Duke University Health System

Consent to Participate in a Research Study
ADULT
Ferritin and Iron burden in SAH (UDISCO Study)

If you are acting as a representative to give consent for another person to participate in this study, "you" throughout this consent form refers to that individual. Your role is to try to determine what the individual would decide to do if competent. If the subject's wishes can't be determined, you should decide what you think is in the person's best interest. If, during the course of the study, the subject regains the ability to make decisions he/she will be asked to read this consent form and decide whether to continue participation.

CONCISE SUMMARY

This is a research study to assess whether deferiprone, a drug that binds iron so that the body can get rid of it, can slow or improve the cognitive decline in patients with a bleed in the brain called a subarachnoid hemorrhage (SAH) from aneurysm (aSAH) compared to standard care. The use of deferiprone in this study, is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration for this purpose.

As part of this study you will have tests, exams and procedures that are for study purposes. You will be randomized (like flipping a coin) to either the study drug deferiprone along with standard of care treatment, or a placebo (a drug that is similar in color and taste to deferiprone but has no active medication ingredients in it, similar to a sugar pill) along with standard of care treatment.

Involvement in this trial will last for 6 months. You will be asked to return to clinic for examination at 6 weeks and 6 months. Each visit will last about an hour.

There are risks to this study drug that are described in this document. Some risks may include: increased or decreased appetite, nausea, vomiting, diarrhea, stomach upset, sleepiness, or colored urine. We do not know if you will benefit from being in this study. However, we hope that, in the future, other people might benefit from this study because it will help us better assess the relationship between iron load and cognitive impairment in patients with subarachnoid hemorrhage. If however, deferiprone was found to improve cognition, it will be the first drug to affect cognition in patients with subarachnoid hemorrhage.

You do not have to participate in this research to be treated for your condition. Your personal healthcare provider can discuss alternatives.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you have been diagnosed with a bleed in the brain called a subarachnoid hemorrhage (SAH) from aneurysm (aSAH). An aneurysm is a bulge in a blood vessel caused by a weakness in the blood vessel wall, usually where it branches. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form

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with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. David Hasan will conduct the study and it is funded a grant from the National Institutes of Health (NIH). Portions of Dr. David Hasan and his research team's salaries will be paid by this grant.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. David Hasan will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this research study is to assess whether deferiprone can slow or improve the cognitive decline in patients with aSAH compared to standard of care.

Patients with aSAH are known to have cognitive decline and most are unable to return to work. This is thought to be due to the iron deposition and iron toxicity after the breakdown of the blood products in the brain. Deferiprone is an iron chelator, which means that it binds iron so that the body can get rid of it. There is animal evidence that it does help with cognition. There is human evidence that it helps reducing the iron burden, but it is not known whether this will slow or improve cognition. Since this is unknown, deferiprone, is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration for this purpose.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 66 people will take part in this study at two different hospitals/medical facilities, and approximately 21 people will take part at Duke.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study you will be asked to sign and date this consent form. You will have the following tests and procedures for research purposes:

- Electrocardiogram (EKG/ECG) – if not already completed as part of your standard workup
- Magnetic Resonance Imaging (MRI) at the start and then again before you are discharged from the hospital
- Blood work to assess your white blood cell count (WBC) and liver function (about 2 teaspoons of blood)
- Medication started, either the deferiprone or placebo (depending on which one you were randomized to, which is like flipping a coin a 50/50 chance) twice daily for 14 days. You will not

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know which medication you have been randomized to and nor will your study team. Deferiprone or placebo will be administered orally (by mouth) or via nasogastric (NG) tube (a tube that goes into your nose and down to your stomach) twice a day for 14 days.

- If you have a tube to drain the fluid from your brain called Cerebral Spinal Fluid (CSF), we will collect the CSF daily while you have the tube
- If you don't have the tube to drain the CSF, we will do a Lumbar Puncture (LP) at the start and then again on day 14 (whichever comes first). If you have the tube and it is removed before day 14, an LP will be performed; however, if the tube is removed closer to discharge, no LP will be done.
- Another EKG will be done at study day 10
- Daily blood work to check your WBC for 14 days and then at the 6-week clinic visit (about 1 teaspoon of blood each time)
- Liver function blood work (1 teaspoon of blood) repeated at study day 10
- Computed Tomography (CT) scan will be done at the 6-week visit. This is part of your standard of care treatment and will be billed to your insurance.
- Cognitive testing will take place at 6 months (visit may last 30-60 minutes)
- MRI will be repeated at 6 months

The aneurysm will be treated with coiling within 12 hours from stroke event per standard of care and consent for that procedure will be obtained separately.

The study is double blinded, which means that both you and your study team will not know if you are receiving the deferiprone or the placebo.

Cognitive Tests: At your 6-month clinical follow-up visits, we will ask you a set of questions to assess your thinking ability via neurocognitive tests. These tests will take about an hour each time.

