons for non-allocation
	• Recruitment rate
	• Treatment adherence
	• Retention rate
	• Number of participants with outcome data and reasons for non-availability
	• Effectiveness of blinded follow-up
	• Incidence and type of adverse events, protocol violations and trial withdrawal
	Secondary Outcomes:
	• Laboratory (Day 1-2)
	  ○ U&E's
	  ○ e-GFR
	  ○ serum osmolality to correlate response to mannitol
	• Glasgow Coma Scale (GCS) (Day 5±2 days)
	• National Institutes Health Stroke Scale (NIHSS) (Day 5±2 days)
	• Number of patients who had urinary tract infection (Day 5±2 days, Day 28)
	• Number of patients who had sepsis (Day 5±2 days, Day 28)
	• Mortality (Day 5±2 days, Day 28)
	• Disability (Barthel Index, Day 180)
	• Mood (Zung depression scale [ZDS], Day 180)
	• Cognition (TICS-M Day 180)
	• Quality of life (Euro-[EQ] QOL; EQ-VAS, Day 180)-

	• Health economic assessment (EQ-5D, Day 180)
	• Death or dependency (modified Rankin scale, Day 180)
	• Length of stay (Day 180)
	• Discharge destination (Day 180)
	• Long-term outcomes post Covid-19 and ICH (Day 180)
	• Number of patients who were transferred to high dependency unit
	• Number of patients needing high dependency or intensive care unit
	• Number of patients undergoing neurosurgical intervention
	• Recurrent stroke
	• Number of patients intubated and ventilated
	• Mechanistic
	  ○ Follow-up CT scan to assess changes in oedema volume, oedema extension distance, haematoma volume, midline shift, hydrocephalus (Day 5±2 days)
	• **Safety outcomes**:
	  ○ death
	  ○ thrombophlebitis
	  ○ hyper/hyponatremia
	  ○ pulmonary oedema
	  ○ hypotension
	  ○ renal impairment
	  ○ Serious adverse events (SAEs) up to day 28, fatal SAEs until day 180

Statistical methods	Analysis will primarily be descriptive to address the feasibility objectives of the trial. A full Statistical Analysis Plan will be finalised prior to database lock.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**DETAILS OF FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health Research Grange House, 15 Church Street Twickenham, TW1 3NL Tel. 020 8843 8000 www.nihr.ac.uk/ccf	Research for Patient Benefit (RfPB) Programme Call 44 Reference NIHR-203080 (£249,934)

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ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor will monitor the study conduct against nationally agreed standards. The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study.

Nottingham University Hospitals NHS Trust is the main research sponsor for this trial. For further information regarding the sponsorship conditions, please contact:

Nottingham University Hospitals NHS Trust
Research & Innovation, Nottingham Health Science Partners
C Floor, South Block
Queens Medical Centre
Derby Road
Nottingham
NG7 2UH
email: ResearchSponsor@nuh.nhs.uk

This protocol describes the MACE-ICH trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the clinical trial. Problems relating to this clinical trial should be referred, in the first instance, to the Chief Investigator.

This clinical trial will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). The trial will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

This trial will run according to the University of Nottingham's Standard Operating Procedures as trial management is provided by the University of Nottingham.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Roles and responsibilities are detailed in section 10 of this study protocol.

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CONTRIBUTOR(S)	DETAILS OF CONTRIBUTION
Dr Kailash Krishnan Consultant Stroke Physician Queen's Medical Centre, Nottingham University Hospitals NHS Trust Nottingham Tel: 01159249924 email: kailash.krishnan@nuh.nhs.uk	Protocol writing and final approval
Professor Philip M Bath Stroke, Mental Health and Neuroscience University of Nottingham D floor South Block Queen's Medical Centre Nottingham NG7 2UH UK Tel: 0115 823 1765 email: philip.bath@nottingham.ac.uk	Protocol writing and final approval
Professor Nikola Sprigg Professor of Stroke Medicine Stroke, Mental Health and Neuroscience University of Nottingham D floor South Block Queen's Medical Centre Nottingham NG7 2UH UK Tel: 0115 823 1765 email: nikola.sprigg@nottingham.ac.uk	Protocol writing and final approval
Professor Christine Roffe Professor of Stroke Medicine Keele University Stoke-on-Trent ST4 7QB Tel: 01782671655 email: Christine.roffe@uhnm.nhs.uk	Protocol writing and final approval
Professor Timothy England Clinical Associate Professor and Honorary Consultant Physician Royal Derby Hospital Uttoxeter Road	Protocol writing and final approval

Derby DE22 3DT Tel: 01332724668	
Professor Jesse Dawson Professor of Stroke Medicine and Hon Consultant Physician Queen Elizabeth University Hospital University of Glasgow Glasgow G51 4TF Tel: 01414515868 email: jesse.dawson@glasgow.ac.uk	Protocol writing and final approval
Dr David Hewson Consultant Anaesthetist & Honorary Assistant Professor Department of Anaesthesia & Critical Care C Floor, East Block, Queen's Medical Centre Nottingham University Hospitals NHS Trust NG7 2UH Tel: 01159249924 email: david.hewson@nuh.nhs.uk	Protocol writing and final approval
Professor Rob Dineen Professor in Neuroradiology Radiological Sciences, Precision Imaging Beacon, University of Nottingham and NIHR Biomedical Research Centre Queen's Medical Centre Nottingham University Hospitals NHS Trust Nottingham NG7 2UH Tel: 01159249924 email: rob.dineen@nottingham.ac.uk	Protocol writing, input into neuroradiology and final approval
Dr Mary Joan Macleod Senior Lecturer in Clinical Pharmacology Department of Medicine and Therapeutics Polwarth Building The Institute of Medical Sciences University of Aberdeen Aberdeen	Protocol writing and final approval
Dr Lisa Woodhouse	Protocol writing, statistical input and final approval

Stroke, Mental Health and Clinical Neurosciences University of Nottingham Tel: 0115 823 1765 email: L.woodhouse@nottingham.ac.uk	
Mr Philip Johnson PPI representative	Protocol writing and final approval

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LIST of CONTENTS

General

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LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Computerised Tomography
GCS	Glasgow Coma Scale
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EudraCT	European Clinical Trials Database
e-GFR	estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GP	General Practitioner
EQ-5D	European quality of Life-5 Dimensions questionnaire
IMP	Investigational Medicinal Product
IV	Intravenous
ISRCTN	International Standard Randomised Controlled Trials Number
EQ-VAS	European quality of life-visual analogue scale
mRS	modified Rankin Scale
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MRIS	Medical Research Information Service
NIHR	National institutes of Health Research
NIHSS	National Institutes of Health Stroke Scale
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research and Development
R&I	Research & Innovation
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic blood pressure
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics

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SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TMG	Trial Management Group
U&Es	Urea and electrolytes
UK	United Kingdom

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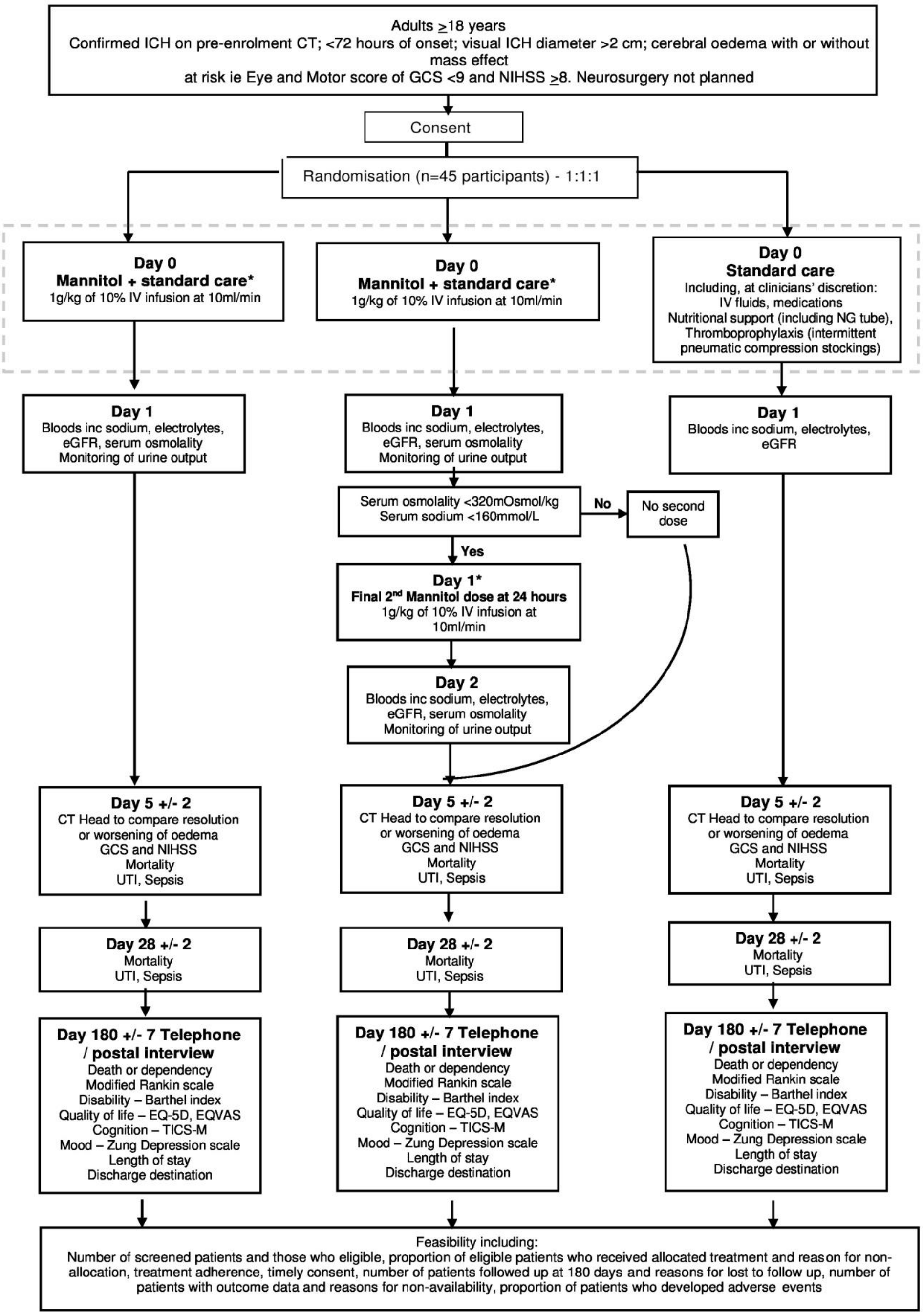
TRIAL FLOW CHART



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TRIAL PROTOCOL

MAnnitol for Cerebral oEdema after acute IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial

1. BACKGROUND

Acute spontaneous intracerebral haemorrhage (ICH) accounts for up to 15% of 150,000 strokes each year in the UK, and to date, management is largely supportive.(1, 2) Mortality in ICH is significantly higher compared to ischaemic stroke (IS) (~34% versus 12% at one month) and data from the national stroke audit (SNNAP) indicates that up to 80% of survivors are left with significant disability long-term.(3) Trials testing surgical evacuation of haematoma or limiting haemorrhage expansion have not shown benefit and consequently, research into treatment targets such as cerebral oedema are warranted. Oedema starts within hours of ICH from clot retraction releasing serum into the surrounding brain, peaking at around 72 hours and continues for days (due to blood-brain barrier disruption and inflammation).(4, 5) Large ICH (~15%) cause significant swelling(6) and the only treatment with some evidence is surgical decompression.(2) However, surgery is not routinely available and excludes older patients who comprise the majority of haemorrhagic strokes. Moreover, the operation has its own risks and complications.

