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

IRAS Reference: 1004870

Participant Information Sheet; Version 2.0, Dated 27Jul2023

Principal Investigator: [Site to Insert]

Logo

Description automatically generated

**Contact details**

**Chief Investigator**

**Name:** Dr Kailash Krishnan

**Address:** Stroke, Department of Acute Medicine, C floor, West Block, Queen’s Medical Centre, Nottingham, NG7 2UH **Telephone:** 01159249924

**Principal Investigator**

**Name:** [Site to Insert]

**Address:** [Site to Insert]

**Telephone:** [Site to Insert]

**Research Nurse**

**Name:** [Site to Insert]

**Address:** [Site to Insert]

**Telephone:** [Site to Insert]

**Emergency out of hours contact:** Dr Kailash Krishnan, 07771 542 937

# **What is the purpose of the study?**

Strokes from bleeding into the brain, known as intracerebral haemorrhage, affects about 15,000 adults in the UK each year and to-date there is no effective treatment. Brain swelling after intracerebral haemorrhage is common and can worsen damage, resulting in severe disability or death. Large haemorrhages (~10-15%) cause brain swelling very quickly, and the only option is to do a major operation, remove a part of the skull and make more space for the brain to expand. It is unclear whether surgery is beneficial, and the operation has its own risks. So, finding treatments that prevent or stop brain swelling after intracerebral haemorrhage could reduce death or disability.

Mannitol is a widely available drug and as an injection through a vein can reduce brain swelling after severe head injury or liver damage. It is cheap, readily available, and easy to give. Small studies suggest that mannitol may also reduce brain swelling after intracerebral haemorrhage, but no definite study has been performed.

We want to test whether it is possible to do a small study of mannitol in intracerebral haemorrhage, to find out how acceptable and manageable it is, to inform a larger study. We plan to recruit patients who have suffered an intracerebral haemorrhage with, or at risk of brain swelling into this study.

In order to do a proper comparison, we need to give some people the active drug (in this case mannitol) and others, no active drug (standard care alone). In this trial, participants will be allocated randomly, like the roll of a dice, to three groups: a single mannitol injection, two mannitol injections, or standard care alone. Participants will have blood tests and clinical assessments before, during and after-treatment. We will also do a repeat head/brain scan on all participants to see whether there are differences in the number showing signs of further bleeding and brain swelling.

We want to see whether information from this study will help guide a larger trial, to enable doctors to decide whether a treatment like mannitol can be used in patients with intracerebral haemorrhage, with or at risk of brain swelling, to try to prevent death and improve recovery.

# **Who has reviewed this study?**

Research in the NHS is usually looked at by an independent group called a Research Ethics Committee, to protect your safety, rights, well-being, and dignity. This study has been reviewed and given a favourable opinion by the NHS, Leicester Central Research Ethics Committee.

The study has also been reviewed and approved by the Health Research Authority and, the Research & Innovation department of Nottingham University Hospitals NHS Trust. Nottingham University Hospitals NHS Trust will act as the ‘Sponsor’ (i.e., the lead NHS hospital) for this research. The Trial / Study Coordinating Centre, at the University of Nottingham, will manage the conduct of the study. The NIHR Research for Patient benefit scheme will fund this research.

# **Why have I been asked to take part?**

You are being invited to take part because you have had a stroke caused by bleeding into the brain – this is called intracerebral haemorrhage and you have or are at risk of having brain swelling. We think that you are eligible for this study and we are inviting 45 participants like you to take part in the study.

# **Do I have to take part?**

No. It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you decide to take part, you are free to leave the study at any time and without giving a reason.

If you withdraw, we will still keep records relating to the treatment given to you, as this is valuable to the study. A decision to withdraw at any time, or a decision not to take part, will not affect the quality of care you receive.

# **What will happen to me if I take part in the study?**

Your involvement in this study will last for 6 months. In this trial we plan to test whether treatment with mannitol is acceptable and manageable for participants and researchers, in order to inform a larger study.

On the day you enrol, we will ask questions about your stroke, general health, medical history before the stroke, perform a medical examination and you will have a CT scan of the brain to confirm that you have had a stroke from bleeding in the brain. All of these are part of your routine, standard medical care regardless of whether you take part in this study or not. If you are a woman who might become pregnant, you will be asked to have a pregnancy test (urine or blood) before taking part.

Once we confirm that you are eligible to take part in this study, we will approach you to give permission to take part (consent). If you are unable to give consent, we will approach your relative/carer or an independent doctor to seek consent on your behalf to include you in the study, unless there is a reason not to.

