The University of Alabama at Birmingham

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY AND AUTHORIZATION TO USE PROTECTED HEALTH INFORMATION

TITLE OF STUDY: A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1 ("STARS")

(For purposes of this trial, only children between the ages of 8 years to less than 16 years of age will be enrolled)

IRB Protocol Number: F090202002

PRINCIPAL INVESTIGATOR: Bruce Korf, MD, PhD
Co-Principal Investigator: Alyssa Reddy, MD

Sponsor: The United States Army – The Department of Defense

"You" refers to "You" or "Your Child" throughout this document

INTRODUCTION: We would like to invite you to be part of a research study. Before you decide if you would like to participate, we want you to know why we are doing the study. We also want you to know about any risks (anything unexpected that might happen) and what you will be expected to do in the study.

This form gives you information about the study. Your doctor will talk to you about the study and answer any questions you have. We encourage you to discuss this study with your family and anyone else you trust before making your decision. We will ask you to sign this form to show that you understand the study. We will give you a copy of any forms you sign to keep.

PURPOSE OF STUDY: You are being asked to participate in this study because you have neurofibromatosis type 1 (also called NF1) and are aged 8 to almost 16 years. As many as 65% of children with NF1 have learning disabilities, such as difficulty with memory and attention.

At present, there is no known drug treatment available to treat the majority of these learning problems. We would like to use a drug called Lovastatin to see if your learning difficulties improve using this medication. Lovastatin has been used in children with other medical problems such as increase in the blood cholesterol. This medication has been safe and well tolerated in those patients. Some parts of learning that may improve include your ability to pay attention and memory. Lovastatin is FDA approved in children for the treatment of high cholesterol and has been tolerated well in patients ages 10 to 17. However, Lovastatin has not yet been FDA approved for use in children with NF1 and learning disabilities, nor do we know if this drug will be effective in improving learning, memory and attention. It is an experimental drug for children

_____ Patient's Initials

with NF1. We want to know if Lovastatin is as well tolerated in children with NF1 as it is tolerated in children with high levels of cholesterol and if Lovastatin improves learning and memory in children with NF1 and learning disabilities.

PROCEDURE: A complete medical history and physical examination will be performed (including a neurological examination) to confirm each participant's NF1 diagnosis and to document any complications that they might have from the disease. Height, weight, head circumference, blood pressure and pulse will be recorded.

1. Neuropsychological testing will be performed before initiation of treatment and at 16 weeks while on the study. A final post treatment neuropsychologic test will be administered eight weeks after completing medicine requirements for the study.
2. Prior to entering the study you will have a small amount of blood drawn to measure blood counts, blood chemistries, and liver and kidney function. Females of childbearing age will have a pregnancy test. Additional labs will be done as needed to monitor side effects of medication. This will involve taking 6mL (approximately 1 teaspoon) of blood at each draw. All participants will receive Lovastatin or placebo capsule. Both are taken orally. You will not know if you are going to be assigned to a particular group. Your doctor will also not know, but can find out if necessary. You will take the medication as a capsule taken after dinner every day. At the 2nd week you will increase the number of capsules as described below. You must be able to swallow the capsule to be part of this study.

Group	**Initial – Week 1**	**Start**	**Weeks 3-15**
Lovastatin – Placebo	Neuropsychology + Clinical Exam + Labs	1 capsule @ 20mg.	2 capsules @ 20mg. each

3. Participants will continue on their assigned dose until the end of the study period which is a total of 14 weeks.
4. While on study each participant will be evaluated at week 2, 4, 8, 12 16 and follow-up. At each visit a history and physical will be repeated as well as the blood work described above, except for visit 2. Females of childbearing age will also repeat a urine pregnancy test at week 8 and 16. Side effects of the medication will be reviewed as well as a drug count to make sure the medication is being taken correctly.
5. Certain medications or foods can affect the levels of Lovastatin in the blood and should be avoided. A complete list of medications that need to be avoided will be given to you.

   Please consult your doctor if you are taking any of those medications. You should also not eat grapefruit or drink grapefruit juice while you are on this study because it can also affect the level of Lovastatin in blood.

YOU MAY BE TAKEN OFF STUDY FOR THE FOLLOWING REASONS:

- You decide to withdraw from the study
- Your doctor may tell you to stop taking part in the study at any time if he/she believes it to be in your best interest.

_____ Patient's Initials

- You develop significant side effects or medical condition(s) that would be harmful for you to continue with the study medication.