Mannitol, an osmotic diuretic, is readily available in most UK hospitals and easy to administer intravenously. It is licensed to treat cerebral oedema and used in traumatic brain injury (TBI) and hepatic encephalopathy. (7, 8) Mannitol is known to stroke physicians: some use it regularly, occasionally or never.(9) Little is known about its effects in ICH: to date, studies have been low quality and underpowered.(9) Current UK stroke guidelines do not recommend the routine use of mannitol(1) and experts insist that clinical trials in ICH are urgently needed.(10)

2. RATIONALE

There is an urgent need to develop effective treatments for ICH, the most severe type of stroke and associated with significant mortality (~50%). A key question is management of severe cerebral oedema, estimated to affect ~1,500 patients in the UK each year.(1, 11) Computed Tomography (CT) scanning is routinely performed in acute stroke patients and is cheap, quick, and readily available. ICH is reliably seen on plain CT and the presence of oedema identified as area of low density surrounding the haemorrhage.(12) Significant brain swelling often leads to reduced consciousness (low Glasgow Coma Scale, GCS), worsening of neurological deficit (higher National Institutes of Health Stroke Scale, NIHSS) and if untreated, causes death or severe disability. CT scanning in such patients is likely to show changes such as midline shift, sulcal effacement or hydrocephalus. With advances in neuroimaging, measurement of haemorrhage size and oedema volume is feasible (13) so assessment of change is possible. Both baseline haematoma volume and oedema volume are independently associated with poor outcome (6, 14) and early expansion increases the risk of acute neurological deterioration and death.(6) If oedema can be prevented or reduced with effective treatment,

outcomes may improve. This in turn, would reduce the need for home or institutional care, patient and carer stress and costs.

Review of evidence

General

Mannitol has been used by physicians for >40 years. It is known to lower intracranial pressure (ICP) by drawing water from the brain interstitium into the intravascular space.(7, 18) It is also thought to reduce blood viscosity, facilitating flow and oxygen delivery to the brain. As a free-radical scavenger, mannitol might act as a neuroprotectant.

Pre-clinical studies

Mannitol has demonstrated benefit in three animal models of intracranial haemorrhage. (Table 1)

Table 1. Pre-clinical studies

Year	Animal	Model	Effect of mannitol
1999 (19)*	Dog	ICH	Reduced ICP
2006(20)**	Rat	SAH	Reduced ICP and death
2018(21)***	Rat	ICH	Reduced oedema, brain inflammation and death

*compared mannitol with two doses of hypertonic saline (3% or 23.4%)

**comparison between 4 groups: normal saline, mannitol, dextran with hypertonic saline 2 ml/kg and hypertonic saline 4ml/kg respectively

***5ml/kg of 20% mannitol over 3 minutes given 5 hours after ICH and repeated every 12 hours; four doses in total

Proof-of-concept in ICH

Studies testing Cerebral Blood Flow (CBF) in ICH patients have reported varying results, from no change with low-dose mannitol (0.9g/kg) to transient increase using higher dose (1.5 g/kg) (Table 2). One study evaluating haemodynamics in ICH using transcranial Dopplers found that 125 ml of 20% mannitol reduced ICP in the affected cerebral hemisphere and 250 ml decreased ICP in both hemispheres.(22) Observational data from the INTERACT-2 trial (>1500 patients) showed that mannitol was associated with better outcomes in patients with haemorrhages >15 ml.(23) There were no significant differences in adverse events (cardiac, renal or neurological) in those who received treatment.(23) Another study reported no difference in functional outcome at 3 months following use of mannitol.(24) However, comparisons were made with patients having brain herniation to those with mild stroke and did not receive treatment.(24)

Table 2. Effect of mannitol on CBF in ICH patients

Year	N	Dose	Equivalent dose based on 70 kg	Total dose in 24 hours	Effect
1978(25)	300	0.9g/kg	63 g	63 g	No CT scan; no change
1998(26)	1	20% solution 200 ml	40 g	40 g	Transient Increase in CPP and reduced ICP
2004(27)	21	20 g 20%	20 g	20 g	No change
2005 (28)	128	20 g 4 hourly 20%	20 g	120 g	No difference in death or disability
2007(29)	24	1.5 g/kg 20%	105 g	105 g	Transient improvement in CBF after single dose
2011(30)	20	20% bolus/100 ml infusion	20 g	20 g	Increased CBF and lowered PI
2013(22)*	30	125 ml of 20% mannitol over 15 minutes; 250 ml of 20% mannitol over 30 minutes 6 hours later	25 g+50 g	75 g	Increase in CBF in both cerebral hemispheres and reduced ICP

CPP: cerebral perfusion pressure; PI: pulsatility index
*Mean ICH volume was 21.9 ml

Mannitol for stroke

A systematic review of mannitol versus control for acute stroke found three small trials including 226 participants.(9) Of these, two trials included ICH patients. The trials varied in their design, inclusion criteria, duration and intensity of treatment.(9) At the end of follow-up, there was no significant difference in functional outcome between those randomised to mannitol compared to no treatment, however, the confidence intervals were wide so it is difficult to draw any definite conclusions.(9)

One meta-analysis comparing hypertonic saline with mannitol including ICH patients found that both were effective regardless of clinical definition of elevated ICP.(18) However, the patient numbers were small and the effect on long-term outcomes were unknown.(18)

The most effective regimen for mannitol is unclear with both bolus doses and continuous infusions compared in traumatic brain injury; the results suggest that bolus may be effective (31). Guidance on the most

appropriate dose is limited: evidence suggests higher doses may be more effective.(31) Experts highlight that risks with treatment are low compared to potential benefit in life-threatening cerebral oedema.(18, 32)

2.1. Assessment and Management of Risk

The assessment and management of risk with mannitol and mitigations are detailed in section 17.

3. RESEARCH QUESTIONS/AIM

3.1. Objectives

3.1.1. Primary Objective

To determine the feasibility and inform the design and conduct of an adequately powered, pragmatic, prospective multi-centre RCT testing mannitol as a treatment for cerebral oedema in spontaneous ICH.

Formal hypothesis testing for effectiveness or efficacy is not undertaken in this feasibility study.

3.1.2. Secondary Objective

To provide preliminary data on the effect of mannitol on secondary outcomes including clinical, radiological, laboratory, safety and health-economics.

3.2. Primary Outcomes

Patient feasibility

- Ability to access eligible ICH patients to calculate study screening, eligibility, recruitment and retention
- Number of eligible patients recruited and reasons for not recruiting
- Proportion of eligible patients who received allocated treatment and reasons for non-allocation
- Treatment adherence
- Number of participants with outcome data and reasons for non-availability
- Through collection of adverse events, examine the acceptability, safety, and tolerability of mannitol in participants
- Assess the acceptability of the study protocol
- Evaluate the strengths and barriers to recruitment and retention

Site and clinician feasibility

- Determine the feasibility of clinicians to identify eligible patients
- Ability to obtain timely consent
- Evaluate the effectiveness of blinded follow-up
- Evaluate the ability to administer mannitol and monitor participants
- Through non-compliance/deviation reporting and withdrawal reporting, assess the delivery of the trial protocol, identify potential causes of violation and trial withdrawal

Outcome feasibility

- Evaluate the feasibility of collecting the proposed outcome measures including follow-up at day 180, acceptability to participants and trial staff

3.3. Secondary Outcomes

The following measures are expected to be secondary outcomes in a definitive trial and will be collected for this study:

- **Day 1-2:** Urea and electrolytes (U&E's); e-GFR and serum osmolality to correlate response to mannitol
- **Day 5±2days:** neurological deterioration (increase in NIHSS > 3); GCS; mortality; urinary tract infection; sepsis
- **Radiological:** follow-up CT after treatment (Day 5±2 days) for comparison with pre-enrolment imaging to assess changes in oedema volume, haematoma size/volume, maximum diameter, midline shift, hydrocephalus.
- **Day 28:** mortality; urinary tract infection; sepsis
- **Day 180** (blinded central follow-up via telephone/postal interview): death or dependency (modified Rankin scale; mRS) disability (Barthel Index); mood (Zung depression scale, ZDS); cognition (Telephone Interview of Cognitive Status, TICS-M); quality of life (Euro-[EQ] QOL; EQ-VAS); health economic assessment (EQ-5D); length of stay; discharge destination. The long-term outcomes post Covid-19 and ICH are not yet fully defined and may include additional yet undefined neurological complications. These will also be collected.
- Number of patients transferred to high dependency unit or intensive care unit
- Number of patients intubated and ventilated
- Number of patients who underwent neurosurgical intervention
- Recurrent stroke (ischaemic or haemorrhagic)
- **Safety outcomes:**
    - Death
    - Thrombophlebitis (defined as pain with at least three of the following: skin redness, hyperthermia, phlebitis cords, feeling of heaviness and tenseness requiring treatment)
    - Hyper/hyponatremia
    - Pulmonary oedema
    - Hypotension;
    - Renal impairment
    - Serious Adverse Events (SAEs) up to day 28, fatal SAEs until day 180

The outcomes detailed above will be measured through:

- Collection of all pseudonymised paper screening logs to ensure compliance which will allow the exploration of strengths and barriers
- Completion of CRF's, which will include questions on follow-up investigations and reasons they were not performed; patient variable questions (survival; who answered follow-up questionnaires) including allowing for free-text to explain why follow-up information may not have been collected.
- Site monitoring visits and collection of protocol deviations/violations
- Regular TMG meetings

3.4 Success criteria

This feasibility trial will be deemed a success and progress to a definite trial if the following criteria are met in regards to the following objectives:

- The recruitment rate is ≥ 80% of the target recruitment rate
- The retention rate is >80%
- Regular performance reviews indicate that participants and research staff find the protocol and intervention to be acceptable.

If these thresholds are not achieved, potential adaptations to the trial methods will be explored to identify if issues can be overcome in a definitive trial.

Objectives	Outcomes	Success criteria
To determine if the feasibility trial recruitment rate supports a definitive trial	Rate of recruitment derived from target	≥ 80%
To determine if the retention rate supports a definitive trial	Rate of retention	>80%
Performance reviews	*	Supportive

4. TRIAL DESIGN

A multicentre, multiple-armed, prospective, randomised, open-label, blinded-endpoint feasibility trial. The trial may be adapted if the success criteria detailed in section 3.4 are not met, to help guide a definitive trial.

5. TRIAL SETTING

The trial setting is in UK secondary care, in approximately ten hospitals providing acute stroke services. Participants will be recruited from participating sites, who will be identified using the National Institute of Health Research (NIHR), Clinical Research Network (CRN) feasibility resources, and adoption of the study onto

the NIHR CRN portfolio will be applied for. Each site will have dedicated local Stroke Research nurses to facilitate participant recruitment and follow-up.

Each site will have a Principal Investigator (PI) assigned who holds the appropriate training and qualifications, for example, Good Clinical Practice (GCP). Each PI will be responsible for the research activity conducted and participants recruited at their site, during the course of the trial.

Identification of potential participants

All patients admitted with acute intracerebral haemorrhage will be screened for this trial. We recommend that this should be a continuous process as patients could be admitted at any time and may become eligible for the trial very quickly. All information will be entered and maintained at each site to determine the number of patients assessed for eligibility, reasons for exclusion and reasons participants declined the trial. These logs will be monitored to identify patterns relating to recruitment rates. Recording of this information is also required to allow reporting according to the CONSORT statement. This information will include reviewing personal information of patients and will only be undertaken by a member of the patient's clinical care team, prior to informed consent. Following informed consent, this may be reviewed by a member of the research team. Space will be provided on CRF's to indicate areas that are unclear, or data which we are failing to capture.

