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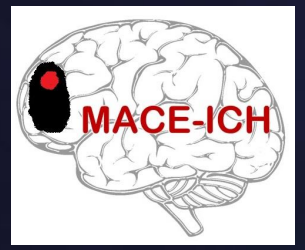
Research & Innovation

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

INVESTIGATOR TRAINING



IRAS: 1004870

CTA: 19162/0239/001-0001

Chief Investigator: Dr Kailash Krishnan

Consultant Stroke Physician, Nottingham University Hospitals NHS Trust

Associate Professor of Stroke Medicine, University of Nottingham

FUNDED BY
NIHR | National Institute for Health and Care Research

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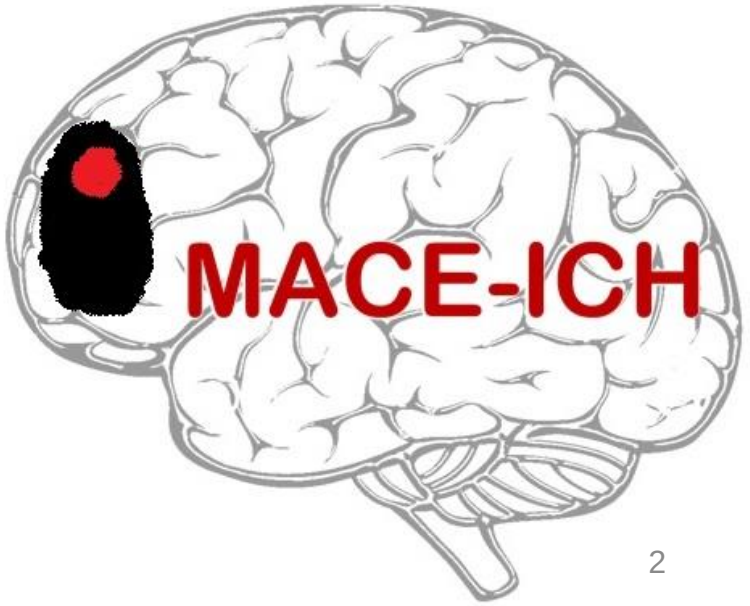


Regulatory Framework for Clinical Trials

UK Legislation

Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019
Medical Devices Regulations 2002
General Product Safety Regulations 2005
Data Protection Act and General Data Protection Regulation 2018
Care Act 2014
Medicines and Medical Devices Act 2021
ATMP Regulation 1394/2007

ICH GCP / ISO 14155/ Declaration of Helsinki

NUH Trust R&I

NUH R&I Trust Policy and NUH R&I Standard Operating Procedures (SOPs)

UK Research Governance

Department of Health
(NHS Act 2006, Health and Care Act 2022)

Framework Agreement between the Health Research Authority, Health and Social Care Northern Ireland, NHS Scotland and Health and Care Research Wales:

UK policy framework for health and social care research v3.3, 7 Nov 2017

Health Research Authority (HRA)

(arm's length body of the DoH)

Bring together review of governance/legal compliance and independent ethical opinion.

- Research Ethics Committee (REC)
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- NHS Approval (C of C&C)

HRA Approval

Funding disclosures

- MACE-ICH is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme, grant reference NIHR-203080

Trial Registration:	ISRCTN15383301
CTA reference:	19162/0239/001-0001
EudraCT Number:	2022-000283-22
IRAS Project ID:	1004870
Trial Sponsor:	Nottingham University Hospitals NHS Trust

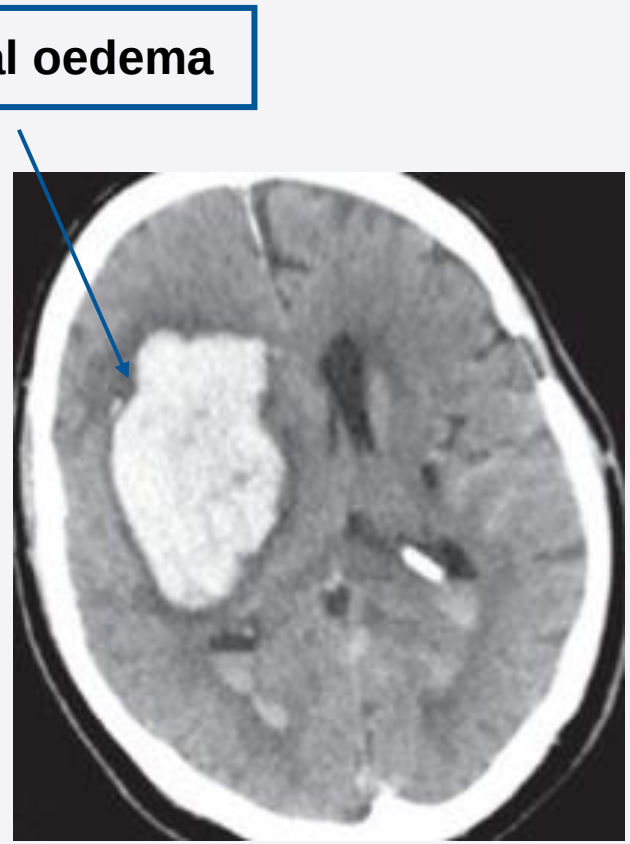
FUNDED BY
NIHR | National Institute for Health and Care Research

This project is funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR-203080). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Background

Intracerebral Haemorrhage (ICH)

- Highest mortality (~50%) of all stroke subtypes
- 15% of 150,000 strokes each year in the UK
- ~22,500 ICHs each year in the UK
- ~1,500 patients experience severe brain swelling
- Greater brain swelling/oedema ➔ increased risk of death or severe disability (mRS =4-5)

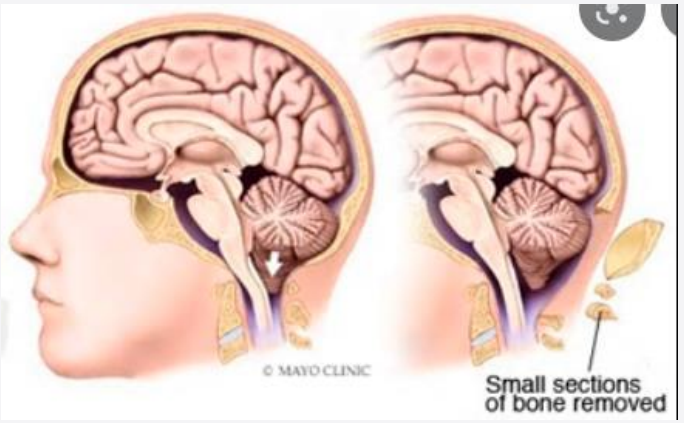


Background

Treating ICH patients with brain swelling

Currently very limited treatment options:

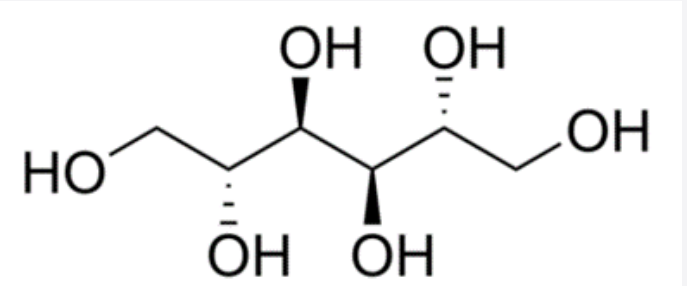
- Surgical decompression?
  - Proven in ischaemic stroke, unclear in ICH
  - High risk of complications, particularly for elderly patients
  - Not routinely available
- Corticosteroids
  - No evidence
  - Likely to worsen patient's condition
- Osmotherapy, e.g. mannitol
  - A potential solution?



Background

Mannitol

- Metabolically inert in humans and occurs naturally in fruits and vegetables.
- Osmotic diuretic
  - Inhibits the reabsorption of water and sodium
  - Elevates the osmolality of blood and renal filtrate
  - Increases production of urine
  - Helps to eliminate excess water from the body
- Readily available in most UK hospitals
- Easy to administer intravenously
- Licensed to treat cerebral oedema and used in traumatic brain injury and hepatic encephalopathy
- Current UK stroke guidelines do not recommend the routine use of mannitol
- Some stroke physicians use mannitol regularly, but little is known about its effects in ICH



Background

Review of evidence: Pre-clinical

- Mannitol has demonstrated benefit in three animal models of intracranial haemorrhage.

Year	Animal	Model	Effect of mannitol
1999*	Dog	ICH	Reduced intracranial pressure (ICP)
2006**	Rat	SAH	Reduced ICP and death
2018***	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

Review of evidence: proof of concept in ICH

- Results of studies investigating the effects of mannitol on cerebral blood flow (CBF) in ICH patients have been varied:

Year	N	Dose	Equivalent dose based on 70 kg	Total dose in 24 hours	Effect
1978	300	0.9g/kg	63 g	63 g	No CT scan; no change
1998	1	20% solution 200 ml	40 g	40 g	Transient Increase in CPP and reduced ICP
2004	21	20 g 20%	20 g	20 g	No change
2005	128	20 g 4 hourly 20%	20 g	120 g	No difference in death or disability
2007	24	1.5 g/kg 20%	105 g	105 g	Transient improvement in CBF after single dose
2011	20	20% bolus/100 ml infusion	20 g	20 g	Increased CBF and lowered PI
2013*	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; ICP: intracranial pressure; PI: pulsatility index; CBF: cerebral blood flow *Mean ICH volume was 21.9 ml

Background

Review of evidence: proof of concept in ICH

- Observational data from the INTERACT-2 trial (>1500 patients)
  - Mannitol was associated with better outcomes in patients with haemorrhages >15 ml.
  - There were no significant differences in adverse events (cardiac, renal or neurological) in those who received treatment.
- Another study reported no difference in functional outcome at 3 months following use of mannitol.
  - However, comparisons were made with patients having brain herniation to those with mild stroke and did not receive treatment.

Background

Review of evidence: mannitol for stroke

- Systematic review of mannitol versus control for acute stroke:
  - Three small trials identified (n=226)
  - 2/3 trials included ICH patients
  - Trials varied in design, inclusion criteria, duration and intensity of treatment
  - At follow-up, no sig difference in functional outcome between mannitol and control groups however, the confidence intervals were wide, so it is difficult to draw any definite conclusions
- Meta-analysis comparing hypertonic saline with mannitol
  - Included ICH patients
  - Both were effective, regardless of clinical definition of elevated ICP
  - Patient numbers were however small and the effect on long-term outcomes were unknown
- Most effective regimen for mannitol is unclear
  - Bolus (as opposed to continuous) may be effective
  - Guidance on dosage is limited: higher doses may be more effective
  - Experts highlight that risks with mannitol treatment are low compared to potential benefit in life threatening cerebral oedema.

Study Design, Objectives and Outcomes

MACE-ICH 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.

- A multicentre, prospective, randomised, open-label, blinded-endpoint trial (of mannitol versus standard care)
- 45 patients with spontaneous ICH (≤72 hours) with (and/or at risk of developing) cerebral oedema
- Randomised 1:1:1 across 10 UK based NHS Trusts:
  - Arm 1: 1 g/kg 10% single dose mannitol infusion at 10ml/min
  - 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
  - Arm 3: Standard care alone
- ~ 4-5 participants per site across 24 months of recruitment

Blinding to treatment allocation:

✗ Participants
✗ Site researchers/investigators
✗ Clinical staff preparing/administering the IMP
✓ Central day 180 follow-up coordinators
✓ Brain imaging adjudicators

Study Design, Objectives and Outcomes

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.