Lab tests: While you are on the study drug therapy or standard of care, the blood that is drawn weekly for standard clinical purpose, will be sent for additional testing for research purpose to monitor your liver enzymes, to ensure that you are not having any reaction to the drug. The CSF will be collected from the tube in your brain and sent for testing from day 1 of enrollment to day 7-10, depending on whether you still have the tube or not. Your spinal fluid is sent for testing of iron handling protein. These extra liver enzyme tests as well as the spinal fluid collection will be done for research purposes only.

Imaging: Soon after you are admitted, before you are discharged and at a 6-month clinical follow-up, you will undergo an MRI (~45 minutes) to assess the quantity of iron deposits in your brain and to measure structures in your brain that are related to cognition (amygdala and hippocampus). These scans will be done for research only but will be included in your medical record.

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HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 6 months.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

We may learn things about you from the study activities, which could be important to your health or to your treatment. If that happens, Dr. Hasan will let you know.

WHAT ARE THE RISKS OF THE STUDY?

You may experience one or more of the risks indicated below from being in this study.

You may have minor headaches during the spinal fluid collection, which usually resolves quickly. We can offer you pain relief medication if this occurs.

Deferiprone

Physical side effects of the study drug deferiprone are described below. The risks below were described in previous studies in participants who do not have the same condition as you.

Likely / Common (more than 35%)

Mild

- Increased or decreased appetite.

Less Likely/ Less Common (10-35%)

- Stomach upset
- Nausea
- Vomiting
- Diarrhea
- Sleepiness
- Colored urine

Rare (less than 10%)

Life Threatening

- Agranulocytosis (loss of all white blood cells) (1.7%)
- Neutropenia (Low white blood cell count)

Serious

- Elevated liver enzymes (5%)
- Cardiac toxicity: This drug has caused abnormal heart rhythms in people prone to abnormal heart rhythms called QT prolongation

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- Joint pain or disease (like arthritis)

Mild

- Allergies
- Indigestion
- Bodily pain (in back or arms/legs)
- Headache
- Weight change

Diazepam (Valium)

Likely/Common (more than 10%)

- Drowsiness

Less Likely/Less Common (5-10%)

- Headache
- Nasal discomfort

Reproductive Risks: Pregnancy after a subarachnoid hemorrhage is associated with an increased risk of maternal complications, including blood clots or another hemorrhage. In addition, the effects of deferiprone on embryo development can be fatal. CT scanning is not often recommended in early pregnancy unless medically necessary because of potential risk to the baby. Women who are pregnant, breast-feeding, or intend to become pregnant are therefore not allowed to participate in this study.

If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood pregnancy test will be done and it must be negative in order to continue. In women 40 years old and older, blood pregnancy tests can sometimes give a false positive or indeterminate result and additional testing may be needed to confirm your eligibility.

You and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study or use an effective method of contraception for the same length of time once your study doctor informs you that it is safe to resume sexual activity. Because some birth control methods need to be stopped around the time of your surgery or may increase the risk of blood clots your study doctor will discuss options with you, depending on your current method, your personal preferences, and the level of effectiveness required by this study.

Because no birth control method is 100% effective, you should notify your study doctor immediately if you think there is any chance you could be pregnant. If pregnancy is confirmed, your study doctor will continue to follow you to collect information on your health during pregnancy and, if appropriate, on the health of the baby.

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Risks of CT Scan: Computed Tomography (CT) is a way to make x-ray images of the inside of the body. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures that show structures inside your body more clearly than regular x-ray pictures. During the procedure, a technologist will take you into the CT scan room where you will lie down on the patient table (usually on your back) inside of the CT machine. You should get comfortable because it is very important that you not move during certain parts of the test.

CT examinations differ depending on the part of your body being studied. For example, if your abdomen is being studied, a series of pictures will be taken from your lower chest to your lower pelvis. During the study, you will be asked to hold your breath so that the pictures will not be blurred. The machine will make some noise, and the table will move during the scan. Also, you may receive signals from the technologist or from the machine about your breathing. Before or during the study, you may be given an injection of a contrast liquid in your vein to allow the radiologist to obtain clearer images of your organs. If you have any discomfort during the test or after the injection, be sure to tell the technologist.

Risks From Imaging Tests That Use Radiation
If you take part in this research, you may have one or more CT brain perfusion scans, which use radiation. To give you an idea about how much radiation you will get each time a CT brain perfusion scan is done, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year called the 'natural background'. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. The chart below the amount of time in the natural background that gives an amount of radiation that is about equal to the amount of radiation each time you have the test.

A possible health problem seen with radiation exposure is the development of cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is also shown in the chart. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

Test	'Natural Background Time' Equivalent for Each Time This Test is Done	Extra Cancer Risk Each Time This Test is Done
CT Brain Scan	1 Years	Very Low

You may have a number of medical imaging exams that are part of the regular care for your condition, and you would have them whether or not you participate in this research. These studies will not add to the risk of the research. However, if you have concerns about the overall radiation exposure, you should discuss them with your physician.