Co-enrolment with other clinical trials

Co-enrolment between certain trials is allowed, at the discretion of the CI; an up-to-date list of trials which MACE-ICH can co-enrol with, and at which time points, will be available on the trial website. Participants may be co-enrolled in up to 2 studies (MACE-ICH plus one other, authorised study), so as to minimize participant burden, so long as there is no impact on the integrity or safety of either study. Full discussion between the CI's regarding co-enrolment for each study should be documented when making this decision. Co-enrolment agreements will be in place for any studies which will co-enrol, and these will be signed by the sponsor for each study, and also by the co-enrolling site PI's. Agreements will be in place for co-enrolment between interventional and non-interventional studies.

If the same data is being collected at the same timepoint, e.g. EQ-5D, then to reduce participant burden, the CI's should decide between themselves who will do this, and how the data will be shared. Appropriate contracting will be put into place for the sharing/transfer of the data for the different studies.

Participants will be required to be consented separately for all studies for which they are co-enrolled.

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IRAS number:1004870

SHORT TITLE/ACRONYM: MACE-ICH

6. ELIGIBILITY CRITERIA

6.1. Inclusion criteria

- Adults (≥18 years)
- Spontaneous ICH confirmed by CT scan with estimated largest diameter > 2 cm
- ≤72 hours of ictus (or from last seen healthy)
- Cerebral oedema with or without evidence of mass effect
- At risk of cerebral oedema (limited GCS <9 (eye opening and motor component) and NIHSS≥8)
- Signed consent (patient, personal or professional representative or independent physician)

The clinical course in the early hours and days after ICH is dynamic so patients who do not fit the inclusion criteria on admission will be eligible if they subsequently deteriorate and develop signs or radiological features which meet the inclusion criteria within 72 hours.

In the event that more than one scan is available for a particular patient, the investigator will assess eligibility, taking into account the clinical information and which scan best meets the inclusion criteria. The scan used for eligibility will be documented and collected. This pre-enrolment scan will be used to compare with the post-treatment scan at day 5±2days.

Assessment of maximum haemorrhage diameter and cerebral oedema
The rationale for > 2 cm diameter is based on observational data from a blood pressure lowering trial where such patients are at risk of poor outcome. (16) Moreover, patients with haemorrhages > 2 cm were more likely to receive mannitol in another study.(23) Visual assessment of maximum haemorrhage diameter has been shown to have strong agreement with measured diameter and is reproducible.(13)

Assessment for visual estimate of maximum haemorrhage diameter (>2 cm) and presence of cerebral oedema will be performed by investigators at sites prior to enrolment.

Most UK hospitals routinely use the Picture Archiving and Communication Systems (PACS) to display and store CT scans of patients and the system is readily accessible. A visual estimate of the maximum diameter is pragmatic and based on the longest diameter in any plane. This method has been shown to be reliable, reproducible and comparable to measured haemorrhage diameter.(13) Moreover, this has the advantage that it can be applied in the absence of special measurement tools in emergency settings.

On plain CT scans, cerebral oedema is identified as areas of reduced hypodensity surrounding the haemorrhage. (Figure 1) Standard CT brain viewing settings (window width, 100 HU; window level, 40 HU)

highlight the contrast between grey and white matter, whereas narrow window settings (window width, 30 HU; window level 30 HU) highlight focal areas of hypodensity.(12)

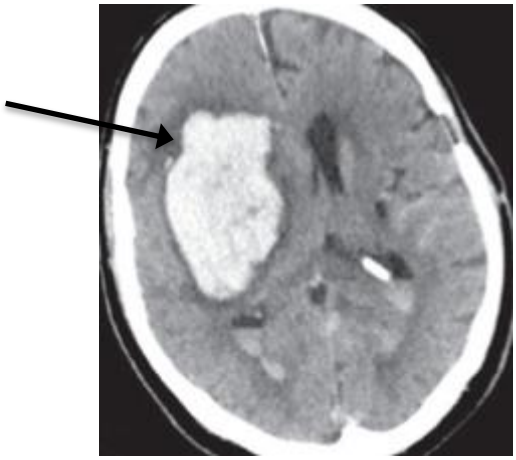

Figure 1. CT scan of the brain showing acute intracerebral haemorrhage with extension into the ventricles and midline shift from spontaneous rupture of the right middle cerebral artery. The white area indicates the haematoma and the surrounding area (arrowhead) showing dark regions indicate cerebral oedema. The region of oedema is visibly hypodense (darker) than the corresponding area in the contralateral hemisphere.

6.2 Exclusion criteria

Patients will be excluded if they meet one or more of the following criteria:

- GCS<5
- Premorbid mRS >3
- Isolated subarachnoid haemorrhage
- Haemorrhage known to be from: trauma or venous thrombosis or arteriovenous malformation or brain tumour or transformation of cerebral infarct or cerebral aneurysm or thrombolytic drug
- Known hypersensitivity to mannitol
- Severe renal failure (e-GFR<30ml/min or dialysis)
- Severe pulmonary oedema/cardiac failure
- Hypotension at baseline (SBP <90 mm Hg)
- Anuria
- Patient unwilling to participate
- Geographical or other factors which prohibit follow-up
- Pre-existing comorbidity with pre-ictal life expectancy <6 months
- Severe dementia
- Planned for palliative care
- Severe hypernatremia (sodium >160 mmol)
- Severe hyponatremia (sodium <125 mmol)
- Women of child-bearing potential with a positive pregnancy test at the time of admission or lactating
- Patients in whom peripheral intravenous cannula cannot be placed

- Planned neurosurgery

Broad inclusion criteria have been developed to reflect the diverse presentation of patients with ICH. The optimal timing for treatment is unknown and we have chosen ≤ 72 hours based on when patients are likely to develop brain swelling and/or at risk of further expansion.(6)

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1 Recruitment

Eligible participants will be selected from secondary care, in approximately ten acute stroke services in the UK. They will be recruited from sites, supported by NIHR CRN infrastructure (trial adoption will be sought from the network). These hospitals will have dedicated local Stroke Research Nurses to support recruitment and follow-up. Patients admitted to acute stroke units or emergency departments will be initially approached by members of the treating team. The investigator or their nominee will discuss with the potential participant or their relative/carer (personal legal representative) or professional legal representative all aspects relating to the trial. If needed, a hospital interpreter will be used, following usual hospital procedures, to discuss participation in the trial, information sheets and consent forms.

It will be explained to the potential participant, personal or professional legal representative that entry into the trial is voluntary and that treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal, it will be explained that the data collected up until the point of withdrawal cannot be erased and we will seek consent to use the data in the final analysis where appropriate.

7.2 Consent

The consent process for this trial is summarised in Figure 2.

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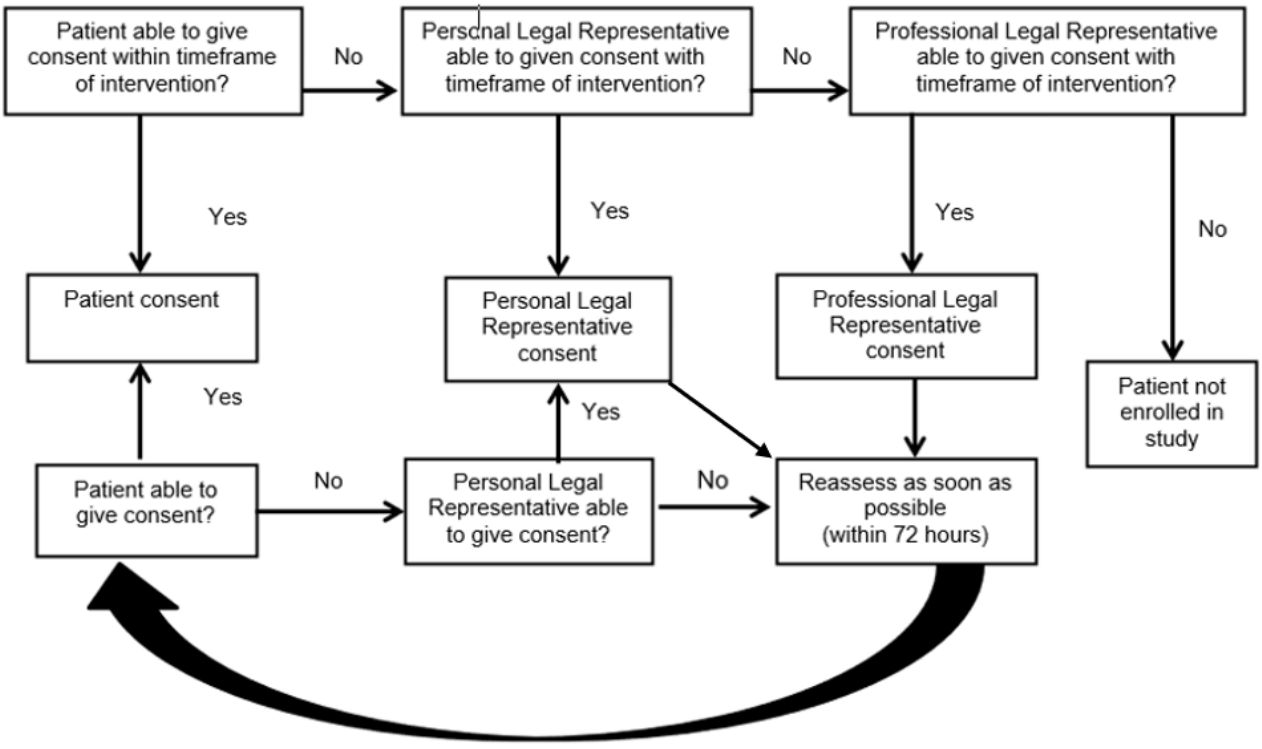

Figure 2: Flow chart for the process of consent

Intracerebral haemorrhage is a medical emergency which has no effective treatment and significant cerebral oedema can lead to rapid deterioration, worsening of neurological deficit and if untreated, death or severe disability. Intracerebral haemorrhage can cause significant brain injury and many patients may not be physically or mentally capable of giving informed consent to participate in a clinical trial. Mannitol, an osmotic diuretic, is readily available in most UK hospitals and easy to administer intravenously. It is licensed to treat cerebral oedema and used in traumatic brain injury (TBI) and hepatic encephalopathy (7, 8). In intracerebral haemorrhage the need for urgent treatment, in an attempt to prevent fatal deterioration, means that it would be inappropriate to delay treatment until fully informed consent can be obtained from an incapacitated patient. The normal process will be using a professional legal representative. However, if a patient has capacity or a personal legal representative is available, then these methods should be used for consent. It is essential that delays in the consent process are minimised.

Therefore, the following procedure will be used for giving information and obtaining informed consent in MACE-ICH.

Patients able to provide consent

Informed consent of each participant will be obtained, in writing prior to enrolment.

The consent form will be signed and dated by the participant before they enter the trial. The investigator (or nominee) will explain the details of the trial and provide a Pictorial Information Sheet. The investigator or nominee will explain to the participant that they will receive the usual care for ICH and may also receive treatment with mannitol in addition to usual care. It will be explained that this study aims to test whether a larger trial could help to improve treatment for ICH.

The Pictorial Information sheet has been developed to accelerate the process to treatment in a medical emergency such as ICH. This was successfully used in TICH-2 (Ref: ISRCTN93732214), RIGHT-2 (Ref: ISRCTN 26986053) and DASH (Ref: ISRCTN 67038373). The method was discussed and supported by stroke survivors from the Nottingham Stroke Research Partnership Group. The investigator (or nominee) will answer any questions that the participant has concerning study participation.