Prior to treatment, your information will be entered into a computer which, like the roll of a dice will randomly allocate you to one of three groups: single mannitol injection; two mannitol injections or standard medical care alone. There is a one-in-three chance you will receive a single mannitol injection, a one-in-three chance you will receive two mannitol injections, and a one-in-three chance you will receive standard medical care alone (no mannitol injections). There is therefore a two-in-three chance that you will receive at least one dose of mannitol. Using randomisation to put patients into groups is the best way to get a true answer as to whether a treatment works or not. Once allocated by the computer, you will be told whether you will receive a single mannitol injection or two mannitol injections or standard medical care alone. Standard medical care means that you will receive and continue to have monitoring and other treatments, which is the same as for all stroke patients.

The study treatment (mannitol) will be started as soon as possible once you have decided that you wish to take part in the study, if you are randomised to receive this. A trained nurse will be responsible for giving your mannitol injection, and this will be given slowly through a drip. Through the drip, the mannitol will be delivered directly into your bloodstream. The length of the treatment will depend upon your body weight: the more you weigh, the longer the treatment will take to be given. For example, if you weigh 40kg, the treatment will take 40 minutes to be given, and if you weigh 100kg, the treatment will take 100 minutes to be given.

We will take blood samples from a vein in your arm to make sure that there are no harmful effects with treatment: one before we start the study treatment and a second extra sample 24 hours after treatment to check the salt levels in the blood stream. If you are allocated to two doses of mannitol, we will take a third blood sample the following day to check the salt levels in your blood stream. Wherever possible, these will be taken with any routine samples your doctor asks for.

We will need to make sure that your kidneys are working properly so a nurse or a member of the treating team will monitor the amount of urine passed during and after treatment. A urinary catheter, (a hollow tube) may be placed into the passage through which you normally pass urine (urethra). The catheter will be placed by a nurse or a doctor and the urine collected into a drainage bag. The catheter will be removed once treatment is complete unless the treating doctor has another reason to keep it in.

During the next 5 days, a nurse will check your condition looking in particular for side effects of the treatment. On all participants, we will perform a head/brain scan 5-7 days after treatment. This scan is additional to what you would receive as normal clinical care, and this is to see whether there is any effect on bleeding or brain swelling with treatment.

The head/brain scan will take less than 5 minutes to do but you will need to go to the x-ray department for the scan, which may take approximately an hour.

We will contact your GP or check with the NHS Information Centre to check on your condition six months after your stroke and, to confirm your contact details. You will then be contacted for a telephone consultation with a member of the research team. This may also be conducted by postal questionnaire if you prefer. This is to check your health condition at that time. It will involve asking how well you are recovering after the stroke, how you are able to move around, about how you feel your life has been affected after the stroke, your mood, and some brief memory tests. In order to make this evaluation of the study as objective as possible, the person who telephones you will be a member of the research team from the University of Nottingham and will not know if you received the active treatment (mannitol) or not. We will ask your permission for a personal legal representative (such as a relative or carer) to provide this information on your behalf during the follow-up, in the event you become either non-contactable or incapacitated during the course of the study, and thus unable to provide the information yourself.

Being part of the study will require a modest time commitment to complete the questionnaires (around 10-15 minutes for each questionnaire). However, this information we collect will be very useful to help us to know how best to treat patients with intracerebral haemorrhage in the future.

Participants will not be paid to participate in the study. There will be no charge for participation in the trial, including for trial medication.

There is a possibility you may also be approached to take part in other studies. You will be provided a separate information sheet and consent form for any other study. Where possible, if both studies require the same information, for example, the same questionnaire completing at the same time, we will only ask you to complete one, and your responses will be used across both studies, to reduce any burden on you. We do not know whether you will benefit from being enrolled in other studies, but we would like to give you the option to do so. A list of other studies that you may also participate in (if you are eligible) is available on the study website: https://stroke.nottingham.ac.uk/mace-ich/.

# **What do I have to do?**

We will ask you to take this information sheet and consider whether you wish to take part in this study. If you decide to proceed, or would like further information before making a decision, please ask any questions you need to ask. We will ask you to sign a consent form if you wish to proceed. There is also a contact number given at the start of this information sheet for you to phone if you become worried at any time. In the unlikely event of an emergency occurring during the conduct of the study, we may contact your nominated next of kin.

# **What are the possible benefits?**

Your participation in this study may reduce the symptoms of intracerebral haemorrhage, may save your life, and may improve long-term recovery. However, we cannot promise that this study will help you and that is why we are undertaking this research. Your participation in this study is voluntary. We hope that the information we get from your involvement will provide benefit to other people who have a stroke in the future.