Primary (feasibility) outcomes

- **Number of eligible patients recruited and reasons for not recruiting**
- Ability to access eligible ICH patients to calculate study screening, eligibility, recruitment and retention
- 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
- Identify strengths and barriers to recruitment and retention
- Determine the feasibility of clinicians to identify eligible patients
- Ability to obtain timely consent
- Effectiveness of blinded follow-up
- Ability to administer mannitol and monitor participants
- Assess the delivery of the trial protocol, identify potential causes of violation and trial withdrawal
- Evaluate the feasibility of collecting the proposed outcome measures including follow-up at day 180, acceptability to participants and trial staff

Study Design, Objectives and Outcomes

Secondary objective

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

Secondary outcomes

- **Day 1-2:** U&E's, e-GFR; serum osmolality to correlate response to mannitol;
- **Day 5±2 days:** Glasgow Coma Scale (GCS); National Institutes Health Stroke Scale (NIHSS); follow-up CT scan to assess changes in oedema volume, oedema extension distance, haematoma volume, midline shift, hydrocephalus; number of patients who had urinary tract infection; number of patients who had sepsis; mortality
- **Day 28:** Number of participants who had urinary tract infection; number of participants who had sepsis; mortality
- **Day 180 (central follow up):** Disability (Barthel Index); Mood (Zung depression scale [ZDS]); Cognition (TICS-M); Quality of life (Euro-[EQ] QOL; EQ-VAS); Health economic assessment (EQ-5D); Death or dependency (modified Rankin scale); Length of stay; Discharge destination; Long-term outcomes post Covid-19 and ICH.
- **Other:** Number of participants needing and transferred to high dependency or intensive care unit; Number of participants undergoing neurosurgical intervention; Recurrent stroke; Number of participants intubated and ventilated
- **Safety outcomes:** death; thrombophlebitis; hyper/hyponatremia; pulmonary oedema; hypotension; renal impairment; Serious adverse events (SAEs) until day 28, fatal SAEs (and safety outcomes) up to day 180

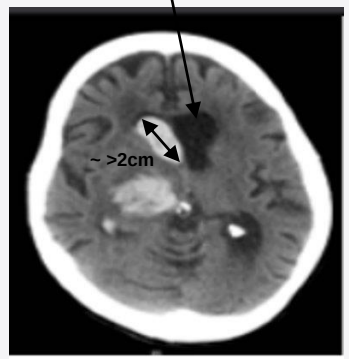
Eligibility

Inclusion criteria

- Adults ≥18 years
- **Spontaneous ICH (confirmed by CT scan) with <u>estimated</u> largest diameter >2cm**
- ≤72 hours since onset (or from last seen healthy)
- Cerebral oedema with or without evidence of mass effect

  OR
- At risk of developing oedema (limited GCS <9 (eye opening and motor only) and NIHSS≥8)
- Signed consent (participant, personal or professional representative or independent physician).

Cerebral oedema



<u>NB:- ICH secondary to the following is NOT spontaneous ICH:</u>

- Ruptured aneurysm
- Vascular malformation (e.g. isolated IVH & bilateral small hyperdensities)
- Tumor or abscess
- Ischaemic stroke (haemorrhagic transformation of infarct)
- Thrombolysis
- Venous infarct
- Trauma

Eligibility

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

Final decision on eligibility rests with the treating physician

Eligibility

Eligibility sign-off

- Eligibility must be signed off by a medic
- The medic does not need to be on the delegation log
- Any eligibility confirmation sign-off should be clearly documented in the participant's medical notes
- An 'Eligibility Checklist' is available, e.g:

University of Nottingham

MACE-ICH

Nottingham University Hospitals NHS

ISRCTN 15383301
IRAS 1004870

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

Eligibility Checklist V1.1

	Inclusion Criteria *(All must be 'YES' for the patient to take part)*	**Yes**	**No**
1	Adult (18 years and over)		
2	Spontaneous ICH confirmed by CT scan with estimated largest diameter > 2 cm		
3	≤72 hours of ictus (or from last seen healthy)		
4	Cerebral oedema with or without evidence of mass effect **OR** At risk of developing oedema (limited GCS <9 (eye opening and motor only) and NIHSS>8) *If recording *'Yes'*, please indicate which of the above is applicable*		
5	Signed consent (patient, personal or professional representative or independent physician)		

	Exclusion Criteria *(All must be 'NO' for the patient to take part)*	**Yes**	**No**
1	GCS<5		
2	Premorbid mRS >3		
3	Isolated subarachnoid haemorrhage		
4	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		
5	Known hypersensitivity to mannitol		
6	Severe renal failure (e-GFR<30ml/min or dialysis)		
7	Severe pulmonary oedema/ cardiac failure		
8	Hypotension at baseline (SBP <90 mm Hg)		
9	Anuria		
10	Patient unwilling to participate		
11	Geographical or other factors which prohibit follow-up		
12	Pre-existing comorbidity with pre-ictal life expectancy <6 months		
13	Severe dementia		
14	Planned for palliative care		
15	Severe hypernatremia (sodium >160 mmol)		
16	Severe hyponatremia (sodium <125 mmol)		

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MACE-ICH Eligibility Checklist V1.1 20231124

Eligibility must be signed off by a Medic

*(The medic does **not** have to be on the delegation log)*

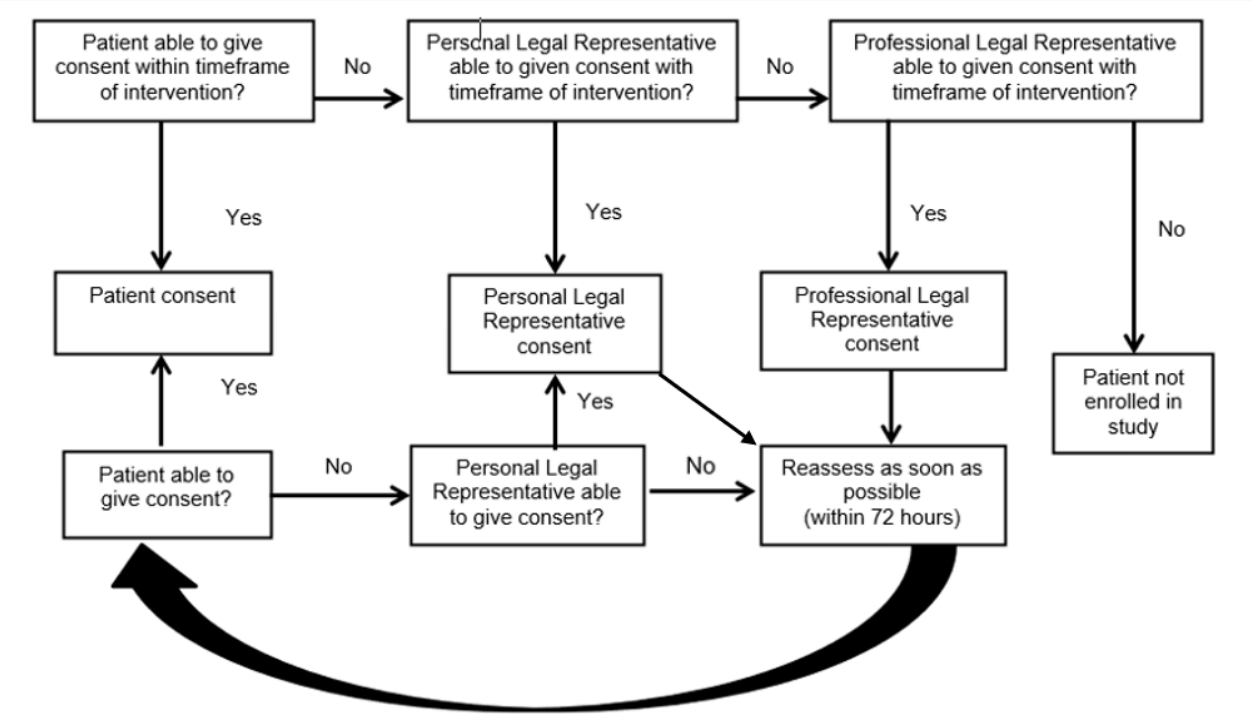
_____ _____
(Name) (Signature)

_____ _____
(Occupation) (Date)

Consent Process

Hierarchy approach

1. Patient has capacity: Patient gives consent
2. Patient lacks capacity: Relative or close friend likely to know patient wishes provides consent
3. Patient lacks capacity and no relatives or close friends available: Independent doctor provides consent



Consent must be taken by someone appropriately trained and on the delegation log

- **Consent must be taken by a medic on the delegation log**
- **The consent process must be fully documented in the patient's medical notes**

Consent Process

Patient has capacity

Patient consent process

- All participants who are able to, will provide written informed consent
- The investigator (or nominee) will explain the trial and provide a Pictorial Information Sheet
- If requested, a more detailed information sheet will be provided
- Potential participants should be given as long as they need to consider consent, but it should be explained to the potential participant that this is an emergency treatment with a potentially small therapeutic time window
- If the patient is unable to write, witnessed verbal consent (or a mark made by the patient with intent to sign) may be recorded on the consent form by someone unconnected with the study

Consent Process

Patient lacks capacity: a personal legal representative is available

Personal legal representative consent process

- The investigator will approach the patient's relative, partner or close friend who is able to represent the patient's views
- Provide them with a pictorial information sheet (and a more detailed information sheet if requested)
- Explain what is involved in the trial and answer any questions
- Written consent for the patient's inclusion in the trial obtained by completing the consent section of the pictorial information sheet or the Legal Representative Consent form
- 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 at the hospital
- Full informed written consent will be obtained from the patient if capacity is regained
- The participants' decision to withdraw will overrule the decision of the personal legal representative

Consent Process

Patient lacks capacity: a personal legal representative is not available

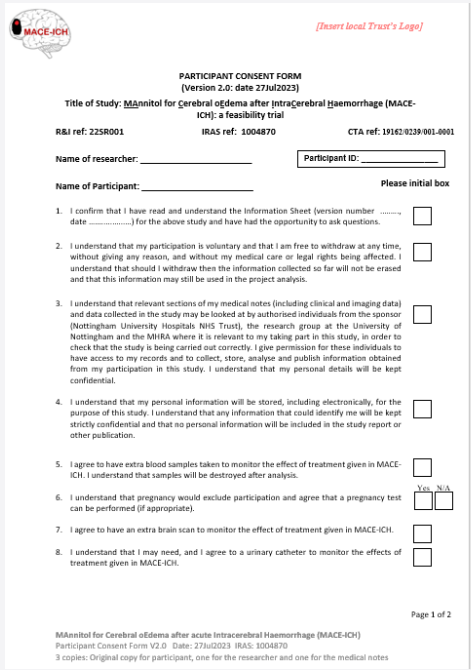
Professional legal representative consent process

- The investigator will approach an independent doctor (unconnected with the trial)
- Provide them with the full legal representative information sheet (it is not possible to use the pictorial information sheet for independent physician consent)
- Ask if they would be willing to act as the patient's professional legal representative
- If appropriate, obtain their written consent for the patient's inclusion in the trial by completing the Legal Representative Consent form
- If an independent doctor is not available, the patient will not be enrolled
- All attempts to gain written/verbal consent from a personal legal representative must be explored before independent physician consent can be gained. **These attempts must all be documented in the patient's medical notes**
- 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

Consent Process

Please localise the consent forms, GP letter and participant information sheets prior to printing

Participant consent form



PARTICIPANT CONSENT FORM
(Version 2.0: date 27Jul2023)

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

R&I ref: 22SR001 IRAS ref: 1004870 CTA ref: 19162/0239/001-0001

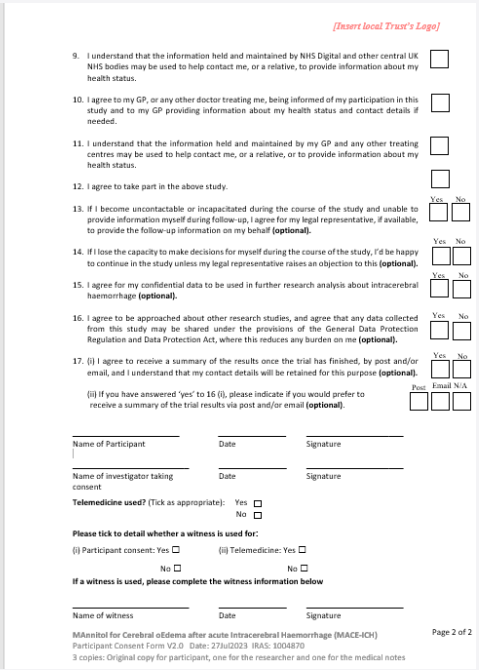
Name of researcher: _____ Participant ID: _____

Name of Participant: _____ Please initial box

1. I confirm that I have read and understand the Information Sheet (version number ....., date .....) for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far will not be erased and that this information may still be used in the project analysis.
3. I understand that relevant sections of my medical notes (including clinical and imaging data) and data collected in the study may be looked at by authorised individuals from the sponsor (Nottingham University Hospitals NHS Trust), the research group at the University of Nottingham and the MHRA where it is relevant to my taking part in this study, in order to check that the study is being carried out correctly. I give permission for these individuals to have access to my records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.
4. I understand that my personal information will be stored, including electronically, for the purpose of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication.
5. I agree to have extra blood samples taken to monitor the effect of treatment given in MACE-ICH. I understand that samples will be destroyed after analysis.
6. I understand that pregnancy would exclude participation and agree that a pregnancy test can be performed (if appropriate). Yes N/A
7. I agree to have an extra brain scan to monitor the effect of treatment given in MACE-ICH.
8. I understand that I may need, and I agree to a urinary catheter to monitor the effects of treatment given in MACE-ICH.