Consent will be sought from participants for the central coordinating team to contact a personal legal representative in the event they become incapacitated and are unable to provide information during the six-month follow-up. Similarly, the legal representative may also be contacted if the participant becomes uncontactable during their participation in the trial. If there is no suitable personal legal representative, or the participant is not willing to have such a person approached, then they can still participate in the trial and their wishes will be noted in their hospital notes and CRF. If requested, a more detailed information sheet will be provided. Potential participants will be given as long as they need to consider consent. It will be explained to the potential participant that this is an emergency treatment, with a potentially small therapeutic window.

If the patient is unable to write (e.g. dominant hand weakness, dyspraxia, ataxia), witnessed verbal consent (or a mark made by the participant with intent to sign) may be recorded on the consent form by someone unconnected with the study.

Patients unable to give consent

The ability of a patient to give consent will be determined by the treating stroke physician. If a patient is incapacitated from the stroke (e.g. confusion, reduced consciousness, dysphasia, reduced consciousness), the following procedure will be followed:

Personal legal representative available

The investigator (or nominee) will approach the patient's relative (or other personal legal representative such as partner or close friend) who is able to represent the patient's views, including any known views of the patient about trial participation, considering the clinical situation and emotional distress and provide pictorial information about the trial. If requested, a more detailed information sheet will be provided, and further information will be provided upon request.

The investigator or nominee will explain to the participant's personal legal representative that the patient will receive the usual care for ICH and may also receive treatment with mannitol in addition to

usual care. It will be explained that this study aims to test whether a larger trial could help to improve treatment for ICH. The investigator or nominee will also seek consent from the personal legal representative for the central coordinating centre to contact them at Day-180 to provide follow-up data on behalf of the participant, if the participant is unable to provide the information themselves. Consent from the legal representative for central storage of their contact details and their involvement in the trial will also be sought. If consent is given, these details will be stored in a secure, encrypted, password-protected database linked to the participant number, enabling the follow-up to be done centrally.

The consent form will be signed and dated before the patient is enrolled. If the relative or representative objects to the inclusion of the patient into the trial, the patient will not be enrolled. If a relative or representative is not physically available but happy to speak on the phone, the same procedure will be followed but the printed paper consent form will be countersigned by a witness unconnected with the study (an independent doctor or nurse)and signed by the relative as soon as they arrive to the hospital. If the relative is unhappy to speak on the phone or unable to decide, the patient will not be enrolled. (Figure 2). The definition of a personal legal representative in England, Wales and Northern Ireland is 'a person not connected with conduct of the trial who is suitable to act as legal representative by virtue of their relationship with the adult and willing to do so'. The definition of a personal legal representative in Scotland is 'any guardian or welfare attorney who has the power to consent to the adult's participation in research'. If there is no such person, the adult's nearest relative is defined in section 87(1) of the Adults Incapacity (Scotland) Act 2000.

Personal legal representative not available
If an eligible patient lacks capacity and if no relative is available, the investigator will approach an independent doctor (unconnected with the trial), provide them with the legal representative information sheet and ask if they would be willing to act as the patient's professional legal representative, and if appropriate, obtain their written consent for patient inclusion into the trial using the legal representative consent form. If a doctor unconnected with the study is not available, the patient will not be enrolled.

If possible, full informed written consent will be obtained from the patient or their personal legal representative as soon as practically possible (within 72 hours). The participant's decision to withdraw will overrule the decision of the personal or professional legal representative.

The requirements of the relevant ethics committee will be adhered to at all times. Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form, which will be signed by the participant, or relevant personal or professional legal representative.

Assessment through telemedicine

Telemedicine is already in place in many hospitals and increasingly expanding to out-of-office hours (often standard of care in many stroke services and particularly during the Covid-19 pandemic). Where the patient is being assessed and treated via telemedicine by a member of the medical team who is appropriately trained and listed on the delegation log, the process of consent is as above, and the printed paper consent form will be countersigned by a witness unconnected with the study. The paper consent form will be signed by the investigator upon arrival to their hospital site. If the patient does not wish to decide by telemedicine, they will not be enrolled. This process was successful in the large TICH-2 trial (Ref: ISRCTN93732214) and DASH trial (Ref: ISRCTN 67038373).

7.3 Randomisation

Participants eligible for inclusion and for whom consent has been obtained will be randomised centrally through the internet, using a secure randomisation system via an electronic database.

Patients will be randomised 1:1:1 to one of three groups:

- Arm 1: Standard care plus 1 g/kg 10% single dose mannitol infusion at 10ml/min
- Arm 2: Standard care plus 1 g/kg 10% mannitol at 10ml/min followed by a second dose 1 g/kg repeated at 24 hours
- Arm 3: Standard care alone

Randomisation will be in real time over a secure internet site with minimisation on prognostic factors including age, time since stroke onset, limited GCS and visual estimate of maximum haemorrhage diameter. In the event that the trial website cannot be accessed or server failure, the investigators should follow the university working practice document for computer system disaster recovery, which will allow the participant to be randomised following standard operating procedures. This document will be given to the PI at participating sites.

7.3.1 Method of implementing the allocation sequence

The unpredictable allocation sequence will be generated and will be programmed into the computerised randomisation system. The research team at each site will conduct the randomisation via secure logins to the web-based system. Randomisation using a minimization algorithm and release of allocation only after enrolment, consent and baseline data collection will ensure allocation concealment.

7.4 Blinding and unblinding

This trial will compare two different dosages of mannitol versus standard care, including monitoring of participants before, during and after treatment, collection of key clinical assessments (Day 5±2days, GCS and NIHSS) and presence or absence of adverse effects. So, it is not feasible for participants and researchers/investigators to be blinded. Clinical staff preparing and administering the IMP's will also not be blinded to treatment allocation. However, follow-up assessments and adjudication of brain imaging will be conducted centrally by assessors blinded to randomisation and treatment allocation.

As this is an unblinded trial, code-breaking will not be required. If some contra-indication to mannitol develops after randomisation (e.g. anuria or severe congestive cardiac failure), the trial treatment should be stopped. In order to minimise bias that could be introduced through knowledge of which treatment the participant has received, unblinded staff will be kept to a minimum and will be asked not to reveal treatment allocation to anyone.

The Chief Investigator and sponsor shall be informed immediately (within 24 hours) of any serious adverse events and the Chief Investigator shall determine the seriousness and causality in conjunction with any medical practitioners.

7.5 Trial procedures and assessments

Assessments	**Screening**	**Baseline (Pre-treatment, Day 0)**	**During infusion (Arms 1 and 2 only) (Day 0-1*)**	**Follow-up (Day 1-2)**	**Follow-up (Day 5±2 days)**	**Discharge or Day 28 (whichever is sooner)**	**Day 180 ±7 (telephone or postal interview, blinded central follow up)**
CT scan	X[1]				X[3]		
Clinical assessment	X[2]	X[2]		X[2]	X		
Consent	X						
Screening for eligibility	X	X					
Demographics and medical history	X						
Concomitant medication check	X			X			
Pregnancy test	X[5]						
Randomisation	X						
FBC[7], CRP[7], and Biochemistry (U&E incl. Na and e-GFR)	X	X		X		X	
Serum osmolality				X			
Blood pressure	X	X	X[4]	X[4]			
Intravenous 0.9% saline			X**	X**			

Assessments	**Screening**	**Baseline (Pre-treatment, Day 0)**	**During infusion (Arms 1 and 2 only) (Day 0-1*)**	**Follow-up (Day 1-2)**	**Follow-up (Day 5±2 days)**	**Discharge or Day 28 (whichever is sooner)**	**Day 180 ±7 (telephone or postal interview, blinded central follow up)**
Monitoring of urine output[Π]			X	X			
mRS / GCS / NIHSS	X			X[9]	X[9]		X[6]
Barthel Index							X
DNACPR status					X[8]		
EuroQOL (EQ5D)							X
TICS-M							X
ZDS							X
Adverse events	X	X	X	X	X	X	
SAE's[¶]	X	X	X	X	X	X	X
Mortality / Participant status	X	X		X	X	X	X

mRS: modified Rankin scale; SAE: serious adverse events; TICS-M: Telephone Interview for Cognition Status.

*including those randomised to 1 g/kg 10% mannitol at 10ml/min followed by a second dose 1 g/kg repeated at 24 hours

** Participants should receive 0.9% intravenous saline if systolic BP reduces to ≤ 90 mm Hg

[¶] All SAE's will be collected until day 28, and fatal SAE's and safety outcome events (thrombophlebitis hyper/hyponatremia; pulmonary oedema; hypotension; renal impairment) will be collected until day 180

[1] Routine pre-enrolment clinical scan for index stroke

[2] Routine clinical assessment

[3] Additional scan for oedema volume, haematoma size/volume, maximum diameter, midline shift, hydrocephalus

[4] Blood pressure should be checked before the infusion, during the infusion and again on completion of the infusion for Arms 1 and 2. Additional blood pressure will be performed as clinically indicated. Blood pressure should be checked on two occasions 5 minutes apart on the same arm at each time point and the mean of the two results is used for the final readings

[5] Pregnancy testing will be performed prior to selection in all women of child-bearing potential (i.e fertile, following menarche and until becoming post-menopausal unless permanently sterile). Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy

[6] mRS only

[7] Collected as part of patients routine testing

[8] Checked for duration of patient admission

[9] GCS and NIHSS only

[π]Monitoring of urine output will be according to local clinical practice and may include placement of a urinary catheter. If a catheter is placed, it will be removed after treatment

7.5.1 Schedule of assessments

Clinical assessments

Patients will be assessed clinically at baseline (history, examination, investigations, diagnosis) in line with local clinical practice (e.g. Accident and Emergency department or on the Hyper-acute/Acute Stroke Unit), and pre-infusion (day 1), and end of treatment (day1-2) for Arms 1 and 2.

Participants will be assessed face-to-face before treatment (pre-treatment day 1) and follow-up post-treatment (Day5±2 days). See Trial Flow Chart and section 7.5 for details.

Laboratory analyses

All participants will have blood tests taken as part of routine clinical care at the time of presentation whether or not they go on to participate in the trial. Blood samples will be labelled and analysed locally at each hospital site in accordance with local practice, to comply with the 2018 Data Protection Act. Each participant in Arm 1 and 2 will have one blood test for urea and electrolytes and serum osmolality after the infusion and the results will be made available to the treating clinical team. Participants in Arm 2 will have a further blood test after the second infusion. See Trial Flow Chart and section 7.5 for details. Additional blood tests can be performed by the clinical team as clinically indicated. Once analysed, samples shall be destroyed as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

Neuroimaging

All participants will have a diagnostic CT head/brain scan as part of routine clinical management prior to enrolment (all acute stroke patients have a CT scan performed on admission to hospital) and repeated at day 5 (±2 days) after treatment. If a participant has any additional clinically indicated imaging (e.g. due to clinical deterioration, decompression of haematoma), the scan should be submitted to the trial coordinating centre. The feasibility of measuring change in oedema volume and proof-of-concept (i.e. whether mannitol affects cerebral oedema), will be analysed centrally by assessors blinded to treatment allocation. Scans will be adjudicated centrally by an expert neuroradiologist blinded to treatment assignment and follow-up imaging, using assessments updated from ENOS, TICH-2 and RIGHT-2 trials.(15-17)

Follow-up

Follow-up will be performed at day 180 after the stroke, by blinded members of the central research team, via telephone in the first instance or as a postal interview and is standard practice in stroke trials.(15, 17, 33)

Telephone follow up will allow assessment of cognition and other outcomes, however discussions with stroke survivors have revealed that they find communication by post less intrusive. In that situation, postal follow up will be used.