# **What are the disadvantages?**

Treatment with any drug can result in side effects. Common side effects of mannitol are increased urination, nausea, vomiting, fever, chills, headache, runny nose, chest pain, rash, dizziness, or blurred vision. The drug can cause burning, pain or swelling around the needle when it is given as an injection and the treating team will closely monitor you for this.

Mannitol can affect the salt levels in the blood, cause damage to the kidneys, worsen bleeding in the brain, or lung congestion, but how often this happens is not known. If you have previously suffered from severe or long-term kidney disease or severe lung congestion, you may not be able to participate in this study.

Because mannitol is already routinely used to reduce brain swelling from liver damage or severe head injury, we expect the potential benefits of the drug (stopping or preventing brain swelling in intracerebral haemorrhage) to outweigh the risk of side effects. However, we do not know this for certain and will monitor participants for side effects.

You will have blood tests from the vein in your arm and this can cause mild discomfort/pain and slight bruising.

You must inform your doctor or member of the research team if you feel that you have had a reaction to the medication.

You will have one CT scan of the head/brain performed as part of the trial which will be extra to what you would have if you did not take part. This is exactly the same CT scan which you had when you first came to hospital. The scan itself takes less than 5 minutes and does not involve any injections. The scan uses X-Rays, which in large amounts can be harmful, but for this extra CT head/brain scan the additional risk to you from the scan has been judged to be extremely small.

You will need to be followed up by the research team for 6 months after starting the study.

# **Will my taking part in this study be kept confidential and how will my data be used?**

All the information about your participation in this study will be kept confidential. We will keep all information about you safe and secure.

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper, and electronically at your treating hospital and at Nottingham University Hospitals NHS Trust, and the University of Nottingham, under the provisions of the General Data Protection Regulation and the Data Protection Act. Your name will not be passed to anyone else outside the research team or the sponsor, who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms. Under UK Data Protection laws, Nottingham University Hospitals and the University of Nottingham are joint Data Controllers (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). There is a possibility you may also be approached to take part in other studies, sponsored by either Nottingham University Hospitals NHS Trust, or the University of Nottingham. You will be provided a separate information sheet and consent form for each study. Where possible, if both studies require the same information, for example, the same questionnaire completing at the same time, we will only ask you to complete one, in order to reduce any burden on you, and your responses will be used across both studies. This may require sharing of some of the study data for this purpose. Any data sharing will be in accordance with agreements between Nottingham University Hospitals NHS Trust (the sponsor for this study), and the sponsor for any other study you are participating in, and will be in accordance with the provisions of the General Data Protection Regulation and the Data Protection Act.

If you withdraw consent from further study treatment, your data will remain on file and will be included in the final study analysis.

Your contact information will be kept by the University of Nottingham for 6 months after the end of the study so that we are able to contact you about possible follow-up studies (unless you advise us that you do not wish to be contacted). This information will be kept separately from the research data collected and only those who need to will have access to it. In line with Good Clinical Practice guidelines, at the end of the study, all other data (research data), will be securely archived for a minimum of 25 years. Arrangements for confidential destruction will then be made.

Your GP (and other doctors who may be treating you) will be notified that you are taking part in this study.

The information collected about you may also be shown to authorised people from regulatory organisations, including the Medicines and Healthcare products Regulatory Agency and the sponsor to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant.

We will need to use information from you, your medical records, and your GP for this research project. This information will include your:

* Initials
* Date of birth
* NHS number (or CHI number, for Scottish sites)
* Full name
* Ethnicity
* Contact details for follow-up (telephone number, mobile number, or email address, if available)
* Contact details for a legal representative (telephone number, mobile number, or email address, if available)
* Address
* GP contact details

held by site and / or sponsor for the research.  People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records / your hospital / your GP. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won’t be able to let you see or change the data we hold about you.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

You can find out more about how we use your information:

* at [www.hra.nhs.uk/information-about-patients/](https://www.hra.nhs.uk/information-about-patients/)
* our GDPR leaflet available on request from [researchsponsor@nuh.nhs.uk](mailto:researchsponsor@nuh.nhs.uk); or by the following link [www.nuh.nhs.uk/gdpr](http://www.nuh.nhs.uk/gdpr)
* by asking one of the research team
* by emailing the Data Protection Officer for NUH at [dpo@nuh.nhs.uk](mailto:dpo@nuh.nhs.uk), or UoN at dpo@nottingham.ac.uk.
* by ringing the Data Protection Officer for NUH on 0115 924 9924 (extension 63975), UoN at 0115 951 5151, or by visiting [www.nuh.nhs.uk/gdpr](http://www.nuh.nhs.uk/gdpr)
* https://www.nottingham.ac.uk/utilities/privacy

# **Informing your General Practitioner/Family doctor (GP)**

If you are enrolled in the study, we will inform your General Practitioner and other doctors involved in your care.