Page 1 of 2

MAnnitol for Cerebral oEdema after acute Intracerebral Haemorrhage (MACE-ICH)
Participant Consent Form V2.0 Date: 27Jul2023 IRAS: 1004870
3 copies: Original copy for participant, one for the researcher and one for the medical notes



9. I understand that the information held and maintained by NHS Digital and other central UK NHS bodies may be used to help contact me, or a relative, to provide information about my health status.
10. I agree to my GP, or any other doctor treating me, being informed of my participation in this study and to my GP providing information about my health status and contact details if needed.
11. I understand that the information held and maintained by my GP and any other treating centres may be used to help contact me, or a relative, or to provide information about my health status.
12. I agree to take part in the above study.
13. If I become uncontactable or incapacitated during the course of the study and unable to provide information myself during follow-up, I agree for my legal representative, if available, to provide the follow-up information on my behalf **(optional).** Yes No
14. If I lose the capacity to make decisions for myself during the course of the study, I'd be happy to continue in the study unless my legal representative raises an objection to this **(optional).** Yes No
15. I agree for my confidential data to be used in further research analysis about intracerebral haemorrhage **(optional).** Yes No
16. I agree to be approached about other research studies, and agree that any data collected from this study may be shared under the provisions of the General Data Protection Regulation and Data Protection Act, where this reduces any burden on me **(optional).** Yes No
17. (i) I agree to receive a summary of the results once the trial has finished, by post and/or email, and I understand that my contact details will be retained for this purpose **(optional).** Yes No

(ii) If you have answered 'yes' to 16 (i), please indicate if you would prefer to receive a summary of the trial results via post and/or email **(optional)**. Post Email N/A

Name of Participant Date Signature

Name of investigator taking consent Date Signature

Telemedicine used? (Tick as appropriate): Yes ☐ No ☐

Please tick to detail whether a witness is used for:

(i) Participant consent: Yes ☐ No ☐ (ii) Telemedicine: Yes ☐ No ☐

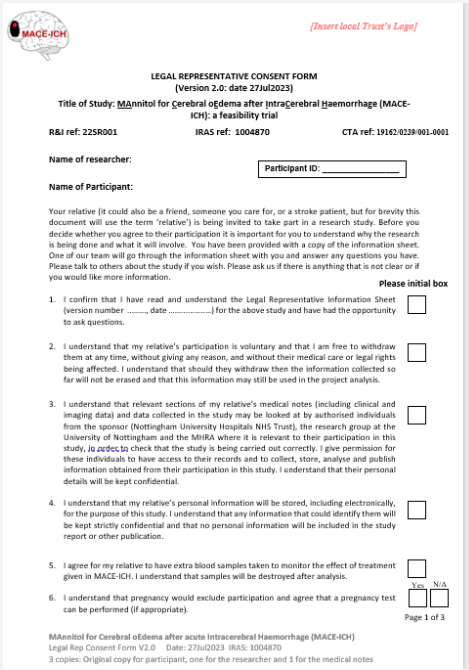
If a witness is used, please complete the witness information below

Name of witness Date Signature

Page 2 of 2

MAnnitol for Cerebral oEdema after acute Intracerebral Haemorrhage (MACE-ICH)
Participant Consent Form V2.0 Date: 27Jul2023 IRAS: 1004870
3 copies: Original copy for participant, one for the researcher and one for the medical notes

Legal representative consent form



LEGAL REPRESENTATIVE CONSENT FORM
(Version 2.0: date 27Jul2023)

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

R&I ref: 22SR001 IRAS ref: 1004870 CTA ref: 19162/0239/001-0001

Name of researcher: Participant ID: _____

Name of Participant:

Your relative (it could also be a friend, someone you care for, or a stroke patient, but for brevity this document will use the term 'relative') is being invited to take part in a research study. Before you decide whether you agree to their participation it is important for you to understand why the research is being done and what it will involve. You have been provided with a copy of the information sheet. One of our team will go through the information sheet with you and answer any questions you have. Please talk to others about the study if you wish. Please ask us if there is anything that is not clear or if you would like more information.

Please initial box

1. I confirm that I have read and understand the Legal Representative Information Sheet (version number ....., date .....) for the above study and have had the opportunity to ask questions.
2. I understand that my relative's participation is voluntary and that I am free to withdraw them at any time, without giving any reason, and without their medical care or legal rights being affected. I understand that should they withdraw then the information collected so far will not be erased and that this information may still be used in the project analysis.
3. I understand that relevant sections of my relative's medical notes (including clinical and imaging data) and data collected in the study may be looked at by authorised individuals from the sponsor (Nottingham University Hospitals NHS Trust), the research group at the University of Nottingham and the MHRA where it is relevant to their participation in this study, in order to check that the study is being carried out correctly. I give permission for these individuals to have access to their records and to collect, store, analyse and publish information obtained from their participation in this study. I understand that their personal details will be kept confidential.
4. I understand that my relative's personal information will be stored, including electronically, for the purpose of this study. I understand that any information that could identify them will be kept strictly confidential and that no personal information will be included in the study report or other publication.
5. I agree for my relative to have extra blood samples taken to monitor the effect of treatment given in MACE-ICH. I understand that samples will be destroyed after analysis.
6. I understand that pregnancy would exclude participation and agree that a pregnancy test can be performed (if appropriate). Yes N/A

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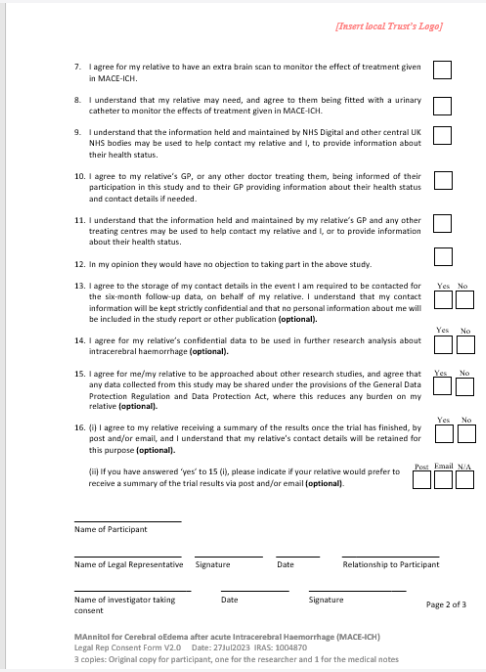
MAnnitol for Cerebral oEdema after acute Intracerebral Haemorrhage (MACE-ICH)
Legal Rep Consent Form V2.0 Date: 27Jul2023 IRAS: 1004870
3 copies: Original copy for participant, one for the researcher and 1 for the medical notes



7. I agree for my relative to have an extra brain scan to monitor the effect of treatment given in MACE-ICH.
8. I understand that my relative may need, and agree to them being fitted with a urinary catheter to monitor the effects of treatment given in MACE-ICH.
9. I understand that the information held and maintained by NHS Digital and other central UK NHS bodies may be used to help contact my relative and I, to provide information about their health status.
10. I agree to my relative's GP, or any other doctor treating them, being informed of their participation in this study and to their GP providing information about their health status and contact details if needed.
11. I understand that the information held and maintained by my relative's GP and any other treating centres may be used to help contact my relative and I, or to provide information about their health status.
12. In my opinion they would have no objection to taking part in the above study.
13. I agree to the storage of my contact details in the event I am required to be contacted for the six-month follow-up data, on behalf of my relative. I understand that my contact information will be kept strictly confidential and that no personal information about me will be included in the study report or other publication **(optional).** Yes No
14. I agree for my relative's confidential data to be used in further research analysis about intracerebral haemorrhage **(optional).** Yes No
15. I agree for me/my relative to be approached about other research studies, and agree that any data collected from this study may be shared under the provisions of the General Data Protection Regulation and Data Protection Act, where this reduces any burden on my relative **(optional).** Yes No
16. (i) I agree to my relative receiving a summary of the results once the trial has finished, by post and/or email, and I understand that my relative's contact details will be retained for this purpose **(optional).** Yes No

(ii) If you have answered 'yes' to 15 (i), please indicate if your relative would prefer to receive a summary of the trial results via post and/or email **(optional)**. Post Email N/A

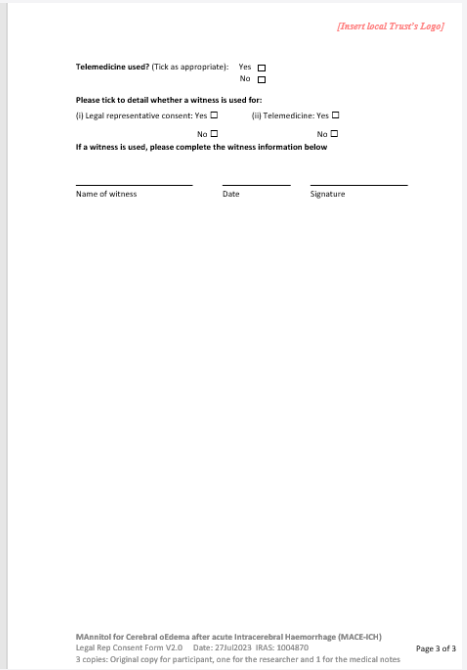
Name of Participant

Name of Legal Representative Signature Date Relationship to Participant

Name of investigator taking consent Date Signature

Page 2 of 3

MAnnitol for Cerebral oEdema after acute Intracerebral Haemorrhage (MACE-ICH)
Legal Rep Consent Form V2.0 Date: 27Jul2023 IRAS: 1004870
3 copies: Original copy for participant, one for the researcher and 1 for the medical notes



Telemedicine used? (Tick as appropriate): Yes ☐ No ☐

Please tick to detail whether a witness is used for:

(i) Legal representative consent: Yes ☐ No ☐ (ii) Telemedicine: Yes ☐ No ☐

If a witness is used, please complete the witness information below

Name of witness Date Signature

Page 3 of 3

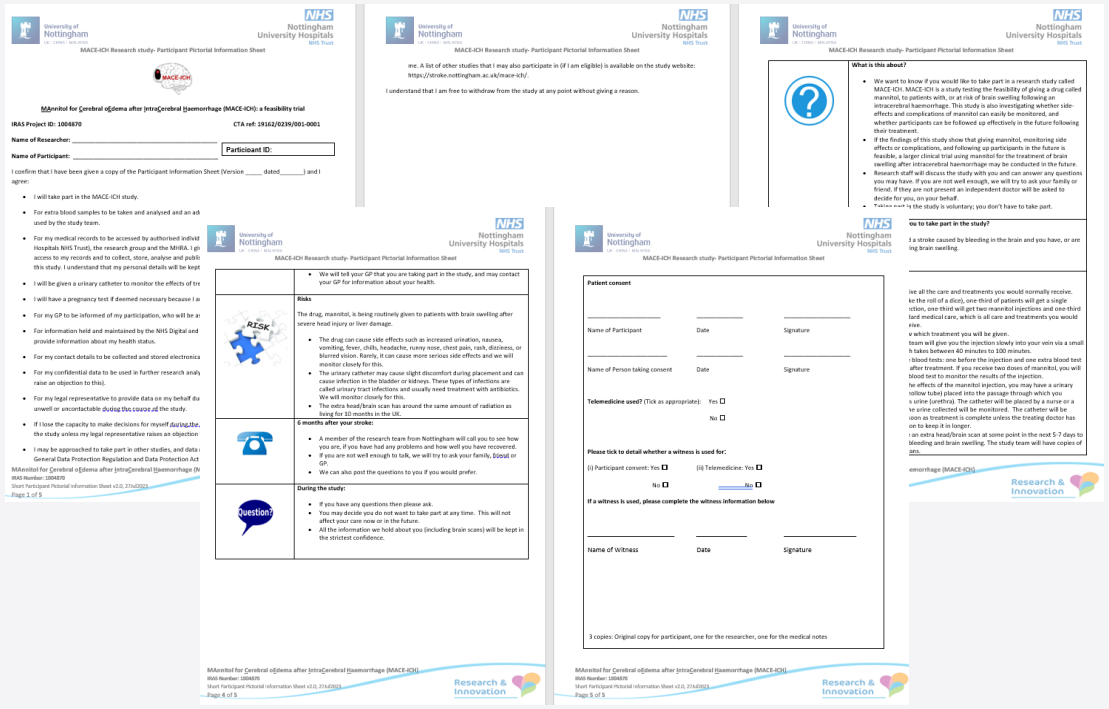
MAnnitol for Cerebral oEdema after acute Intracerebral Haemorrhage (MACE-ICH)
Legal Rep Consent Form V2.0 Date: 27Jul2023 IRAS: 1004870
3 copies: Original copy for participant, one for the researcher and 1 for the medical notes