If a participant is not contactable after a certain period by three telephone attempts, the participant's nominated legal representative will be contacted to provide the information on their behalf. If this call is unsuccessful, a postal follow up will be sent to the participant's home address for completion. If the postal questionnaire is not returned, we will check patient status again with their GP. If the participant's vital status is still confirmed as alive, then contact with the participant will be attempted one final time to provide the information. If contact is unsuccessful then they will be listed as lost-to-follow-up.

The Follow-up forms will capture how this data was completed and who completed this. This is standard practice in stroke trials and several large trials have shown this to be feasible.

Participants will be asked to respond to individual components assessing dependency (mRS), disability/activities of daily living (BI), cognition (TICS-M), ZDS, quality of life (Health Utility Status derived from EQ-VAS, Euro-QOL), mood (Zung Depression Scale) and patient disposition.(34-37) It is planned for these to be replicated in the feasibility and definitive trial. Moreover, face-to-face follow up at the recruitment site could be subject to bias in an open design, and face-to-face follow-up could increase the risk of potential exposure to Covid-19.

The researchers will not contact the participant or their family directly at day 180; they will first contact the participants General Practitioner (GP) or obtain information through the Medical Research Information Service (MRIS), at the NHS Information Centre to check their health status. Permission to contact the GP and for central follow up at day 180 will be sought at the time of consent.

If the participant lacks capacity or is unable to answer some questions, a relative/friend/carer may respond on the participant's behalf.

7.6. Withdrawal Criteria

The investigator or their nominee shall emphasise that consent regarding trial participation may be withdrawn at any time without affecting the quality or quantity of their future medical care or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be performed before informed consent has been obtained.

<u>Withdrawal from treatment</u>

Participation in this trial is voluntary and participants may withdraw from receiving treatment at any point without giving a reason. The study medication may be stopped at any time by the investigators or the treating clinician if deemed in the patient's best interest. Treatment with mannitol (one dose /second dose depending on randomisation to Arm A or B) will be in addition to 'best medical care'. Follow-up will continue unless participants indicate that they wish to withdraw from the whole trial.

Removal of participants due to adverse events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the investigator. In the event that treatment is not complete due to the adverse event, they will remain in the trial and follow-up information (day 180+/-7) will be collected. However, the participant may wish to withdraw from any trial-related activities at any stage without giving a reason, and this decision will be respected.

Where possible, reasons for withdrawal will be collected, as one of the primary feasibility outcome measures for the study.

8. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT

8.1 Product Characteristics

Intravenous mannitol (Mannitol 10% solution for Infusion BP, Baxter Healthcare Limited PL 00116/0367)
Mannitol 10% is a licensed product and a summary of the product characteristics is available.(38)
1g/kg of 10% intravenous Mannitol solution will be infused at 10ml/min according to body weight (see infusion protocol in section 8.3). The administration set will include a final in-line filter because of the potential to form crystals. The infusion will be administered under aseptic precautions through a large peripheral intravenous cannula. Detailed instructions will be provided in the accompanying infusion set and administered by clinical staff in accordance with local policy.

8.2 Legal status of the drug

Prescription only medicine (POM).

In line with the SmPC (Baxter. Mannitol 10% solution for Infusion BP SmPC. [last reviewed 28 March 2017]. Available from https://www.medicines.org.uk/emc/product/1839), the current licence for use in the European Union includes 'Reduction of intracranial pressure and cerebral oedema, when blood-barrier is intact'.

8.3 Summary of Product Characteristics (SmPC)

Baxter. Mannitol 10% solution for Infusion BP SmPC. [last reviewed 28 March 2017]. Available from https://www.medicines.org.uk/emc/product/1839

This will be checked at regular intervals throughout the trial and any updates will be notified to sites via an amendment.

8.4 Supply, packaging and labelling

Standard NHS supplies will be used.

8.5 Dosing and treatment regimen

Providing the patient meets the inclusion criteria, they will be randomly assigned to either:

- Arm 1: Standard care plus 1 g/kg 10% single dose mannitol infusion at 10ml/min
- Arm 2: Standard care plus 1 g/kg 10% mannitol at 10ml/min followed by a second dose 1 g/kg repeated at 24 hours
- Arm 3: Standard care alone

Participants randomised to Arm 2, to receive the second dose at 24 hours will receive mannitol only if the serum osmolality is <320 mOsm/Kg and sodium <160 mEq/L.

The following infusion protocol has been developed with input from critical care physicians and pharmacists:

Weight (kg)	**Dose (based on 1g/kg)**	**Volume and rate of Mannitol 10% solution (infuse at 10mL/min = 600mL/hour)**
40	40g	400mL over 40mins
45	45g	450mL over 45mins
50	50g	500mL over 50mins
55	55g	550mL over 55mins
60	60g	600mL over 60mins
65	65g	650mL over 65mins
70	70g	700mL over 70mins
75	75g	750mL over 75mins
80	80g	800mL over 80mins
85	85g	850mL over 85mins
90	90g	900mL over 90mins
95	95g	950mL over 95mins
100	100g	1000mL over 100mins
*There is no formal guidance about dosing in extremes of bodyweight. Review risk / benefit with fluid balance and comorbidities. Infusion time can be extended if concerns re: fluid overload.		

The infusion protocol was developed with input from the pharmacy department, Nottingham University Hospitals NHS Trust. We believe that this protocol which we have developed is simple, easy to implement and this research will assess the feasibility and acceptability to participants and researchers for wider dissemination and implementation in a definitive trial within the NHS.

We believe that it is important to compare two mannitol groups versus standard care to assess whether there is any indication of a clinical and/or radiological difference in response, which could be important in the design of a definitive trial.

Justification of dose

We have chosen 1g/kg as it has been tested before and not exceeded in a single dose in previous trials. Moreover, a large number of UK hospitals have confirmed that 1 g/kg is commonly used as a single dose (email communication, Department of Pharmacy, Nottingham University Hospitals NHS Trust). A direct comparison of previous studies shows that for an average patient weighing 70 kg, previous doses of mannitol varied from 20-120 g and this proposal is well within this range at 70g/24 hours.

Evidence suggests that higher doses could be effective (i.e. 2g/kg) but is not definite. Treatment with mannitol is associated with side effects so with input from critical care physicians and local pharmacists, we have incorporated safety checks (blood tests, blood pressure monitoring, monitoring of urine output) into the trial protocol.

Another rationale for 10% mannitol is that it is unlikely to crystallise and is easy to store on a ward. As a result, a large number of UK hospitals (including sites which have expressed interest in this trial) have switched to using 10%. There is no guidance on which concentration of mannitol is more effective(18, 39) but 10% is readily available, may have less side-effects(18) and we anticipate that the infusion protocol will be simple and easy to implement.

Participants will receive 0.9% saline if systolic BP reduces to $\leq$ 90 mm Hg. Using 0.9% saline in this setting is not known to worsen cerebral oedema.(40)

Urine output will be monitored during the infusion and on completion of treatment. A urinary catheter is not mandatory but if inserted, should be removed after treatment unless there is another reason according to the treating clinician.

Placebo

There is no placebo for this trial. All participants randomised to standard medical care must be managed according to local acute stroke care protocols. Best medical care will be in accordance with national guidance(1) and include administering nutrition, medications and application of intermittent pneumatic compression stockings. Treatments which have not shown to be effective including corticosteroids, glycerol or hypertonic saline should not be administered. Other experimental drugs should not be administered.

8.6 Drug supply and handling

Hospital sites should source their own supplies of mannitol, from standard hospital supplies. Mannitol 10% solution for infusion is supplied as a pre-mixed infusion and should be stored at room temperature (15-25°C). Every attempt should be made to avoid sudden shock of the product (e.g. dropping) to prevent crystallisation. The infusion should be visually inspected before administration to ensure it is free from particles or crystallisation and suitable for use and be administered via an infusion pump using a giving set with an in-line filter (15 micron) as in section 8.5. At the end of each infusion, the bag, tubing, and intravenous line should be visually inspected.

As in the case of previous stroke trials, medication may be kept on the relevant ward or department to be accessible and allow treatment to start promptly as soon as the patient is randomised. The IMP will be kept in a secure, limited access storage area, such as a clinical room used for other drug storage and/or preparation. The treatment will be kept as ring fenced trial medication with study specific labelling.

Once a patient is randomised to mannitol, treatment should be prescribed on the patient's drug chart or on the electronic prescribing and medicines administration system, referenced as part of the MACE-ICH trial. Treatment should be recorded as having been administered to that patient on the medicines prescribing and administration chart, with batch number and expiry recorded in the CRF as per below drug accountability section. If for any reason the study drug is stopped (e.g. intravenous cannula change), treatment must be commenced as soon as possible and continued. In the event of the infusion being stopped for >15 minutes during the infusion or if more than 10% of the infusion is not administered, the reason should be recorded in the CRF.

Side effects

Common side effects with mannitol include cough, headache, and vomiting. The following are reported as side effects with intravenous use but the frequency is not known: arrhythmia; asthenia; azotemia; chest pain; chills; coma; compartment syndrome; confusion; congestive cardiac failure; dry mouth; electrolyte imbalance; fluid imbalance; hyperhidrosis; hypersensitivity; hypertension; lethargy; metabolic acidosis; muscle complaints; nephrotic syndrome; neurotoxicity; peripheral oedema; rebound increase in intracranial pressure; renal impairment; rhinitis; seizure; thirst; urinary disorders; blurred vision.(38)

8.7 Concomitant and rescue medications and treatment

The intervention (mannitol) will be given in addition to standard medical care. There are no prohibited concomitant treatments, but care should be taken if administering nephrotoxic drugs. No other experimental drugs should be administered.

Treatment Adherence

This is a feasibility trial and adherence will be assessed by examining the participants' drug chart and record of evidence of treatment administration. Adherence will be recorded on the trial's case report forms (CRF) at the

end of treatment. If a decision is made for the participant to have surgical intervention for ICH (evacuation of haemorrhage, insertion of extra ventricular drain), attempts should be made to continue the IMP as far as possible.

Drug accountability
Standard hospital supply will be used. This will be ringfenced and over labelled with an Annexe 13 compliant label by the local pharmacy under the exemption to Regulation 37 of SI2004/1031.

Pharmacy will maintain accountability to record the issue of trial stock to the ward and the return of any unused stock to pharmacy. The research team will record administration of treatment to the participant. The administration of the IMP will be recorded on each participant's CRF. The details will include dates, quantity, batch/serial numbers, expiry dates and trial number assigned to each participant. The investigator(s) will maintain records that document adequately that participants were provided with the correct medication.

Any partially used drug will be disposed of in line with local procedures for intravenous prescription only medicines at the point of care.

Management of overdose
No specific antidotes for the IMP's are available. The IMP's will be administered by qualified nursing staff at each hospital, so overdose is not anticipated.

Urgent safety measures
Any urgent safety measure(s) relating to the trial's IMP will be communicated to the Medicines and Healthcare products Regulatory Agency (MHRA) immediately. They advise that sponsors phone the MHRA Clinical Trial Unit and discuss the event with a safety scientist. The sponsor will notify in writing within three days of action taken. The action will include the actual event, measures taken, justification of why the measures were taken and a substantial amendment.