# **What will happen to the blood and urine samples I give?**

Blood samples will be taken by the medical team responsible for your care in hospital. The samples will be labelled, stored, and analysed according to local, standard NHS policy. Once analysed, the study samples will be destroyed in accordance with the Human Tissue Act.

The results of your blood tests will be made available to your treating doctor or a member of the research team. This is a safety precaution and is important to make sure that treatment is not causing any harmful effects to the salt levels in your blood. We will collect this information as it helps us understand whether treatments like mannitol can be used in patients with intracerebral haemorrhage with, or at risk of brain swelling.

We will collect data on whether you are passing urine and whether you contract any urinary tract infections (UTIs) whilst in hospital. Any urine samples will be collected, labelled, analysed, and destroyed in accordance with your local hospital’s routine practice.

We will not be storing any of your blood or urine samples for the study.

You have the right to withdraw your consent at any time during the study. If consent is withdrawn, then no further data involving your blood and urine samples will be collected. All data up until the point of consent withdrawal, however, cannot be erased and will still be used in the final analysis. If consent is withdrawn, the results of safety blood and urine tests will still be passed to your treating physician, as per your usual care.

# **Will any genetic tests be done?**

No, we will not be collecting any genetic samples.

# **What happens if new information becomes available?**

If new peer-reviewed information on mannitol in intracerebral haemorrhage becomes available in the course of this study, the Chief investigator (named above), members of the study group and the group which is responsible for study oversight (Trial Steering Committee) will review this information and decide whether this will impact on the conduct of this study. In the event that any new information impacts on the study, an updated participant information sheet will be created, and you will be asked to re-consent to continue in the study.

An independent data monitoring committee will monitor the safety of the study’s participants throughout the study and will make sure that any relevant information is taken into account on the ongoing conduct of this study.

# **What will happen if I don’t want to carry on with the study?**

You are free to withdraw from the study at any time without giving a reason. This will not affect the medical care you will receive. If you were to lose capacity during the trial and were unable to decide whether you would like to continue in the trial, and an objection to your continuation was raised by your representative (relative, friend); then you would be withdrawn from the study. If you were to be withdrawn, we will no longer collect any information about you or from you, but we will keep the information about you that we have already obtained. This is because we should not tamper with study records, the information may have already been used in some analyses, and may still be used in the final study analyses.

# **What happens when the study is finished?**

The results from your assessments and scans will be anonymised and combined with other study participants for analysis. The results will be published in a journal where they can be read but it will not be possible for anybody to identify that you took part in the trial. We will then decide whether the results from this research will be used to inform future emergency treatments for patients with intracerebral haemorrhage. If the findings of this clinical trial show that mannitol can be safely given, the effects can be monitored, and participants can be followed up effectively, a larger clinical trial using mannitol for the treatment of brain swelling after intracerebral haemorrhage may be conducted in the future. There is an optional clause in the consent form that seeks your permission to use your confidential data in further research about intracerebral haemorrhage, such as this proposed larger trial.

Once the trial has finished, a summary of the results will be available to send to you by post and/or email (whichever is preferred). Your contact details will be securely retained for this purpose, and there is an optional clause in the consent form that will give you the opportunity to opt in or out of us retaining your details and sending you the summary of results.

# **What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. The researchers’ contact details are given at the start of this information sheet. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure.

Details can be obtained from the hospital or you can contact Nottingham University Hospitals NHS Trust’s (trial sponsor) Patient Advice and Liaison Service (PALS), telephone 0800 183 0204. Alternatively, you may email the PALS team at [PALS@nuh.nhs.uk](mailto:PALS@nuh.nhs.uk), or write to them using the following address: Patient Advice and Liaison Service, Queen’s Medical Centre, Derby Road, Nottingham, NG7 2UH. If you reside in Scotland, please contact the Patient Advice and Support Service (PASS) on 0800 917 2127.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone’s negligence, then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

# **Further Information**

You are encouraged to ask any questions you wish before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor who will be able to provide you with up to date information. If you require any further information or have any concerns while taking part in the study, please contact your study nurse or doctor (both are listed at the top of this document). If you wish to read the research on which this study is based, please ask your study nurse or doctor.

If you decide you would like to take part, then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your medical notes and one will be filed with the study records.

Thank you for taking the time to read this information sheet and to consider this study.

Further information and contact details:

Trial/Study coordinating Centre:

Stroke Trials Unit, Mental Health and Clinical Neurosciences,

Queen’s Medical Centre

Room 2108, D Floor, South Block

University of Nottingham

Nottingham

NG7 2UH

Phone:01158231770