3 copies of consent form –1 patient, 1 medical notes, 1 research

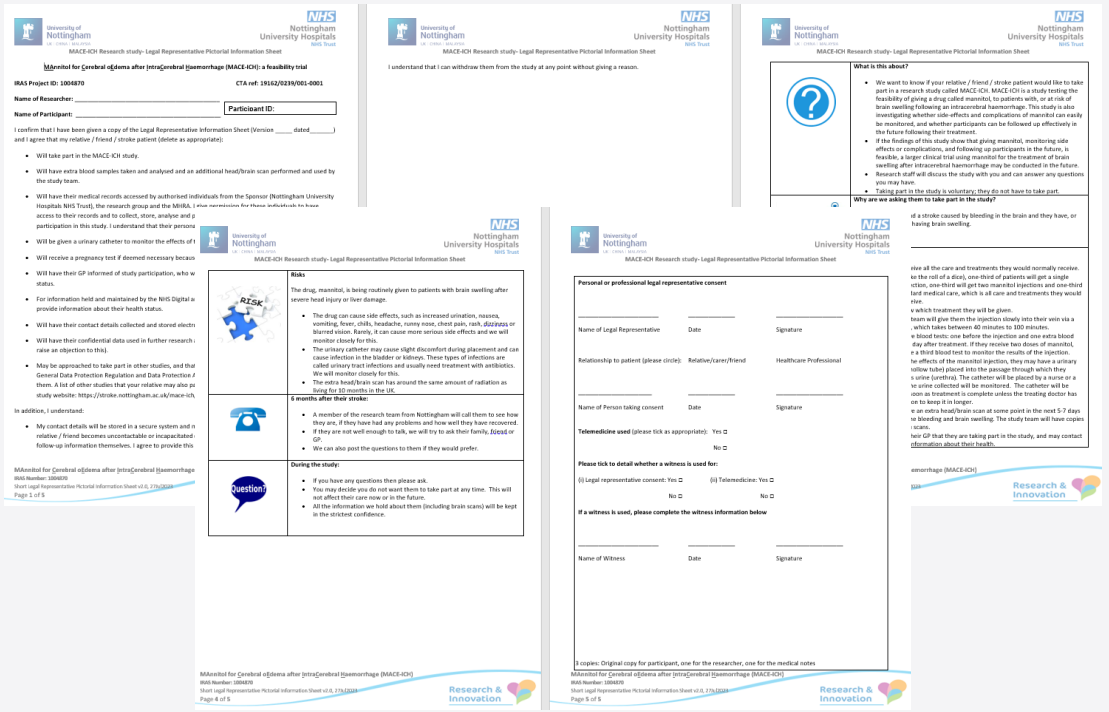
Consent Process

Please localise the consent forms, GP letter and participant information sheets prior to printing

Participant pictorial information sheet



Legal representative pictorial information sheet



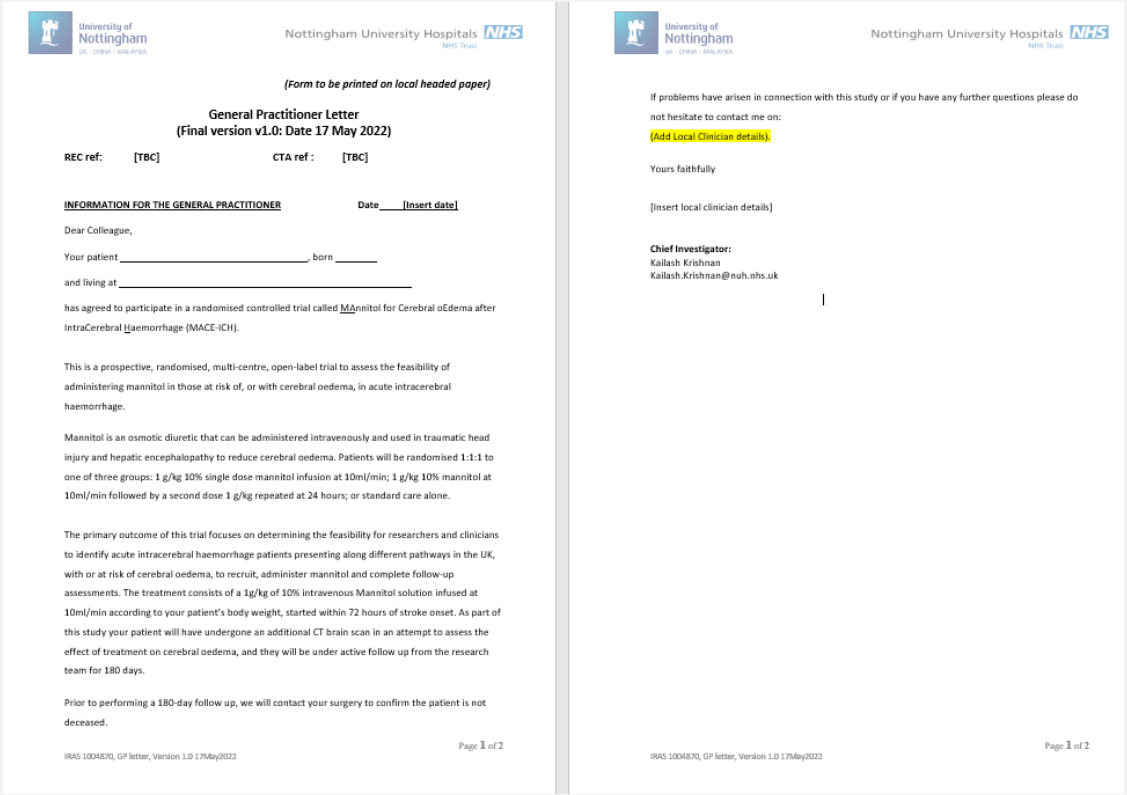
3 copies of consent form –1 patient, 1 medical notes, 1 research

Consent Process

GP letter

- Always send a letter to the participant's general practitioner
- Local header required
- Send with a copy of the participant information sheet
- File a copy in the ISF and in the patient's medical notes
- Anonymised/ identifiable documentation should be kept separate
- Please keep GP letter, consent form(s) and patient details together in the ISF

N.B. If participant documentation is kept in a separate folder, please add a file note to the ISF with exact location



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Nottingham University Hospitals NHS Trust

(Form to be printed on local headed paper)

General Practitioner Letter
(Final version v1.0: Date 17 May 2022)

REC ref: [TBC] **CTA ref :** [TBC]

INFORMATION FOR THE GENERAL PRACTITIONER **Date____(Insert date)**

Dear Colleague,

Your patient _____, born _____

and living at _____

has agreed to participate in a randomised controlled trial called MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH).

This is a prospective, randomised, multi-centre, open-label trial to assess the feasibility of administering mannitol in those at risk of, or with cerebral oedema, in acute intracerebral haemorrhage.

Mannitol is an osmotic diuretic that can be administered intravenously and used in traumatic head injury and hepatic encephalopathy to reduce cerebral oedema. Patients will be randomised 1:1:1 to one of three groups: 1 g/kg 10% single dose mannitol infusion at 10ml/min; 1 g/kg 10% mannitol at 10ml/min followed by a second dose 1 g/kg repeated at 24 hours; or standard care alone.

The primary outcome of this trial focuses on determining the feasibility for researchers and clinicians to identify acute intracerebral haemorrhage patients presenting along different pathways in the UK, with or at risk of cerebral oedema, to recruit, administer mannitol and complete follow-up assessments. The treatment consists of a 1g/kg of 10% intravenous Mannitol solution infused at 10ml/min according to your patient's body weight, started within 72 hours of stroke onset. As part of this study your patient will have undergone an additional CT brain scan in an attempt to assess the effect of treatment on cerebral oedema, and they will be under active follow up from the research team for 180 days.

Prior to performing a 180-day follow up, we will contact your surgery to confirm the patient is not deceased.

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If problems have arisen in connection with this study or if you have any further questions please do not hesitate to contact me on:
(Add Local Clinician details).

Yours faithfully

[Insert local clinician details]

Chief Investigator:
Kailash Krishnan
Kailash.Krishnan@nuh.nhs.uk

IRAS 1004870, GP letter, Version 1.0 17May2022 Page 1 of 2

MACE-ICH Database

Delegation log/database access

https://stroke.nottingham.ac.uk/mace-ich/live/

- Sign off by the PI via the electronic delegation log will allow access to the trial database
- Request access by emailing mace-ich@nottingham.ac.uk along with:
  - Signed CV and GCP (both within last 2 years or as per local policy)
  - Signed training log (either live training or self-directed)
- Account details will then be sent via email
- Staff member will need to accept invitation to participate, which will send a notification to PI
- PI will need to log in and sign off each staff member, which adds the staff member to the online delegation log and database access is granted.
- **Investigators may only work on the trial once signed off on the delegation log**

Log ID	Investigator name/ID	Certificate/ date assessed or trained	Number of correct answers/score		Roles and responsibilities*	Delegation log status
13	[redacted]	P6Y3N6 3 Jun 2021	-	-	Site investigator BFHIJKLNOPQRSTY	9 Aug 2021 12:10 **Authorised** [redacted]
14	[redacted]	Y3K6X6 3 Jun 2021	-	-	Site investigator BFHIJKLNOPQRSTY	9 Aug 2021 12:10 **Authorised** [redacted]

The PI must select whether code J should be applied as a delegated role to take consent (medics only). Code T should be applied as a delegated role to collect trial related blood samples

MACE-ICH Database

Demo database

- The demonstration database is available to be used by site investigators to get an understanding of the database functions and CRF completion, meaning that any potential queries can be resolved prior to opening.
- Log in using the credentials below, which can be found via the MACE-ICH website https://stroke.nottingham.ac.uk/mace-ich/

Demonstration database

For practice, please go to

https://stroke.nottingham.ac.uk/mace-ich/demo/

and use the following credentials.

User	demoinv1
Password	nottingham

MACE-ICH Database

Entry of missing data

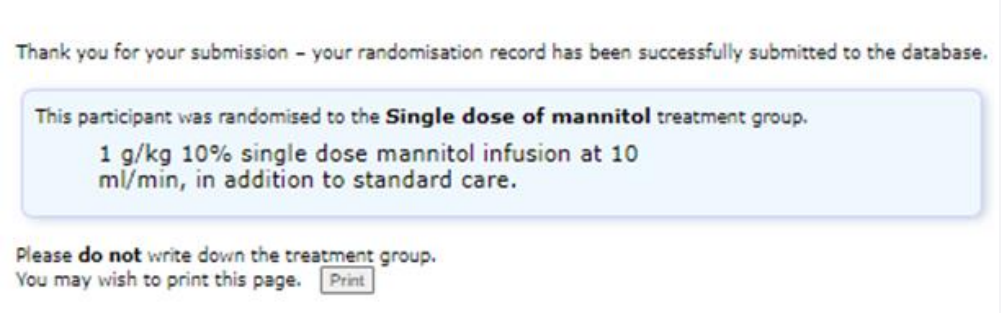
- Some questions on MACE-ICH CRFs may provide the following options:
  - **Not applicable:** should be used if a measure was not required for that participant
  - **Not done:** should be used if data are unavailable, either because a measure was not taken or a test was not performed (every effort should be made to complete the test if still within the time window)
  - **Not known:** should be used if the data are unknown, and every effort has been made to find the data
- For each question on a CRF, you should either enter a value in the central column(s) or use the drop-down lists in the right-hand column to indicate why the value is missing
- The 'Not done' and 'Not known' options relate to missing data. Some required data may be missing for legitimate reasons.
- **To access the hidden 'Not done' and 'Not known' options on the CRFs, please go to the bottom of the page and set the missing data control to 'Yes'. Enter a full explanation and submit the form. After this, you can complete the CRF as usual.**

Randomisation

Online randomisation process

- Patients will be randomised 1:1:1 to receive either:
  - Standard care plus 1 g/kg 10% single dose mannitol infusion at 10ml/min
  - Standard care plus 1 g/kg 10% mannitol at 10ml/min followed by a second dose 1 g/kg repeated at 24 hours
  - Standard care alone
- Randomisation will be performed locally using the trial's secure internet site

- Log into the MACE-ICH online database (https://stroke.nottingham.ac.uk/mace-ich/live/)
- Click to randomise a new patient
- Confirm the patient's eligibility and complete the randomisation form
- Once the form has been submitted, the database will display the allocated treatment
- An email will be sent to staff as confirmation



Randomisation

Emergency randomisation process

1. Randomisation performed by the coordinating centre

- The site investigator is unable to reach the MACE-ICH database from their location, but the MACE-ICH database itself is working. → **The coordinating centre will randomise the patient on behalf of the site**

2. Manual randomisation

- The MACE-ICH database is unavailable, which means that no one (including the team at the co-ordinating centre) can perform any online data entry at all. Manual randomisation means that a person chooses which study 'arm' the participant is allocated to, without the use of computerised randomisation. → **The coordinating centre will perform manual randomisation and input the data once the database is working.**

As soon as the site discovers that they are unable to use the MACE-ICH database to randomise their eligible patient, they should contact the coordinating centre (0115 823 1770).

The office phone is covered between 8am-6pm Monday to Friday (excluding public holidays). For emergency randomisation at other times, please call Dr Kailash Krishnan (emergency contact number listed on the trial website)

Investigational Medicinal Product (IMP)

IMP supply and handling

- **IMP characteristics**
  - Intravenous mannitol (Mannitol 10% solution for Infusion BP, Baxter Healthcare Limited PL 00116/0367)
- **IMP supply**
  - Sites will use their own mannitol from standard NHS hospital supplies
- **IMP storage**
  - 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.
  - IMP may be kept on the relevant ward/department to be accessible and allow treatment to start promptly as soon as the patient is randomised.
  - Room temperature (20-30°C).
  - Sites should follow their standard procedures for temperature monitoring (ideally a min and max temperature every weekday (excluding bank holidays)
  - Avoid sudden shock of the product (e.g. dropping) to prevent crystallisation.
  - The IMP will be kept as ring-fenced trial medication with study specific labelling

Labelling

Batch Number, Expiry Date and Storage Conditions will be included on the original pack labelling.