Participant monitoring and management
We anticipate most participants to be treated on stroke units where ICP monitoring is not routine but assessed using clinical signs (e.g. GCS) or surrogate markers (e.g. mass effect on CT). Critical care experts do not disagree with this approach(39) and one trial showed no difference in mortality for treatment of cerebral oedema based on neurological signs compared to ICP monitoring.(39)

The first few days are critical so the level of nursing staff in stroke units per patient are higher compared to other medical wards and similar to level 2 critical care units.(41) Stroke nurses are trained to set up and administer medications (e.g. intravenous antihypertensives, thrombolytics, mannitol)(1, 41) and perform assessments (e.g. GCS, NIHSS) so patients receiving treatment or those at risk of deterioration following ICH,

before or after neurosurgery are routinely monitored and escalated as appropriate. We therefore anticipate any potential risks to participants to be mitigated by the monitoring and environment described.

All participants entered into the trial, whether allocated to mannitol or standard medical care, must be managed according to local acute stroke care protocols. Such protocols are not specified by this trial, but will be in accordance with national guidance(1).

9. PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. 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 either the reporting medically qualified professional or the Sponsor 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 participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

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

When considering co-enrolment with other interventional studies, the potential risks of combining these interventions with mannitol will be discussed by the TMG. The Pharmacy Lead for Stroke will be consulted for their opinion on pharmacodynamics, pharmacokinetics and the length of a minimum wash-out period. Similar considerations will be made for other non-CTIMP interventions. A co-enrolment agreement between the Sponsor of both trials will be signed. Should a safety event be experienced by a co-enrolled participant, this will be reported and adjudicated according to protocol. A record of co-enrolled participants will be made available to the Data Monitoring Committee of each co-enrolled study.

When deciding an AE's causality, the PIs at each site will assess this in the first instance, and it would be reported to both studies in accordance with the reporting criteria for each study - the (S)AE would then be reviewed by the CI / CIs if reported to both studies to confirm causality. For MACE-ICH, this is also subject to independent medical review.

9.2 Operational definitions for (S)AEs

An abnormal blood result, vital sign or ECG is not considered Adverse Event unless one or more of the following are present:

- meets the criteria for a serious adverse event (SAE)
- needs corrective treatment
- considered by the investigator to be clinically significant

An AE does not include:

- a medical or surgical procedure, but the condition which led to the procedure will be an AE
- previous disease or condition present or found at the start of the study but did not worsen

- where an untoward medical occurrence has not happened (e.g. admissions for prescheduled cosmetic elective surgery, social admissions)
- overdose of concomitant medications with no signs or symptoms
- disease or disorder being studied or sign or symptom of the disease or disorder but no more severe than expected for the participant

All adverse events including during infusion and post-treatment will be collected. All adverse events will be assessed for seriousness, expectedness, and causality. Serious adverse events are common in haemorrhagic stroke. For a full list of expected SAE's which are expected following the administration of mannitol, and would be indistinguishable from the clinical manifestation of severe haemorrhagic stroke, that are not subjected to expedited reporting, investigators should refer to Appendix 2.

The elimination half-life of mannitol is approximately 2 hours, longer when renal failure is present, so adverse events occurring within the first 28 days after treatment will be assessed for seriousness, expectedness, and causality. In addition, fatal SAE's and safety outcome events (thrombophlebitis; hyper/hyponatremia; pulmonary oedema; hypotension; renal impairment) will be reported until day 180.

In all cases, AEs and / or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor within 24 hours of site becoming aware. These events may be discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation, or review of the participant medical records.

Causality

Treating investigators are responsible for all causality and seriousness evaluations of adverse events. The Chief Investigator is responsible for expectedness for seriousness evaluations for serious adverse events (SAEs), and may upgrade, but not downgrade, causality assessments:

Unrelated: a clinical event including, for example, laboratory result will be considered 'not related' to the trial treatment drug if it is not a reasonable possibility that the event has been caused by the treatment drugs. Factors which point to this assessment include but are not limited to the lack of a temporal relationship to the IMP administration or for which other drugs, chemicals, treatment, or disease provide a plausible explanation.

Possible: a clinical event including, for example, laboratory result with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals, or concurrent disease.

Probable: a clinical event, for example, including laboratory result with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but unlikely to be explained by other drugs, chemicals, or concurrent disease.

Definite: a clinical event, for example, including laboratory result with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but definitely not explained by other drugs, chemicals, or concurrent disease.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as 'possible', 'probable', or 'definite' is an Adverse Drug Reaction. All SAE's will be adjudicated independently for causality.
With regards to the above criteria, medical and scientific judgement shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events
Participants will be asked to contact the study site immediately in the event of an adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator and the Sponsor shall be informed immediately (within 24 hours) of any serious adverse events, and the CI shall review seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial, participant monitoring shall occur during the pregnancy and after delivery to ascertain related adverse events in the mother or the offspring.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual Development Safety Reports. SUSARs will be reported within the statutory timeframes to the MHRA, and REC as stated below. The Sponsor shall ultimately be responsible for the adverse event reporting.

The sponsor contact details for adverse event reporting are:
RDSAE@nuh.nhs.uk

9.3 Protocol Deviations and Violations

Protocol deviation
A protocol deviation is a change/divergence/departure from the protocol, which is unplanned, and does not result in significant consequences. This includes any deviation from the trial protocol that is not listed as a protocol violation. An example of a deviation is given below but this is not exhaustive. Protocol deviations to inclusion/exclusion criteria are NOT permitted and may be considered a serious breach.

The following example would constitute a protocol deviation: follow-up assessment is performed outside the specified time frame.

Protocol Violation

A protocol violation is a divergence from the protocol which is unplanned, and results in significant consequences, for example, by reducing the quality/completeness of the data, or impacts on the safety/rights/welfare of participants.

The following would constitute a protocol violation:

- Participant <18 years of age
- Randomisation >72 hours from onset of symptoms
- No haemorrhagic stroke at time of randomisation
- No brain imaging during index stroke
- Participant enrolled with mRS>4
- Known hypersensitivity to mannitol at the time of randomisation
- Participant enrolled with known severe concomitant illness
- Participant enrolled with known intracranial disease or pathology other than stroke
- Severe coma (GCS<5) at time of randomisation
- Decision already taken for palliative care at time of randomisation
- Female patient pregnant and lactating
- Participant enrolled when not meeting any other inclusion/exclusion criteria
- Failure to obtain consent
- Individual taking consent not authorised to take consent on delegation log
- Failure to comply with the treatment protocol for no particular reason
- Not completing SAE's when appropriate
- Failure to complete outcome assessments as appropriate
- Day 5± 2 days follow-up-- over 7 days past due date
- Day 28 follow-up- over 30 days after due date
- Day 180 follow-up- over 30 days before/after due date

All protocol violations should be reported to the Chief Investigator through the online electronic CRF. The Chief Investigator will inform the Sponsor if a protocol deviation or violation has an impact on participant safety and trial integrity. The Sponsor will advise on measures to address the occurrence, which may include reporting of a serious breach, internal audit of trial data and referral to the trial committees.

9.4 Radiation Exposure

Details of diagnostic or therapeutic ionising radiation
The participant will receive a routine clinical CT head scan at the time of presentation with stroke according to the local imaging protocol, and as part of this study an additional non-contrast single run CT head scan at the end of treatment. The CT scan at the time of stroke is part of routine clinical care whether or not the patient participates in the trial. For patients who are randomised into the trial, the results will be used as baseline data. If patients have additional scans performed for clinical reasons, we will ask for permission to collect copies of these as part of the study.

Trial Procedures
Single run, non-contrast CT head 5±2 days post-treatment.

Details of radioactive materials and dose
The study requires exposure to ionising radiation which are detailed in the protocol. All of the exposures are additional to routine clinical care. The total protocol dose is 2 mSv. This is equivalent to 10 months of natural background radiation in the UK. Ionising radiation can cause cancer which itself manifests after many years or decades. The risk of cancer as a consequence of taking part in this study is 0.01%, which is very low. For comparison, the natural cancer incidence in the general population is about 50%.
The protocol lists a CT head at screening; however, this is from standard care and will be undertaken prior to participation in this study and is therefore not considered a research exposure.

Scan assessment
The scan itself takes about half a minute and does not involve any injections. The scan uses X-Rays, which in large amounts can be harmful, but for this extra CT head the additional risk to the participant from the scan has been judged to be small.

The objective of the exposure is to assess the extent of the haemorrhage and oedema in the brain to see whether it has got worse (expansion) or better (smaller) following treatment.

An alternative would be a Magnetic Resonance Imaging (MRI) scan, but this takes longer, and many patients are unsuitable or unable to tolerate it due to claustrophobia.

The procedure for CT and any doses in lay terms are explained in the participation information sheet.

10. ROLES AND RESPONSIBILITIES AND TRIAL MANAGEMENT

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10.1 Principal Investigator (PI)

The role of the principal investigator will include checking for AEs and ARs post-treatment during follow-up day 1-2.

1. Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor and CI within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with the Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

10.2 Chief Investigator (CI)

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality, and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs (this may be delegated to the Sponsor's independent medical monitor in conjunction with the CI).
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

10.3 Sponsor and Stroke Trials Unit (specifics are set out in the tripartite agreement between sponsor, STU, and CI).

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol
2. Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. 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.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.

8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

10.4 Trial Management Group (TMG)

The trial coordinating centre will be based at the Stroke Trials Unit (STU), University of Nottingham. The Trial Management Group (TMG) will include the chief investigator, trial statistician, senior clinical trial manager, trial manager and project staff based in the Stroke Trials Unit, University of Nottingham. The Chief Investigator has the overall responsibility for this study and shall oversee management.

The data custodian will be the Chief Investigator.

The Sponsor will be Nottingham University Hospitals NHS Trust and the trial will be coordinated by the STU with oversight from the Nottingham Clinical Trials Unit (NCTU). This will include management, data management, database development, maintenance of statistical analysis and reporting. The TMG will be responsible for day-to-day management of the trial. The TMG will be responsible for ensuring that the project milestones are achieved, meeting at least once a month throughout the duration of the trial.

10.5 Trial Steering Committee

A Trial Steering Committee (TSC) comprising lay members and independent academics will be convened and provide trial oversight. The TSC will meet regularly (in person, via Teams videoconference or telephone) at least 12 monthly until trial completion, and will perform the following:

- approve the protocol
- approve necessary changes to the protocol considering feasibility and practicality
- assess protocol compliance
- address issues raised by the coordinating centre and TMG
- receive reports from the Data Monitoring Committee (DMC)
- monitor ethical and regulatory standards
- advise if a definite trial is feasible
- ensure that the results are published

The full responsibilities and membership of the TSC will be detailed using the standard TSC charter.

10.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established and include an independent chair. The DMC will receive safety reports every six months or more frequently if requested and perform unblinded reviews of safety data.
The standard Sponsor DMC charter will be prepared containing membership, terms and conditions and full details of stopping guidelines.

Collaborators and all other others associated with the trial, may write to the DMC through the trial office, to draw attention to any concern they may have about trial interventions, or any other relevant issues.

10.7 Informed Consent and Participant Information

This trial plans to recruit acute haemorrhagic stroke patients. We anticipate that a number of participants will not have sufficient capacity to consent to the study. Given the nature of stroke, we feel it would be unethical to exclude participants who are unable to consent to the study, particularly where they have expressed prior willingness to be involved in research should they lose capacity. Therefore, for those individuals who do not have capacity, we plan to consent a legally authorised representative (close relative, friend, or carer- personal, or medical professional un-associated with the trial) who is able to express the views of the participant and consent on their behalf to the study.

