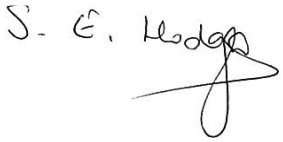
MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial

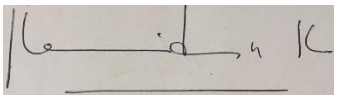
EudraCT NUMBER: 2022-000283-22

PHARMACY MANUAL

Version 1.0, 01Jul2022

Chief Investigator: Dr Kailash Krishnan
Sponsor: Nottingham University Hospitals NHS Trust
Sponsor Reference:22SR001

Written by: (Print & sign)	Sheila Hodgson		Date: 1st July 2022
Title	Clinical Trials Pharmacist.		

Approved by: (Print & sign)	Kailash Krishnan		Date: 11th July 2022
Title	Consultant Stroke Physician		

Applicability

This procedure applies to all pharmacy personnel at participating sites. Its purpose is to ensure that the processes of ordering, storing, labelling, dispensing accounting for and destroying IMP are carried out to the standard required for MACE ICH and in accordance with the applicable ICH-GCP principles.

Responsibilities

All personnel carrying out study related activities should be listed on the MACE ICH Authorised Personnel Log and be appropriately trained and familiar with the trial, its protocol and procedures.

1.Contents

2. Abbreviations

ICH-GCP	International Conference on harmonisation – Good Clinical Practice
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STU	Stroke Trials Unit
PI	Principal Investigator
PSF	Pharmacy Site File

3. Study Contacts

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4. Introduction

This is 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 of the trial protocol are not met, to help guide a definitive trial.

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 definite trial. Lower recruitment would not preclude progression if there is evidence that barriers to recruitment could be overcome.

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). The chosen dose is 1g/kg as this has been tested in traumatic brain injury but not exceeded in a single dose in previous trials.

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 55 mins
60	60g	600ml over 60 mins
65	65g	650mL over 65 mins
70	70g	700mL over 70 mins
75	75g	750mL over 75 mins
80	80g	800mL over 80 mins
85	85g	850mL over 85 mins
90	90g	900mL over 90mins
95	95g	950mL over 95 mins
100	100g	1000mL over 100 mins

*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 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.

5. Study Medication

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 at

https://www.medicines.org.uk/emc/product/1839

6. Storage

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. Medication may be kept on the Stroke Unit or 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

Sites should follow their standard procedures for ambient temperature monitoring. Ideally, a minimum and maximum temperature should be recorded, using a calibrated temperature monitoring device, every weekday (excluding bank holidays).

No special storage is required, but ideally store between 15 - 25°C. Do not refrigerate or freeze.

7. 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

Sample Label:

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 2018-001904-12

Label content will remain as shown above, however the formatting of final versions may vary.

8. Ordering

Hospital sites should source their own supplies from standard hospital supplies.

9. 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.

10. Prescribing

Only the PI or qualified medical doctors delegated with the responsibility of prescribing by the PI should prescribe medication for study patients.

Once a participant is randomised to mannitol treatment, this 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.

11. Dispensing & Accountability

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with UK regulatory requirements. Responsibility can be delegated to the site pharmacy clinical trials staff.

Pharmacy

The site 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 (Appendix 1) must be completed.

The pharmacy clinical trials staff will check that the person completing the Transfer Request Form has delegated responsibility by the PI by reference to the study delegation log.

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 (Appendix 2) and details completed on the MACE-ICH IMP Transfer Request Form.

Stroke Unit/Ward/Department

The Research Team will be responsible for dispensing the IMP to subjects.

Upon receipt of IMP from the site Pharmacy, allocation of IMP to a subject or return of used/unused packs to the site Pharmacy, the details should be recorded on the MACE-ICH Stroke Unit IMP Accountability Log (Appendix 3).

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.

Treatment should be recorded as having been administered to that patient on the medicines prescribing and administration chart, 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

If returning IMP to the site Pharmacy (e.g. unused or expired pack) a MACE-ICH Return of Clinical Supplies form (Appendix 4) must be completed to accompany the packs. The Stroke Unit IMP Accountability Log should be completed, documenting return to the site Pharmacy.

10. Administration

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 of the protocol. 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 in the CRF.

11. Code break & Unblinding

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.

12. 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 (Appendix 5) which should be filed in the PSF.

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.

13 Version Control

This is the first version of the document.

Version Number	Amended By	Amendment Date	Changes implemented by this amendment

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: …….

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				

Appendix 3

MACE- ICH Stroke Unit - IMP Accountability Log

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

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

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.