To comply with Annex 13 labelling requirements, the following label should be added to the infusion bag:

For Intravenous use only

MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH)
Mannitol Infusion 10% (500ml)
To be infused in accordance with the protocol.

Participant Name _____
Participant ID Number _____
Chief Investigator Dr Kailash Krishnan
Sponsor: Nottingham University Hospitals NHS Trust

EudraCT Number 2022-000283-22

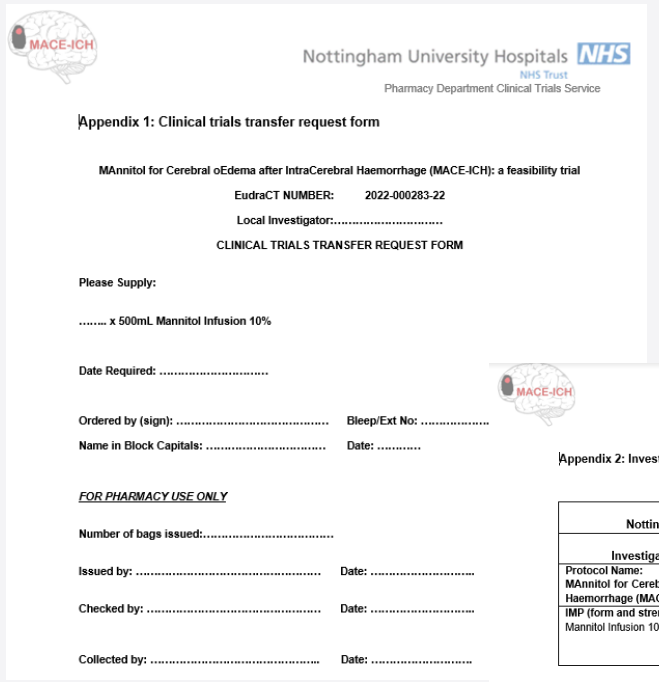
Investigational Medicinal Product (IMP)

IMP dispensing and accountability

Local pharmacy will maintain accountability to record issuing of IMP and return of unused stock.

Pharmacy

- Local pharmacy will be responsible for issuing the IMP to the Stroke Unit or relevant ward or department at site:
  - A MACE-ICH IMP Transfer Request Form must be completed
  - The pharmacy clinical trials staff will check that the person completing the Transfer Request Form has delegated responsibility by the PI
  - All IMP issued by Pharmacy to the Stroke Unit or relevant ward or department must be recorded on the MACE-ICH Pharmacy IMP Inventory Log



MACE-ICH

Nottingham University Hospitals NHS
NHS Trust
Pharmacy Department Clinical Trials Service

Appendix 1: Clinical trials transfer request form

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

EudraCT NUMBER: 2022-000283-22

Local Investigator:.....

CLINICAL TRIALS TRANSFER REQUEST FORM

Please Supply:

..... x 500mL Mannitol Infusion 10%

Date Required: .....

Ordered by (sign): ..... Bleep/Ext No: .....

Name in Block Capitals: ..... Date: .....

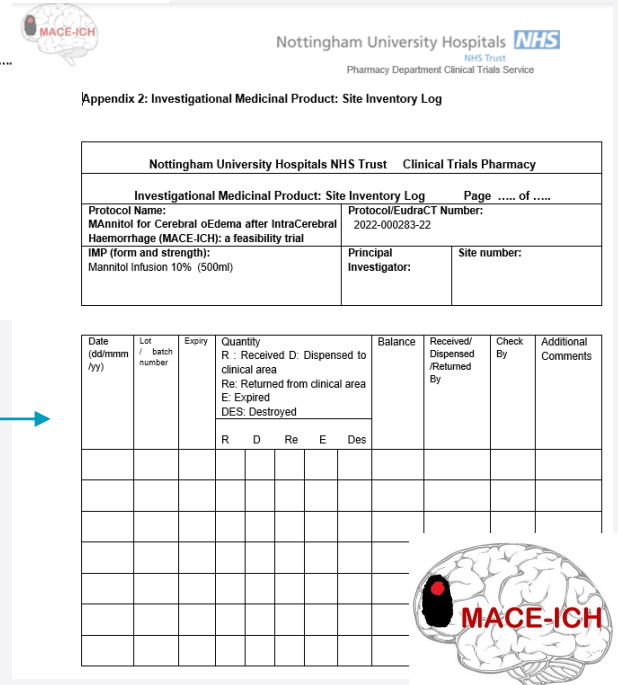
FOR PHARMACY USE ONLY

Number of bags issued:.....

Issued by: ..... Date: .....

Checked by: ..... Date: .....

Collected by: ..... Date: .....



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Pharmacy Department Clinical Trials Service

Appendix 2: Investigational Medicinal Product: Site Inventory Log

Nottingham University Hospitals NHS Trust Clinical Trials Pharmacy		
Investigational Medicinal Product: Site Inventory Log Page ..... of		
Protocol Name: MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial	Protocol/EudraCT Number: 2022-000283-22	
IMP (form and strength): Mannitol Infusion 10% (500ml)	Principal Investigator:	Site number:

Date (dd/mmm /yy)	Lot / batch number	Expiry	Quantity R : Received D: Dispensed to clinical area Re: Returned from clinical area E: Expired DES: Destroyed					Balance	Received/ Dispensed /Returned By	Check By	Additional Comments
			R	D	Re	E	Des				

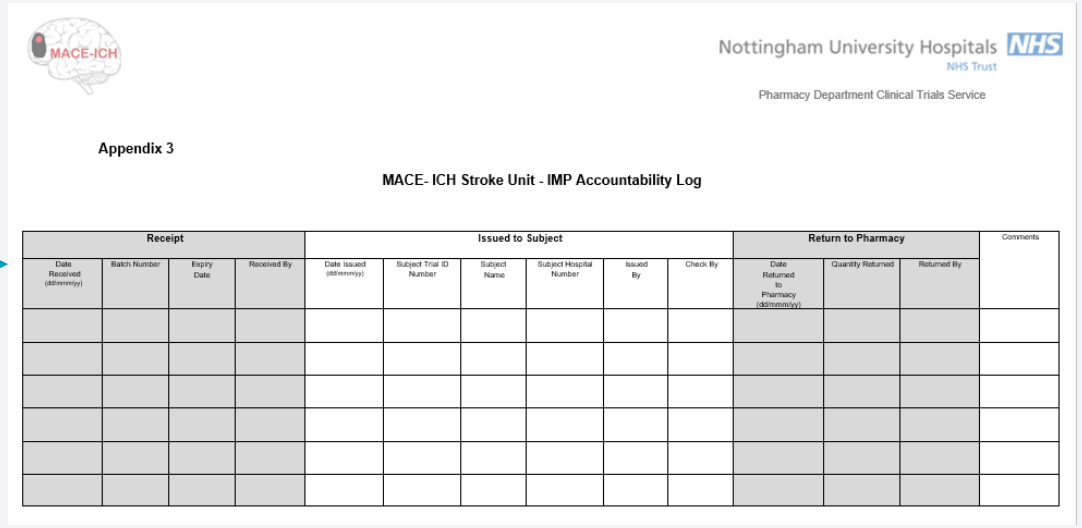
MACE-ICH

Investigational Medicinal Product (IMP)

IMP dispensing and accountability

Stroke Unit/Ward/Department

- Upon receipt of IMP from the site Pharmacy, the details should be recorded on the MACE-ICH Stroke Unit IMP Accountability Log
- Following randomisation of a participant to treatment arm 1 or treatment arm 2, an intravenous infusion bag should be selected from the available trial stock and the participant name and trial number added to the label on the infusion bag.
- If returning IMP to the site Pharmacy (e.g. unused or expired pack) a MACE-ICH Return of Clinical Supplies form must be completed to accompany the packs. The Stroke Unit IMP Accountability Log should be completed, documenting return to the site Pharmacy.



MACE-ICH

Nottingham University Hospitals NHS Trust

Pharmacy Department Clinical Trials Service

Appendix 3

MACE- ICH Stroke Unit - IMP Accountability Log

Receipt				Issued to Subject						Return to Pharmacy			Comments
Date Received (dd/mm/yy)	Batch Number	Expiry Date	Received By	Date Issued (dd/mm/yy)	Subject Trial ID Number	Subject Name	Subject Hospital Number	Issued By	Check By	Date Returned to Pharmacy (dd/mm/yy)	Quantity Returned	Returned By	

MACE-ICH

Nottingham University Hospitals NHS Trust

Pharmacy Department Clinical Trials Service

Appendix 4

RETURN OF CLINICAL TRIAL SUPPLIES

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

Local Investigator: ..... Site:.....

The following clinical trial supplies have been returned to pharmacy

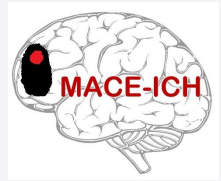
Description	Number of Bags Returned	Batch Number	Expiry Date
Mannitol Infusion 10% 500ml			

Stroke Unit Staff		Date	Pharmacy Staff		Date
Returned by			Checked & Received by		
Print Name			Print Name		

For Pharmacy Use Only

Action	Signature & Date	Outcome	Signature & Date
To be quarantined in pharmacy			
To be sent for destruction			
To be returned to Stock			

1 copy to investigator file 1 copy to pharmacy file

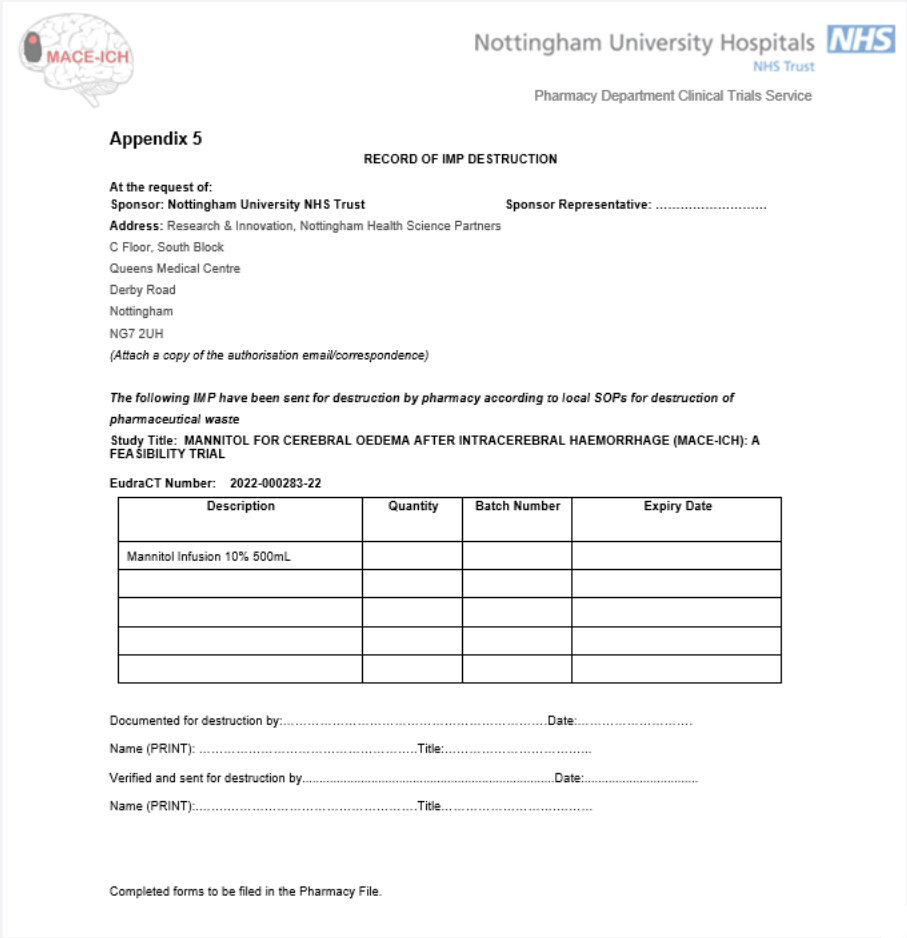


Investigational Medicinal Product (IMP)

IMP dispensing and accountability

IMP destruction

- Retain all returned unused infusion bags in pharmacy until permission is given to destroy.
- Destruction should be carried out by the site Pharmacy according to local SOPs, only after any discrepancies have been investigated and satisfactorily explained.
- Reconciliation will be accepted and confirmed in writing by the sponsor/representative prior to any destruction taking place. Destruction will be documented on the MACE-ICH IMP Destruction Log which should be filed in the pharmacy site file.
- Destruction of any study medication that is unused at the end of the study or has expired should only be completed following written approval from the sponsor.