The process for obtaining participant informed consent will be in accordance with REC guidance, GCP, and any other regulatory requirements that might be introduced. The participant or legally authorised representative (personal or professional) will be allowed to consider the information and have the opportunity to question the investigator or their nominee (as detailed on the delegation of authority and signature log) to decide whether they will participate in the study. The investigator or their nominee (as detailed on the delegation of authority and signature log) and the participant or legally authorised representative (personal or professional legal representative) shall both sign and date the Informed Consent Form before the person can participate in the trial.

The decision regarding participation in the trial is entirely voluntary. The investigator or their nominee shall emphasise that consent regarding trial participation may be withdrawn at any time without affecting the quality or quantity of their future medical care or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be performed before informed consent has been obtained.

A copy of the signed and dated informed consent form will be given to the participant and the original will be retained in the Trial Master File (TMF). A second copy will be filed in the participant's medical notes and a signed and dated note made in the hospital notes that informed consent was obtained for the trial.

The investigator will inform the participant of any relevant information that becomes available during the course of the trial and will discuss whether they wish to continue with the study. If applicable, the participant will be asked to sign the revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

10.8 Duration of the Trial/Study and Participant Involvement

Participant Duration

This trial is planned to recruit participants for 14 months. The participants involvement in the trial will last for 180(±7) days, from randomisation (day 0) until final follow-up at Day 180(±7 days).
Enrolment will begin when the study has obtained full regulatory approval and cease when the final participant has been followed up.

End of trial

For recruited participants, their involvement in the trial will terminate when the trial ends, following the 180 (±7)-day follow-up, or death, whichever occurs first. The end of the trial will be the database lock following completion of the last 6-month follow-up of the last participant.
The Chief Investigator (or nominee) will notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion.

Criteria for terminating trial

The trial may be terminated by the Trial Steering Committee (TSC), for example, on the advice of the DMC, the sponsor, or funders if there is overwhelming evidence of major safety concerns, new information or issues with trial conduct (e.g. poor recruitment as shown in the progression criteria above, loss of resources). The trial may be stopped in one site due to unacceptable performance in recruitment and/or failure to comply with protocol.

10.9 Removal of participants from therapy or assessments

Withdrawal from treatment

Participation in this trial is voluntary and participants may withdraw from receiving treatment at any point without giving a reason. The study medication may be stopped at any time by the investigators or the treating clinician if deemed in the patient's best interest. Treatment with mannitol (one dose /second dose depending on randomisation to Arm A or B) will be in addition to 'best medical care'. Follow-up will continue unless participants indicate that they wish to withdraw from the whole trial.

Missing data and loss to follow-up

All attempts will be made to minimise missing data at baseline and to contact potential participants lost to follow-up. Hospital databases, records from general practitioner and details of third persons given by the participant will be checked to determine whether the participant is alive, health-status and new contact details. If a participant is not contactable after a certain period by three telephone attempts, the participant's nominated legal representative will be contacted to provide the information on their behalf. If this call is unsuccessful, a postal follow up will be sent to the participant's home address for completion. If the postal questionnaire is not returned, we will check patient status again with their GP. If the participant's vital status is still confirmed as alive, then contact with the participant will be attempted one final time to provide the information. If contact is unsuccessful, then they will be listed as lost-to-follow-up.

Withdrawal from trial

Participants may be withdrawn from the trial either at their own request, or that of the personal or professional representative. Participants will be made aware that this will not affect their future care. If a participant withdraws from the trial, they will not have any further follow-up. Participants will be made aware that all data collected up until that point may still be used for final analysis. In the event of discontinuation or withdrawal from the trial the reason will be recorded on the Case Report Form (CRF) where possible. Withdrawn participants will not be replaced.

Removal of participants due to adverse events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the investigator. In the event that treatment is not complete due to the adverse event, they will remain in the trial and follow-up information (day 180+/-7) will be collected. However, the participant may wish to withdraw from any trial-related activities at any stage without giving a reason, and this decision will be respected.

11. STATISTICS AND DATA MANAGEMENT PLAN

Statistics

Methods

A medical statistician blinded to treatment allocation will support analysis using a validated software package. A pre-planned statistical analysis plan (SAP) will be confirmed before the database is locked and release of randomisation codes. The results will be reported as recommended by the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

This is a feasibility study and analysis will be using descriptive statistics. Continuous variables will be summarised using means and standard deviations or medians and interquartile ranges depending on distribution. Whilst some variables will be listed by treatment groups, any analysis would be exploratory.

It is planned for this feasibility study to be undertaken at Nottingham University Hospitals NHS Trust in partnership with nine other acute NHS trusts over 24 months and we will assess the feasibility of rate of recruitment, ability to randomise, administering treatment and follow-up. We anticipate that recruiting at least 45 patients with a high rate of compliance and follow-up data would support the basis for a further grant application to undertake a definite trial. Broad recruitment criteria have been developed to allow inclusivity and mitigate the risk of failing to recruit. Practical issues will be addressed to minimise risk of a future trial from failing.

Sample size

Given the primary aim of this trial is feasibility, which includes the objective of assessing rate of recruitment, a formal sample size calculation is not appropriate. Stroke trials managed by Stroke Trials Unit Nottingham have recruited participants with similar profile to MACE-ICH (ENOS and RIGHT-2 combined-35%; TICH-2-43%; TICH-2: n=1664 within 8 hours from 94 UK hospitals; 0.37 participants/month/site), so we anticipate 45 participants to be recruited from ten hospitals, treated and followed-up within 2 years to demonstrate feasibility.
Early neurological deterioration (within 48 hours) was observed in ~15% of participants in TICH-2 and it is postulated that ICH expansion, oedema or both could have contributed.(42) So, such patients would also be eligible.

Depending on the final sample size calculation for the definitive study, the number of centres and recruitment period could be determined using the information from the rates and recruitment patterns in the feasibility study. Information about set-up times for hospital sites will inform projections for a larger study.

Bias

The following measures will be undertaken to reduce bias:

- Central randomisation with real-time validation using an internet-based database
- Blinded central adjudication of radiological, clinical and safety outcomes
- Analysis by intention-to-treat
- Follow-up assessors blinded to treatment
- Trial registered and statistical analysis plan (SAP) finalised prospectively
- Analysis and reporting of all outcomes
- Training of research staff in protocol and processes

Assessment of efficacy

As this is a feasibility trial of testing potential treatment of cerebral oedema in acute intracerebral haemorrhage, there is no formal assessment of efficacy. We anticipate that a significant proportion of participants with a clinical profile of MACE-ICH would be at high risk of acute neurological deterioration and death. So, a positive effect with mannitol through reducing cerebral oedema could directly impact survival and reduce complications from reduced consciousness (e.g. pneumonia). Even a modest difference using a drug, which is easy to administer and inexpensive would represent a worthwhile benefit to patients and their carers. Indeed, trials of major haemorrhage in trauma patients and surgery for life-threatening cerebral oedema in ischaemic stroke have used death as primary outcome.(43, 44) All feasibility and secondary outcomes will be summarised using descriptive statistics and include mechanistic outcomes to provide added value.

Assessment of safety
Serious adverse events will collected as detailed in sections 9.1-9.2 and will be summarised using descriptive statistics.

Procedure for missing, unused, and spurious data
Any unused data will be reported, with reasons in the final report after trial completion, and in any publication. Spurious and missing data will be reported, but not included in final analyses.

Definition of population analysed
All available data will be used including overall numbers of patients screened and eligible.
Where summaries by treatment group are provided, these will be based on intention to treat population, i.e. according to the treatment the participant was randomised to, with the exception of safety data.

A safety population will be defined to summarise the safety data in this study. Participants will be summarised according to the treatment received irrespective of randomisation.

Summaries of the proportion of participants who would form a per-protocol population in a larger trial, and reasons for exclusion from a per-protocol population will be provided, to allow future planning. No data will be summarised on this population.

12. DATA HANDLING

12.1 Data collection tools and source document identification

This section describes the procedures for the management and assurance of the data collected within the trial, throughout the lifecycle from CRF design through to publication of data, long-term storage, and data sharing. The Sponsors standard operating procedure will be followed for data management.

Case report forms (CRFs)

A bespoke database, tailored specifically for data collection in this trial and incorporating all CRFs, will be used by the trial coordinating centre and participating sites for all data entry. The database will only be accessible to authorised personnel with their own log-in username and password. Accessibility will be restricted to relevant sections of the database according to user roles and responsibilities but will allow access by more than one user at a time. Access will be granted to the Sponsor, trial monitors, auditors, and statutory inspectors on a read-only basis.

Each participant will be assigned a trial identity code number (centre numbers and randomisation), allocated at randomisation, for use on CRFs, other trial documents, and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or middle name initial when available) and age. The date of birth (dd/mm/yy) is entered into the database once for the use of data verification and is not visible when entering study data.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record, of the: participant's name, date of birth, local hospital number or NHS number, address, telephone number, relative/friend's contact details, and Participant Trial Number, to permit identification of all participants enrolled in the trial, so that follow-up may be performed. CRF access shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log'.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out, but not obliterated with correction fluid, and the correction inserted, initialled, and dated.

The Chief or Principal Investigator, or nominee, will sign a declaration to confirm accuracy of the recorded data.

Source Documents

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical charts, laboratory and pharmacy records, radiographs/scan reports and correspondence. A CRF may also serve completely as source data.

At each site, all documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Direct access to source data/documents

Direct access to the CRF, and all source documents including clinical progress notes and copies of laboratory and test results will be granted to authorised representatives from the sponsor, STU, host institution, and the regulatory authorities (e.g. MHRA), to permit trial-related monitoring, audits, and inspections.

12.2 Data Protection

The trial staff and investigators will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant ID number on the CRF and electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act, 2018 which requires data to be anonymised as soon as it is practical to do so. Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by username identifiers and passwords (encrypted using a one-way encryption method). Information about the trial in the participant's medical records/hospital notes will be treated confidentially in the same way as other confidential information. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

13. QUALITY ASSURANCE & INSPECTION

13.1 Insurance and Indemnity

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

13.2 Trial conduct

This trial will be conducted in accordance with the approved version of the protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures. The conduct of this trial will be subject to audit of the Trial Master File (TMF) for inclusion of essential documents; permissions to conduct of the trial; Trial Delegation Log; CVs of trial staff and training received; local document procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion/exclusion criteria, correct randomisation, timeline of assessments); adverse event recording and reporting; drug accountability; pharmacy records and equipment calibration logs.

Ongoing local monitoring and audit of the trial, its conduct and the data shall be carried out by the trial manager or where needed, a nominee of the Sponsor as set out in the UK Framework for Health and Social Care 2017 and Sponsor SOP RES-002 and SOP QMS-004. The audit report shall be made and forwarded to the Trial Steering Committee (TSC).

13.3 Trial data and quality control

Trial data will be monitored by the Trial Manager or where required, a nominee of the Sponsor for confirmation of informed consent; source data verification; data storage and data transfer procedures; local

quality checks and control procedures; back-up and disaster recovery of any local databases and validation of data manipulation.

Entries on CRF will be verified against source data. A sample of CRF's (10% or as per trial risk assessment and/or monitoring plan) will be checked on a regular basis for verification of all entries. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will require a full audit trail and justification.

13.4 Record retention and archiving

The Chief or Principal investigator will maintain all records and documents in compliance with GCP guidelines and the University of Nottingham Code of Research Conduct and Research Ethics regulations. Data collected during the course of the trial will be maintained for at least 7 years or longer by the chief investigator, if required. If the responsible investigator is unable to maintain the trial records, a second person will be nominated to take over the responsibility.