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Risks From Imaging Tests That Do Not Use Radiation

You may have an MRI study as part of this research. MRI uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body, including medical implants, devices such as pacemakers and internal defibrillators, or certain dyes found in in tattoos. We will also keep the MR room locked so that no one carrying metal objects enters the room while you are in the scanner.
If there is any question about potentially hazardous metal within the body, you will not undergo the MRI. This may exclude you from participation in this research study. The MRI involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the MRI. During the MRI, you can have voice contact and physical contact with someone in attendance if you desire. Let the study doctor know if you have a fear of enclosed spaces.

You may have a number of medical imaging exams that are part of the regular care for your condition, and you would have them whether or not you participate in this research. These studies will not add to the risk of the research. However, if you have concerns about the overall radiation exposure, you should discuss them with your physician.

If an oral sedative is required for your MRI(s), the following risks may be applicable to you:

- Drowsiness
- Fatigue
- Muscle weakness
- Ataxia (poor muscle control)
- Falls/Injury

If you do require medication to relax, you should not drive a car, take part in activities like riding a bike, or perform other similar tasks until the next morning, because the medication(s) can affect your thinking for several hours and can slow down your reflexes.

Risks of Drawing Blood: Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

ECG (Electrocardiogram) Risks: Possible side effects of the ECG are skin irritation, itching and redness from the ECG electrode pads.

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Drug and Food Interactions: For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

Risks of a Lumbar Puncture:

- Serious complications of this procedure are rare.
- You may feel some pain for a short while when the needle is being inserted.
- A few hours or days after the lumbar puncture, you may experience headaches, nausea, a fast heart rate, or low blood pressure. These after-effects usually go away on their own after about five days.
- In very rare cases, inflammation, bleeding or other complications that need to be treated in a hospital may arise after a lumbar puncture.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
We do not know if you will benefit from being in this study. However, we hope that, in the future, other people might benefit from this study because it well help us better assess the relationship between iron load and cognitive impairment in patients with subarachnoid hemorrhage. If however, deferiprone was found to improve cognition, it will be the first drug to affect cognition in patients with subarachnoid hemorrhage.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you would receive standard of care treatment without deferiprone.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, imaging studies, and procedures may be reported to the NIH and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives and affiliates of the National Institutes of Health, the Duke University

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Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests, imaging studies, and/or procedures performed. Some of these tests, imaging studies and/or procedures would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the representatives and affiliates of the NIH. Results of tests and studies done solely for this research study and not as part of your regular care will also be included in your medical record.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at Duke University Health System (DUHS). Any research information in your medical record will be kept indefinitely.

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This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
You will not have any additional costs for being in this research study. The study drug (whether deferiprone or placebo), brain MRI scans on admission and before discharge from the hospital and at the 6-month follow-up visit, the CSF testing, the lab tests completed for research purposes only, and the cognitive battery testing will be paid for by the study.

You/your health insurance company will remain responsible for your regular medical care expenses that are not part of this study. Ask your study doctor to discuss the costs that will or will not be covered by the study.

WHAT ABOUT COMPENSATION?
If a hotel stay is required because of study visits or your surgery, you may request up to $150 for one night to subsidize cost. Additionally, you will receive $75 per completed study visit and up to $50 for gas for your vehicle per completed study visit. You will also be offered $150 for each lumbar puncture, if any.

No further compensation will be provided.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. David Hasan at 919-681-2512 during regular business hours and at 319-400-9455 after hours and on weekends and holidays.

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WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your samples and/or data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Hasan in writing and let him know that you are withdrawing from the study. His mailing address is:

Dr. David Hasan
DUMC Box #3807
40 Duke Medicine Circle
Durham, NC 27710

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent. Reasons why this might occur include the finding that there are no benefits from the study or there are more complications than anticipated. If this occurs, you will be notified and your study doctor will discuss other options with you.

A description of this clinical trial will be available on https://clinicaltrials.gov/ as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. David Hasan at 919-681-2512 during regular business hours and at 319-400-9455 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____ _____ _____
Signature of Subject Date Time

_____ _____ _____
Signature of Person Obtaining Consent Date Time

_____ _____ _____
Signature of Legal Representative Date Time

_____
Relationship to Subject

"I have been informed that consent was given by my Legally Authorized Representative for me to be a subject in this research study. I have had the opportunity to review this consent and have had my questions answered to my satisfaction."

_____ "I consent to continue my participation in this study.
Initials

_____ "I do not consent to continue my participation in this study.
Initials

_____ _____ _____
Signature of Subject Date Time

_____ _____ _____
Signature of Person Obtaining Consent Date Time