MACE-ICH

Nottingham University Hospitals NHS
NHS Trust

Pharmacy Department Clinical Trials Service

Appendix 5

RECORD OF IMP DESTRUCTION

At the request of:
Sponsor: Nottingham University NHS Trust **Sponsor Representative:** .....
Address: Research & Innovation, Nottingham Health Science Partners
C Floor, South Block
Queens Medical Centre
Derby Road
Nottingham
NG7 2UH
(Attach a copy of the authorisation email/correspondence)

The following IMP have been sent for destruction by pharmacy according to local SOPs for destruction of pharmaceutical waste

Study Title: MANNITOL FOR CEREBRAL OEDEMA AFTER INTRACEREBRAL HAEMORRHAGE (MACE-ICH): A FEASIBILITY TRIAL

EudraCT Number: 2022-000283-22

Description	Quantity	Batch Number	Expiry Date
Mannitol Infusion 10% 500mL			

Documented for destruction by:.....Date:.....
Name (PRINT): .....Title:.....
Verified and sent for destruction by.....Date:.....
Name (PRINT):.....Title.....

Completed forms to be filed in the Pharmacy File.

MACE-ICH

Investigational Medicinal Product (IMP)

Alternative IMP labelling & accountability process

If preferable, research delivery teams (as opposed to pharmacy) can be responsible for IMP labelling and accountability, but the local process needs to be documented on a file note and sent to the coordinating centre (and filed in the ISF). The following will be acceptable if IMP is already stored on the ward:

1. The research team can overlabel infusion bags with the MACE-ICH label either at the point when a participant is recruited and randomised to receive mannitol OR prior to recruitment such that it is 'ring-fenced' for use in the trial [sites to indicate their local process].
2. The research team will complete the 'Stroke unit accountability log' (Appendix 3) to document IMP administered to participants. The research team will need to retain this in the ISF and email a copy to the coordinating centre upon request.
3. It won't be necessary for the research team to complete the 'IMP transfer request form' (Appendix 1) as the IMP will already be on the ward. Nor will it be necessary for pharmacy to complete the 'Pharmacy IMP inventory log' (Appendix 2) as they will maintain their own local records relating to the IMP being issued/returned to/from the ward.
4. Unused/expired/damaged infusion bags will be destroyed as per local Trust procedures so there is no need for research teams/pharmacy to complete the 'Return of clinical supplies form' (Appendix 4) nor the 'Record of IMP destruction' (Appendix 5). Sites need to confirm their local process on the file note.

Investigational Medicinal Product (IMP)

IMP prescription and administration

- **Prescribing the IMP**
  - IMP should be prescribed by appropriately trained medical practitioners.
    - ***Dr's do not need to be on delegation log to prescribe***
  - Record on the patient's drug chart or on the electronic prescribing and medicines administration system, referenced as part of the MACE-ICH trial.
  - The research team will record administration of the IMP on each participant's CRF, including dates, quantity, batch/serial numbers, expiry dates and trial number assigned to each participant.

- **Administering the IMP**
  - The treatment should be administered by clinical staff in accordance with local policy.
  - The infusion should be visually inspected before administration to ensure it is free from particles or crystallisation and suitable for use.
  - Administer via an infusion pump using a giving set with an in-line filter (15 micron).
  - At the end of each infusion, the bag, tubing and intravenous line should be visually inspected.
  - 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 on the CRF.

Investigational Medicinal Product (IMP)

IMP dosage and treatment regime

- 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

Calculated serum osmolality:

2 × (Na+) + Glucose + Urea (all in mmol/L)

https://www.mdcalc.com/calc/91/serum-osmolality-osmolarity

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

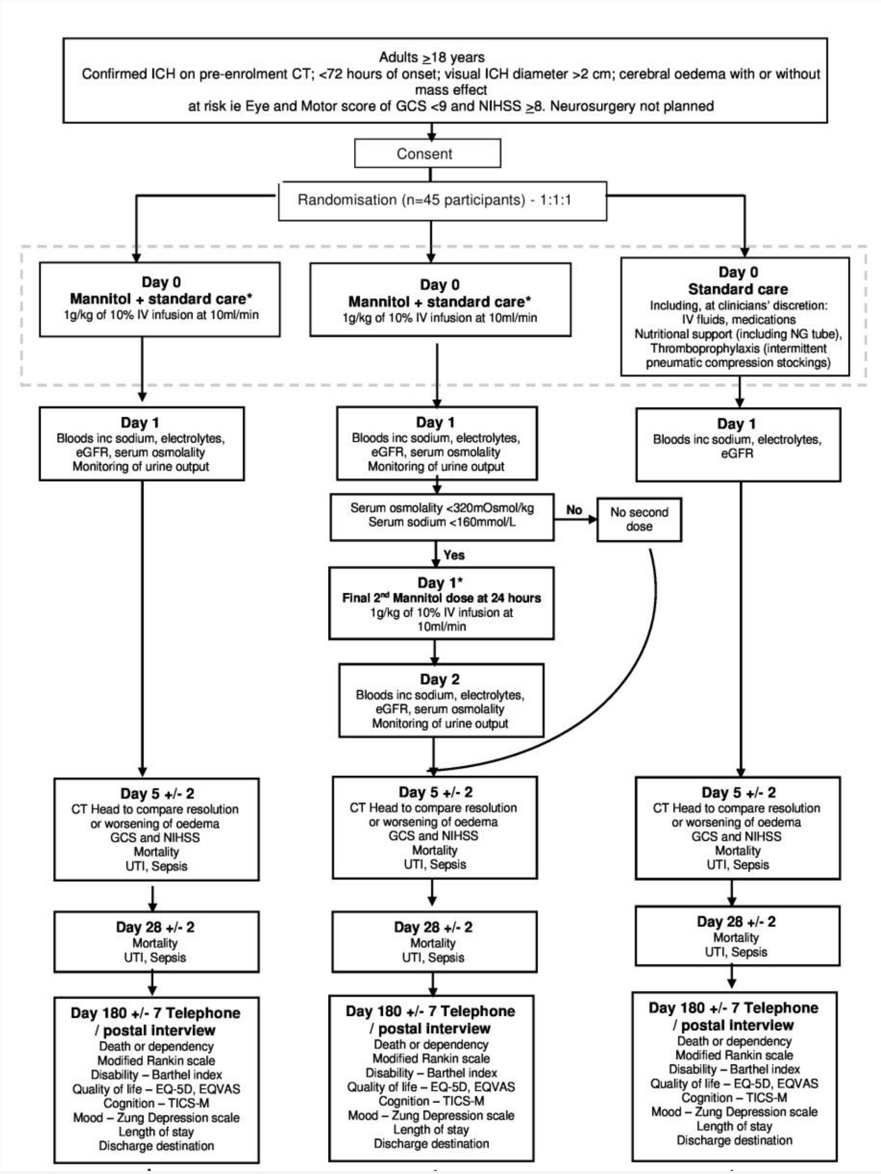
*There is no formal guidance about dosing in extremes of bodyweight. Review risk / benefit with fluid balance and comorbidities. Infusion time can be extended if concerns re: fluid overload.

Investigational Medicinal Product (IMP)

Acute kidney injury (AKI) following mannitol administration

- Mannitol is known to exert pressure on the kidneys due to the effects of hyperosmolality and dehydration.
- Literature reports have been variable, but AKI has been quoted as occurring in between 10-20% patients following mannitol infusion.
- Independent risk factors may include older age, dose above 200g/day (not included in MACE-ICH) and hypertension with DBP>100mmHg.
- The patient cohort included in MACE-ICH may also be at risk of AKI and dehydration due to disease severity, inability to take oral fluids (‘nil by mouth’), infection and concomitant medicines.
- A transient drop in renal function (eg AKI stage 1) may be expected but if recognised early is usually reversible. Every effort should be made to minimise other nephrotoxic medicines (such as diuretics, NSAIDS, aminoglycosides, drugs affecting Renin-Angiotensin system) during treatment with mannitol, and to maintain careful fluid balance.
- Clinical judgement should be used in determining if any renal impairment observed is a minor transient change as part of a patient’s overall clinical picture or a more significant Adverse Reaction (AR) or Serious Adverse Event (SAE) depending on the degree of harm.

Study flow



Blood tests

- **Pre-enrolment:** Blood tests as part of routine clinical care
- **Day 1:** Urea, sodium, eGFR, serum osmolality
- **Day 2:** Urea, sodium, eGFR, serum osmolality

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

Scans

- **Pre-enrolment:** Routine clinical CT head scan
- **Day 5 ± 2 days:** Single run, non-contrast CT head

Blood pressure

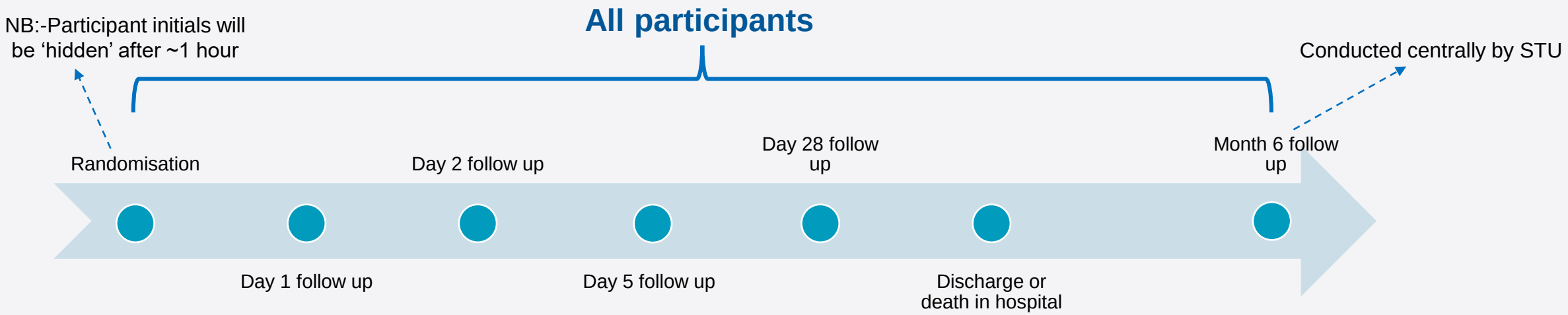
- **Before, during and after infusion:** Average of two measurements, taken 5 minutes apart, to be recorded at each time point
- Participants should receive 0.9% intravenous saline if systolic BP reduces to ≤ 90 mmHg

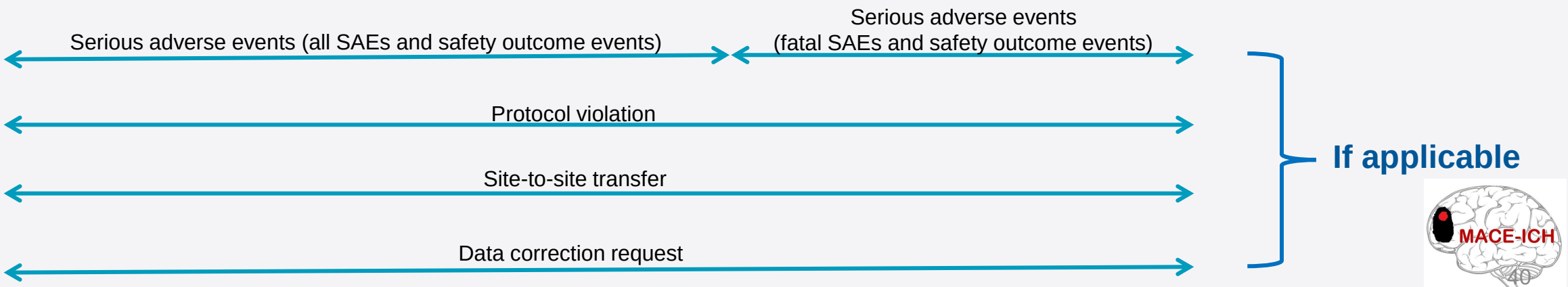
Urine output

- Monitored according to local clinical practice (recorded on day 1 and 2)

Study flow

Case report form schedule of completion





Safety reporting

Definitions

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.

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.

AEs and SAEs are recorded as part of the eCRF completion.