The Trial Master File and trial related documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived for 25 years, as per Good Clinical Practice Guidelines, at secure archive facilities in line with University of Nottingham SOPs. This archive shall include all trial databases and associated meta-data encryption codes. Access to the data is by written request to the Sponsor.

13.5 Discontinuation of the Trial by the Sponsor

The Sponsor reserves the right to stop this trial at any time for failure to meet expected enrolment goals, for safety or administrative reasons. The Sponsor shall take advise from the TSC, DMC and funder as appropriate.

13.6 Statement of Confidentiality

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files. Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researchers will discuss this with the Chief Investigator and where appropriate, report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, Nottingham University Hospitals NHS Trust, the REC, local R&D Departments, and the regulatory authorities.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Regulatory compliance, Research Ethics Committee (REC) review& reports

The trial will not commence before the protocol, consent forms, participant and GP information sheets are approved by the Medicines Health and Regulatory Authority (MHRA), Research Ethics Committee (REC) and the respective NHS Research and Development (R&D) departments. Should a protocol amendment be made that requires REC and MHRA approval, the changes in the protocol will not be implemented until the amendment and revised informed consent forms and participant information sheets have been reviewed and received approval from the REC, MHRA and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC and MHRA are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in full conformity with the Declaration of Helsinki, 2013, principles of Good Clinical Practice (GCP), Medicines for Human Use Regulations and the UK Policy Framework for Health and Social Care Research.

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. It will be the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the trial; if the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results.

14.2 Peer review

The background and the proposed protocol has been externally peer-reviewed. The feedback has been used to make the appropriate amendments. The amended protocol, Participation Information Sheet (PIS), consent forms have been reviewed by the study co-investigators for its scientific robustness and accuracy. The protocol has been reviewed by the R&D department and Sponsor (Nottingham University Hospitals NHS Trust).

14.3 Public and Patient Involvement

This trial which aims to test mannitol in cerebral oedema after acute stroke was presented to the Nottingham Stroke Research Partnership group comprising patients and their carers. They overwhelmingly supported the study objectives, trial design and research into this area. The feedback received has significantly influenced study design. The inclusion criteria have been broadened to reflect real-life presentation of patients to stroke units. The members also felt that all should be done to ensure potential participants are not to be denied access to the trial because they have no capacity. The group, all of whom are stroke survivors, would like the treating stroke physician to be able to enrol patients, acting as a professional legal representative where no personal legal representative is available at the time.

A group member (Philip Johnson) will be a member of the Trial Management Group and another member (Christine Knott) will be a lay member of the Trial Steering Committee. The Stroke Research Partnership Group will also help with dissemination of results.

14.4 Protocol compliance

All sites will have a site initiation visit before recruitment of patients. All the staff who participate in this trial will have training on the protocol. This will minimise any breaches in the protocol. Accidental protocol deviations can happen at any time. They will be documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

14.5 Notification of Serious Breaches to GCP and/or the protocol

The Sponsor will be notified immediately of any case where serious breaches to GCP and/or the protocol apply during the trial conduct phase. The Sponsor will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

14.6 Study finances

Funding source

This study is funded by NIHR RfPB project code 203080.

Participant Stipends and Payments

Participants will not be paid to participate in this trial.

14.7 Access to the final trial dataset

The Chief Investigator and principal investigators at participating sites will have access to the full dataset. It is envisaged that that dataset may be used for secondary analysis, and this will be mentioned in the trial consent form. All patient documentation will reflect the future use of these data in research and REC/HRA approval will be sought before any further research is undertaken.

Data generated as a result of this study will also be available for inspection on request of the Nottingham University Hospitals NHS Trust representatives, the REC, local R&D Departments, and the regulatory authorities.

15. PUBLICATION AND DISSEMINATION POLICY

15.1 Reporting, dissemination, and notification of results

The results of this trial will be published in peer-reviewed journals, or presented at local, national, and international stroke meetings. The report of the results will be in compliance with CONSORT recommendations. The focus will be to explain the feasibility of screening, assessing eligibility, ability to approach, randomise, administer mannitol for acute haemorrhagic stroke patients having or at risk of developing cerebral oedema and complete follow-up.
Our PPI representatives will lead on development and disseminating the results to public audiences. Updates on recruitment, trial progress and results will be communicated through regular newsletters, social media (e.g. Twitter) and on the internet (e.g. trial and NHS websites). We will share a plain summary of the results with the trial participants.
For each publication, the funding body will be acknowledged, and each author will disclose details of their own involvement.

15.2 Authorship eligibility guidelines and any intended use of professional writers

The trial results will be published by the named members of the trial team, on behalf of the MACE-ICH collaborative group. Members of the collaborative group will be listed in the publication, based on contribution. Any secondary publication may be published by individuals, but with appropriate approval and acknowledgement of the collaborative group. For each publication, the funding body will be acknowledged, and each author will disclose details of their own involvement. It is not anticipated that professional writers will be used to assist in manuscript preparation.

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SHORT TITLE/ACRONYM: MACE-ICH

17. APPENDICES

17.1 Appendix 1-Risk Assessment

vLOW ≡ Comparable to the risk of standard medical care

Risk with mannitol and mitigations

1. Unlicensed use of licenced medicine, unfamiliarity (e.g. giving at wrong rate, wrong route, miscalculation). Availability of equipment (pump, in line filters)
   - Mitigated by clear trial protocol, dosing tables. Expected clinical care within acute medical/stroke care environment.
   - Drug dose is for the most part within the licensed dose for lowering ICP (1.5-2g/kg)
2. Summary of Product Characteristics (SPC) lists a contraindication of '*Active intracranial bleeding, except during craniotomy'*.
   - This is likely to be due to the potential for rebound increase in ICP after stopping treatment. Good clinical practice will limit other risk factors for haematoma expansion (e.g. tight BP control, withdrawal / reversal of contributing medicines) and early imaging (in the case of neurological signs or symptoms suggestive of recurrent bleed) will identify and support management. Any difference between intervention and control groups will be reported and analysed.
3. Dose cap in elderly from SPC (50g total) likely to be exceeded
   - Careful patient screening and monitoring. Introduction of serum osmolality / Na monitoring / other U+E in trial protocol will help identify and limit repeat dosing.
4. Renal impairment
   - Monitoring as outlined (may be reversible if picked up early). Licenced preparation outlines cautions for co-administration with nephrotoxics and in pre-existing renal dysfunction – should be established part of GCP.
5. Cardiac dysfunction, fluid overload (e.g. in latent pulmonary oedema/congestive cardiac failure)
   - Screening patients. Known risk cautioned in SPC, clinical monitoring and careful fluid balance as in trial protocol / SPC
6. CNS effects,
   - Monitoring within specialist stroke services. Early identification of severe hypo/hypernatraemia as specified in trial protocol.
7. Electrolyte disturbances
   - Monitoring as in trial protocol / CNS effects as above
   - GCP in identifying and correcting e.g. other drugs that may cause additive effects or pose risks – outlined in SPC
8. Local site reactions (hyperosmolar)
   - Monitoring for early recognition, GCP
9. Hypersensitivity / anaphylaxis reactions

- As listed in SPC, recognition and care within acute stroke ward

10. Crystallisation of solution
    - Use of 10% solution, in line filters

Rationale for trial protocol

This protocol will compare two different dosages of mannitol versus standard care including monitoring of participants before, during and after treatment, collection of key clinical assessments and presence or absence of adverse effects. We believe that it is important to compare two mannitol groups versus standard care to assess whether is any preliminary signal of a clinical and radiological difference in the response for a life-threatening condition such as intracerebral haemorrhage which could be important in a definitive trial. We also believe that comparison to standard care is appropriate as patients with acute intracerebral haemorrhage are treated in accordance with national guidance. This would include important treatments such as blood pressure lowering, nutrition and application of intermittent pneumatic compression stockings.

Monitoring of trial participants

We anticipate that the majority of participants will be treated on acute stroke units where potential life-saving medications such as intravenous alteplase, anti-hypertensives are routinely administered and patients monitored before or after treatment, including those who undergo neurosurgery or mechanical thrombectomy. Investigators and nursing staff will assess participants using standard clinical scales (GCS, NIHSS), as proposed here. Our earlier survey through the British Association of Stroke Physicians showed that clinicians were willing to administer and monitor participants so any potential risks to participants would be mitigated by the environment and level of monitoring.

Monitoring of participant safety

The DMC will monitor safety of trial participants.

17.2 Appendix 2 – Expected events not subject to expedited reporting

After intravenous infusion of mannitol, the following events are expected and would be indistinguishable from the clinical manifestation of severe haemorrhagic stroke. These events are not subject to expedited reporting:

- hypersensitivity
- Other hypersensitivity infusion reactions, including:
- hypertension
- pyrexia
- chills
- sweating
- cough
- musculoskeletal stiffness and myalgia
- pruritis
- generalised pain

- nausea
- vomiting
- headache
- CNS disorders: headache, dizziness, rebound intracranial pressure
- CNS toxicity manifested by: coma, confusion, lethargy
- Eye disorders: blurred vision
- Respiratory, thoracic, and mediastinal disorders: rhinitis
- Gastrointestinal disorders: dry mouth, thirst, nausea, vomiting
- Skin and subcutaneous disorders
- Musculoskeletal and connective tissue disorders: cramps
- Renal and urinary disorders: excessive diuresis, osmotic nephrosis, urinary retention, azotemia, polyuria
- General disorders and administration site conditions: chills, chest pain (angina-like chest pain), fever, asthenia, malaise, infusion site reactions

All of these events above are listed in the Mannitol summary of product characteristics. (38) Occurrence of these events under other circumstances would not be considered expected and would be subject to expedited reporting.

17.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
MA0123	V1.2	[ADD ONCE APPROVED]	Jen Craig, Diane Havard	- Minor spelling, grammar, punctuation, and formatting edits made throughout. - Footers: protocol version/date updated, 'confidential' removed - Page 1: Protocol version/date updated, trial registry number and date added. - Page 4: Trial manager details updated. - Page 7: Trial pharmacist details updated. - Page 9 and 27: co-enrolment details updated - Page 11: Safety outcomes – clarified this includes all SAEs up to day 28 and fatal SAEs to day 180. - Page 14: Timothy England updated from Dr to Professor. - Page 25: Safety outcomes – clarified this includes all SAEs up to day 28 and fatal SAEs to day 180. - Page 33 and 35: update to wording to reflect the DASH trial is now complete. - Page 34: Clarification that the legal representative information sheet and legal representative consent form (not the legal representative pictorial information sheet) need to be used for professional legal representative consent. - Page 36 and 37 (trial procedures and assessments table): 'X' added to 'Follow-up Post-treatment (Day 1-2*)' and 'Follow-up post-treatment (Day 5 +/-2 days)' columns in the mRS/GCS/NIHSS row with a footnote to indicate that only GCS and NIHSS collected at this

				timepoint. 'X' added to indicate blood sample collection in the 'Day 28 or discharge' column. Columns 5 and 6 names edited for clarification. New row added to indicate mortality data collection points. - Page 38: references to 'figure 1' corrected to 'trial flow chart'. Correction of wording to indicate that participants will not have serum osmolality calculated before infusion – this was justified in response to MHRA prior to approval. - Page 46: clarified safety reporting in co-enrolled studies. - Page 49: List of protocol violations updated to align with corresponding CRF. - Page 52: addition of 'senior clinical trial manager' to the TMG, 'via Teams videoconference' added to TSC section. - Page 59: reference to 'Trial Coordinator' changed to 'Trial Manager'