Safety reporting

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 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

Safety reporting

Reporting timeframes

- All SAEs/SARs/SUSARs during infusion and post-treatment up to and including Day 28 will be collected.
- Fatal SAEs and safety outcome events (relating to thrombophlebitis; hyper/hyponatremia; pulmonary oedema; hypotension; renal impairment) will be reported up to and including Day 180
- All SAEs/SARs/SUSARs are reported using the following process:
  - Complete the 'Serious Adverse Event or outcome' CRF on the trial database
  - Completion of the above CRF will partially auto-populate the 'TAFR01912 Serious Adverse Event Reporting Form (CTIMP and Other)'. Please download and complete all remaining items on the form, then email to: RDSAE@nuh.nhs.uk (cc in mace-ich@nottingham.ac.uk)
  - Where event outcome is unknown at the time of the initial SAE report, please complete 'TAFR01911 SAE Follow-up Form' with updates, until resolution of the SAE. This form should be emailed to: RDSAE@nuh.nhs.uk (cc in mace-ich@nottingham.ac.uk)
  - Any SAE updates must also be reported on the trial database using the 'Data correction request' CRF
- After discharge, participants will be asked to contact the study site immediately in the event of a serious adverse event.
- Sites must inform the Coordinating Centre, Chief Investigator and Sponsor immediately (**within 24 hours**) of any serious adverse events, and the CI will review seriousness and causality in conjunction with any treating medical practitioners.
- Sites should record and monitor all adverse events until resolution, stabilisation or until it has been shown that the study treatment is not the cause.
- SAE forms must be signed off by the PI and filed in the site file

Safety Reporting

Identify and record Adverse Event (eCRF)

Assess for Seriousness, Causality, Severity & Expectedness by PI or appropriately qualified, delegated individual

Report SAE, SAR & SUSAR to Sponsor on *TAFR01912, SAE Reporting Form (CTIMP and Other)*

Where event outcome is unknown at time of SAE report, complete and submit *TAFR01911 SAE Follow-up Form* with updates, until resolution of the SAE

Any SAE updates after the initial eCRF completion must be reported on the database using the 'Data correction CRF'

Chief Investigator and Principal Investigator Team Responsibilities (CTIMPs)

Chief Investigator Team Responsibilities	Principal Investigator Responsibilities
Comply with Study Protocol.	Comply with Study Protocol.
Ensure oversight of study safety reporting.	Ensure all Serious Adverse Events (SAE) are assessed for expectedness, relatedness and causality by a medically qualified member of staff.
Report study progress and safety information to the Trial Steering Committee and Data Monitoring Committee.	Report all Serious Adverse Events to the sponsor and Chief Investigator within 24hours.
Chief Investigator has a responsibility to review and evaluate trends and incidences of SAEs across the whole study.	Ensure there are enough medically qualified members of staff delegated to assess SAEs, to ensure that any SAEs can be signed and reported within 24 hours.
Read and comply with sponsor research Standard Operating Procedures.	Ensure the site research team have read and comply with sponsor research Standard Operating Procedures.

MACE-ICH

Protocol deviations and violations

Protocol deviations

- 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.
- Protocol deviations to inclusion/exclusion criteria are NOT permitted and may be considered a serious breach.

Examples:

- **Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:**
- 5±2 day follow-up: 3-6 days past the due date (≥7 days = protocol violation)
- 28±2 day follow-up: 3-29 days before/after the due date (≥30 days = protocol violation)
- 180±2 day follow-up: 7-29 days before/after the due date (≥ 30 days = protocol violation)

Protocol deviations and violations

Protocol violations

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.

Examples (please refer to the protocol for a full list):

- Failure to obtain appropriate consent prior to randomisation
- Randomising/treating a patient who does not meet inclusion criteria
- Patient not receiving the randomised treatment
- Failure to complete SAEs where appropriate

Serious Breach of GCP

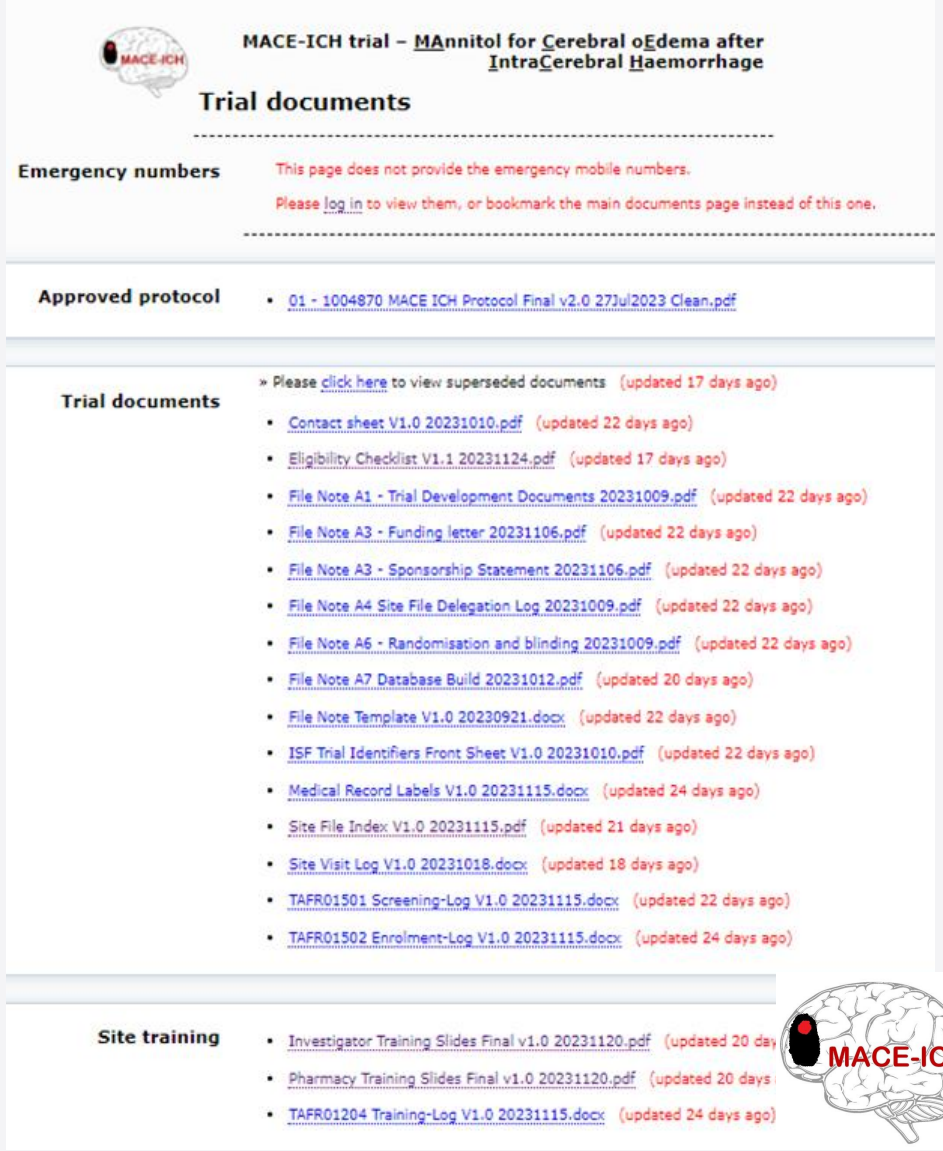
A serious breach of GCP effects to a significant degree the safety of the participant and/ or the scientific value of the trial. A significant breach requires an investigation to find out what happened, why and what will be done to prevent a further occurrence. Sites should adhere to local Trust policy (such as Datix). A serious breach is rare and would trigger escalation by the Sponsor, to the REC.

Protocol deviations and violations

- Complete the protocol violation CRF on the MACE-ICH database
- Document on an ***NUH Non-Compliance Reporting Form TAFR01705***
    - ***Submit to the Sponsor immediately***
        - email R&IQATeam@nuh.nhs.uk (cc in MACE-ICH@nottingham.ac.uk)
- The CI and Sponsor will review the non-compliance and will advise on the appropriate measures to address this.
- Violations are reviewed annually by the DMC (unblinded) and TSC (blinded).
- If in doubt, contact the trial office and sponsor.

Investigator Site File

- Please see the MACE-ICH documents page which can be accessed via the following link: https://stroke.nottingham.ac.uk/mace-ich/docs/
- The coordinating centre will not send hardcopy site files in the post for reasons of sustainability and version control. Sites are welcome to print and maintain a physical ISF if they prefer.
- The coordinating centre will send any amendment notifications electronically with guidance about whether any documents need superseding, we will then put the updated documentation on the MACE-ICH website.
- Must be stored in a secure location and only accessible by the research team



MACE-ICH trial – MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage

Trial documents

Emergency numbers

This page does not provide the emergency mobile numbers.

Please log in to view them, or bookmark the main documents page instead of this one.

Approved protocol

- 01 - 1004870 MACE ICH Protocol Final v2.0 27Jul2023 Clean.pdf

Trial documents

» Please click here to view superseded documents (updated 17 days ago)

- Contact sheet V1.0 20231010.pdf (updated 22 days ago)
- Eligibility Checklist V1.1 20231124.pdf (updated 17 days ago)
- File Note A1 - Trial Development Documents 20231009.pdf (updated 22 days ago)
- File Note A3 - Funding letter 20231106.pdf (updated 22 days ago)
- File Note A3 - Sponsorship Statement 20231106.pdf (updated 22 days ago)
- File Note A4 Site File Delegation Log 20231009.pdf (updated 22 days ago)
- File Note A6 - Randomisation and blinding 20231009.pdf (updated 22 days ago)
- File Note A7 Database Build 20231012.pdf (updated 20 days ago)
- File Note Template V1.0 20230921.docx (updated 22 days ago)
- ISF Trial Identifiers Front Sheet V1.0 20231010.pdf (updated 22 days ago)
- Medical Record Labels V1.0 20231115.docx (updated 24 days ago)
- Site File Index V1.0 20231115.pdf (updated 21 days ago)
- Site Visit Log V1.0 20231018.docx (updated 18 days ago)
- TAFR01501 Screening-Log V1.0 20231115.docx (updated 22 days ago)
- TAFR01502 Enrolment-Log V1.0 20231115.docx (updated 24 days ago)

Site training

- Investigator Training Slides Final v1.0 20231120.pdf (updated 20 da
- Pharmacy Training Slides Final v1.0 20231120.pdf (updated 20 days
- TAFR01204 Training-Log V1.0 20231115.docx (updated 24 days ago)

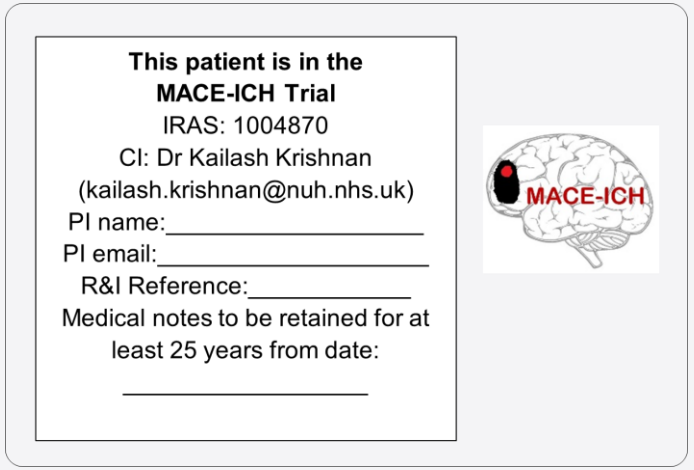
MACE-ICH

Data

Medical notes

- A copy of the consent form, information sheet and GP letter must be added to the patient medical record.
- A label (paper records) or alert (electronic records) should be added to the participant medical records detailing the R&I reference of the trial, the IRAS number, the abbreviated title and the Chief Investigator (CI) and PI contact details. It should be clear that the medical notes need to be kept for at least 25 years.
- A note should be made in the participant medical record with date of consent, consent form, PIS version and who received consent.

Medical notes label (available on the MACE-ICH document website)



Source data

- Original records of clinical findings and observations, or other activities in a clinical trial
- Can be medical records, clinical charts, lab notes, CRF, study diaries/logs etc.

Monitoring

Remote monitoring

- The trial coordinator will carry out the site monitoring visit remotely. A face-to-face visit may be triggered if there are ongoing concerns about a site despite remedies being suggested to resolve issues.
- The expectation is that sites will complete the monitoring documents, which will be signed off by the PI and returned to the Stroke Trials Unit. These documents include an ISF checklist and patient file checklists
- Sites will be notified of a sub-set of patients that have been randomly selected from the trial database to be monitored
- The completed monitoring documents will be reviewed by the trial coordinator and followed up with a report and action list

Monitoring

Document uploads

As part of the ongoing monitoring process, sites will be required to upload documentation to the secure vault for each recruited patient. Please upload as soon as possible after enrolment.

- **Consent form:** upload to secure vault within one working day of obtaining consent
- **Participant contact details:** used for day 180 follow up - upload to secure vault within five working days of randomisation
- **Prescription chart (pseudononymised):** showing correctly allocated treatment for all days- upload to the secure vault at the end of the treatment period
- **Clinical neuroimaging reports (pseudonymised):** for the baseline and day 5 ± 2 day clinical brain scans – upload to the secure vault within five working days of assessment
- **Baseline and day 5 ± 2 day CT scans (pseudononymised)** should be uploaded via the database (encrypted DICOM data) within five working days. If scans cannot be uploaded, please post to us on a CD (see Scan upload WPD for detailed guidance)
- **Blood test results (pseudononymised):** upload to the secure vault within five working days
- **Participant-specific file notes if applicable (pseudononymised):** upload to the secure vault within five working days

Any documentation with patient details should not be sent to the generic MACE-ICH email address

To pseudonymise documents mentioned above, please block out the patient's name and any other identifiable information and add their participant ID to the document. Consent forms should not be anonymised, but the participant ID should be added.

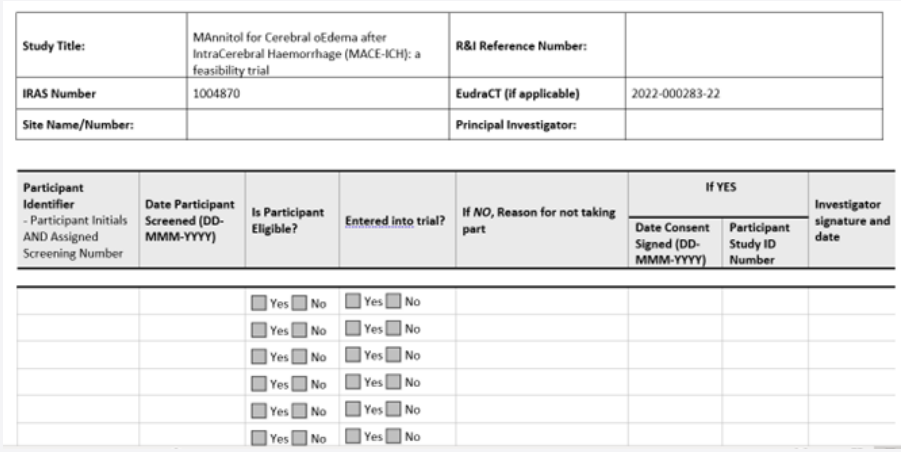
Monitoring

Screening logs

To be sent to mace-ich@nottingham.ac.uk on a monthly basis (**pseudonymised**)

- Please include all patients presenting within 72 hours of their stroke, including:
  - Eligible patients who are recruited
  - Eligible patients who were not approached (no staff available, out of hours etc)
  - Eligible patients who did not want to take part
  - Totals for ineligible patients (i.e., they do not meet the inclusion criteria, or they fulfil one or more of the exclusion criteria – please specify which are applicable)
- The cumulative totals must be recorded and sent across to the coordinating centre monthly

Please note:
Patient details should **not** be sent to the generic MACE-ICH email address – the log must be pseudonymised prior to sending.



Study Title:	MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial	**R&I Reference Number:**	
IRAS Number	1004870	**EudraCT (if applicable)**	2022-000283-22
Site Name/Number:		**Principal Investigator:**	

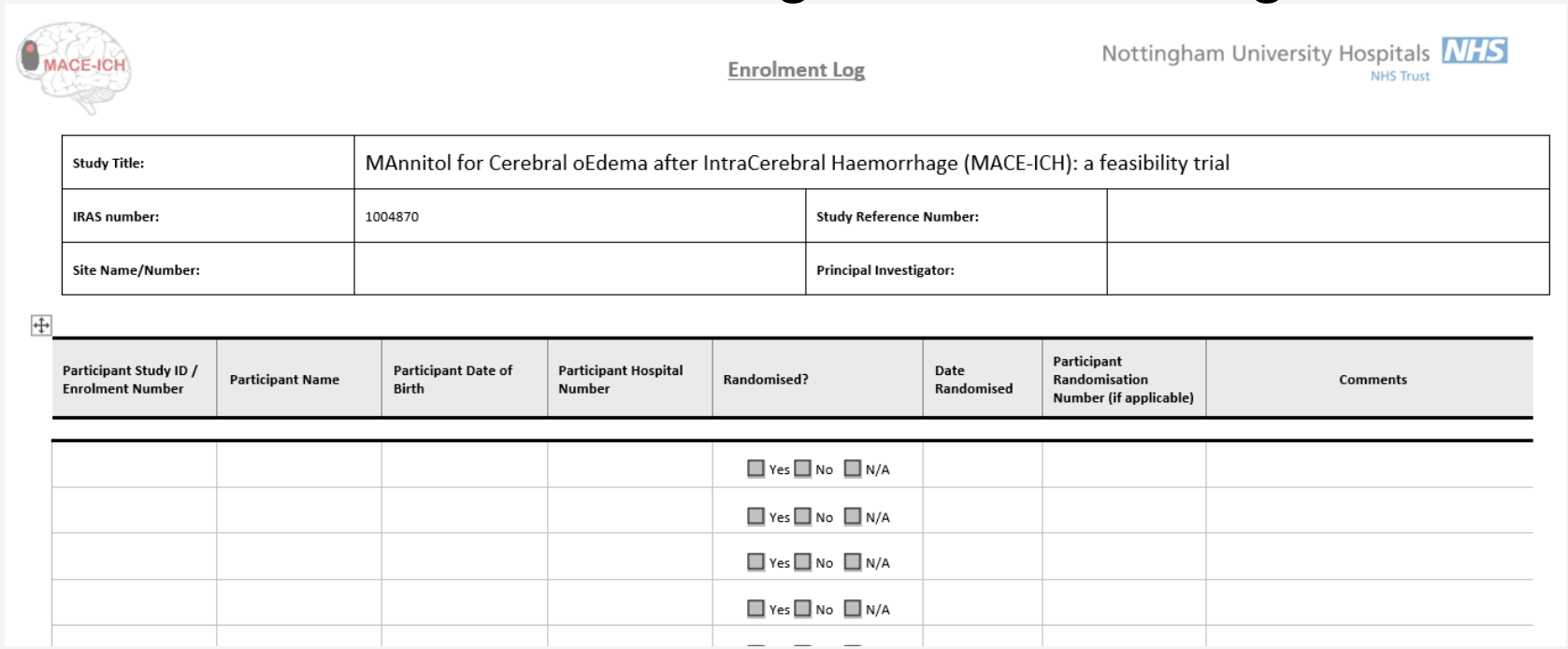
Participant Identifier - Participant Initials AND Assigned Screening Number	**Date Participant Screened (DD-MMM-YYYY)**	**Is Participant Eligible?**	**Entered into trial?**	**If *NO*, Reason for not taking part**	**If YES**		**Investigator signature and date**
					Date Consent Signed (DD-MMM-YYYY)	**Participant Study ID Number**	
		☐ Yes ☐ No	☐ Yes ☐ No				
		☐ Yes ☐ No	☐ Yes ☐ No				
		☐ Yes ☐ No	☐ Yes ☐ No				
		☐ Yes ☐ No	☐ Yes ☐ No				
		☐ Yes ☐ No	☐ Yes ☐ No				
		☐ Yes ☐ No	☐ Yes ☐ No				

Must be completed by someone on the delegation log

Monitoring

Enrolment logs

- To be updated when participants are recruited and stored in the ISF
- Do not need to be sent to the coordinating centre unless requested but will be reviewed during site monitoring visits



MACE-ICH

Enrolment Log

Nottingham University Hospitals NHS
NHS Trust

Study Title:	MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial		
IRAS number:	1004870	**Study Reference Number:**	
Site Name/Number:		**Principal Investigator:**	

Participant Study ID / Enrolment Number	Participant Name	Participant Date of Birth	Participant Hospital Number	Randomised?	Date Randomised	Participant Randomisation Number (if applicable)	Comments
				☐ Yes ☐ No ☐ N/A			
				☐ Yes ☐ No ☐ N/A			
				☐ Yes ☐ No ☐ N/A			
				☐ Yes ☐ No ☐ N/A			
				☐ Yes ☐ No ☐ N/A			

Must be completed by someone on the delegated investigator.

Participant contact details

- The coordinating centre follow-up coordinator will conduct the day 180 telephone follow-up
- Please ensure that the following information is uploaded to the secure vault:

  - Participant trial number
  - Name
  - Home address
  - Telephone number
  - NHS or CHI number
  - GP name and surgery address
  - NOK contact details

- If you have become aware that the patient's contact details have changed, please inform the trial coordinating centre

- **Note**: if the participant cannot be contacted or located, the site research staff will be requested to check the hospital system for changes in address or details

Co-enrolment

- Co-enrolment between MACE-ICH and certain interventional and non-interventional trials will be allowed; 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 (https://stroke.nottingham.ac.uk/mace-ich/).
- New co-enrolment requests need to be discussed on a trial by trial basis with the CI's of both trials and a decision taken by sponsors of both trials, with permission from the relevant safety committees.
- Co-enrolment will be subject to a co-enrolment agreement having been fully executed.
- Please always consider the burden on the patient – they must not be enrolled in more than two trials (i.e. MACE-ICH and one other from the approved list).
- Record co-enrolment on the discharge or death in hospital CRF.

NIHR Associate PI Scheme

NIHR | National Institute for Health and Care Research

- The scheme is open to any healthcare professional willing to make a significant contribution to the conduct and delivery of a study at a local level over a period of at least six months
- The Local PI acts as a mentor to the Associate PI, helping them to understand what it means to be a Local PI on an NIHR portfolio study
- During their time on the Associate PI Scheme, the Associate PI must complete a checklist of study activities and a learning pathway on NIHR Learn. This checklist needs to be signed off by the Local PI and the National Study Coordinator at the end of an Associate PI's time on the scheme
- The NIHR Associate PI Scheme team will then issue a certificate confirming Associate PI Status which can be added to their training portfolio
- For further information, visit the website **www.NIHR.ac.uk/AssociatePIScheme** or scan the QR code below

MACE-ICH

Trial SOPs

Sponsor SOPs for the trial (listed below) can be found on the following website:

https://www.nuh.nhs.uk/guidance-researchers.

- Site Initiation for NUH Sponsored Studies (SOP-RES-010)
- Site Green Light (SOP-RES-011)
- Maintaining Study Files (SOP-RES-014)
- Informed Consent (SOP-RES-015)
- Patient Health Records and Source Data (SOP-RES-016)
- Non-Compliance and Serious Breach Reporting (SOP-RES-017)
- Adverse Event Reporting (SOP-RES-019)
- Annual Progress and Safety Reports (SOP-RES-20)
- Out of hours medical cover (SOP-RES-021)
- Urgent Safety Measures (SOP-RES-022)
- Amendments to Active Research Studies (SOP-RES-024)
- End of Study Notification, Site Close Out and Reporting for NUH Sponsored Studies (SOP-RES-026)
- Archiving and Destruction of Records (SOP-RES-028)

What next?

Before we issue green light and you can start recruiting:

- ✓Signed training log after today's session
- ✓CVs and GCPs for trial staff
- ✓Signed contract
- ✓Confirmation of C&C from R&D
- ✓Staff to be authorised by PI on online delegation log

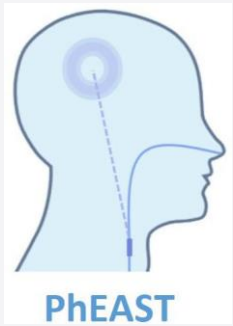
Please can we remind you to add mace-ich@nottingham.ac.uk to your contacts list – not doing so may mean you miss important automated emails from our database (including randomisation and SAE alerts).

Other STU trials

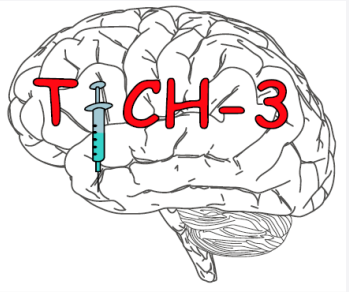
Other trials coordinated by the Stroke Trials Unit

MAPS-2

ENOS–2
Efficacy of Nitric Oxide in Stroke-2

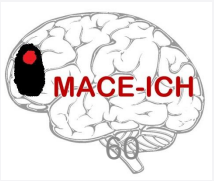


RECAST 3
REMOTE ISCHAEMIC CONDITIONING AFTER STROKE TRIAL 3



Please let us know if you are interested in taking part in any of our other trials by emailing the relevant trial mailbox:

MAPS-2: maps-2@nottingham.ac.uk
ENOS-2: enos-2@nottingham.ac.uk
PhEAST: pheast@nottingham.ac.uk
RECAST-3: recast-3@nottingham.ac.uk
TICH-3: tich-3@nottingham.ac.uk



University of Nottingham
UK | CHINA | MALAYSIA

FUNDED BY
NIHR | National Institute for Health and Care Research

NHS
Nottingham University Hospitals
NHS Trust

Thank you for listening
Any questions?

MACE-ICH

Email: mace-ich@nottingham.ac.uk

Website: https://stroke.nottingham.ac.uk/mace-ich/

Twitter: @MACE_ICH_Trial

Telephone: 0115 823 1770

Dr Kailash Krishnan
Chief Investigator

Di Havard
Senior Trial Manager

Solomon Adegbola
Follow Up Coordinator

Prof Philip Bath
Deputy Chief Investigator

Dr Jen Craig
Trial Manager

Sponsor: ResearchSponsor@nuh.nhs.uk

Emergency contact phone numbers:
Please log in to the MACE-ICH database to access

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