POTENTIAL RISKS/DISCOMFORT: Overall Lovastatin has been well tolerated in children ages 10 to17 as well as in the adult population. The following risks/side effects, which are believed to be associated with Lovastatin include:

Frequency of side effects	**Side effects description**
Common (less than 1 person in every 10 but more than 1 person in every 100)	Gastrointestinal disorders: constipation, dyspepsia (upset stomach)
Uncommon (less than 1 person in every 100 but more than 1 person in every 1000)	Skin and subcutaneous tissue disorders: itching (itchy skin)
Rare 0,01% to 0,1% (less than 1 person in every 1,000)	Eye disorders: blurred vision (problems seeing) Gastrointestinal disorders: abdominal pain, diarrhea, dry mouth, flatulence, nausea, vomiting General disorders and administration site conditions: weakness Hepatic disorders: yellowing of the skin and eyes (choleastic jaundice, hepatitis Metabolism and nutrition disorders: loss of appetite Musculoskeletal, connective tissue and bone disorders: muscle weakness (myopathy), tenderness and muscle pain, muscle cramps Any unexplained muscle pain, tenderness or weakness should be reported promptly. Lovastatin therapy should be discontinued immediately if myopathy is diagnoses or suspected. Nervous system disorders: dizziness, absence of the sense of taste, headache, tingling sensation, tingling and numbness of the feet and legs (losing feeling in the feet and legs) Psychiatric disorders: insomnia (problems falling to sleep), psychic disturbances including anxiety (feeling nervous, frustrated or angry), sleep disorders
Rare 0,01% to 0,1% (less than 1 person in every 1,000)	Skin and subcutaneous tissue disorders: alopecia (losing hair), spotted or red, swollen or peeling, red skin. An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis (allergic reaction), angioedema (swelling beneath the skin), lupus-like syndrome (kidney disorder), polymyalgia rheumatica (pain and stiffness in the hip or shoulder area), dermatomyositis

	(inflammation and skin rash), vasculitis (inflammation in your veins, arteries and capillaries), thrombocytopenia (disorder that can causes an abnormal bleeding), leucopenia (decrease in the number of white blood cells in the blood), eosinophilia (high number of white blood cells), hemolytic anemia (there are not enough red blood cells in the blood), positive ANA (ANA is the antinuclear antibody panel is a blood test that looks at antinuclear antibodies), ESR increase (ESR is a screening test that indirectly measures how much inflammation is in the body), arthritis (inflammation of the joints, arthralgia (joint pain), urticaria (hives, often itchy, red welts on the surface of the skin, asthenia (feeling of weakness), photosensitivity (sensitivity of the skin to a light source), fever, flushing (skin blushing), chills (feeling cold), dyspnea (breathing difficulties) and malaise (generalized feeling of discomfort) Uncommon: elevated transminases (this may be an indicator of liver damage) Rare: other liver function test abnormalities including elevated alkaline phosphatase and bilirubin; increase in serum CK levels.

ADDITIONAL ELEMENTS: (Unforeseeable risks to participant or embryo). It is not known if this study treatment can cause serious harm to unborn children or children who are breast-feeding. For this reason, if you are pregnant or breastfeeding, you will not be allowed to participate in this study. It is advisable that you should not become pregnant while you are on the study treatment and for at least six months after completing your study treatment. If you are of childbearing age and sexually active, you must agree to use birth control (birth control pills, contraceptive implants, condoms or not having sex) while taking the medication and for 6 months after stopping the medication. If you become pregnant while enrolled in this study, your participation will be ended and you should understand that there is an unknown risk to an unborn baby. If you are able to become pregnant, you will be given a pregnancy test before starting the study and possibly at other times during the study.

Since the long-term effect of lower lipid levels in children on Lovastatin is unknown at this time, having normal range cholesterol is a criterion for enrollment. Your cholesterol levels will be checked several times during this trial.

Please be aware that you could miss approximately six (6) whole or half days of school to participate in this trial. You are encouraged to discuss your decision to participate with your school to comply with the absenteeism policies and to arrange to make-up any missed work.

VOLUNTARY PARTICIPATION: There will be no penalty or loss of benefits to which you are otherwise entitled if you decide to withdraw from the study. You may choose not to participate in this study. If your doctor thinks that any treatment other than what you will get in this study would be better for you, your doctor will inform you of other options. At present, however, there is no other standard treatment available for learning disabilities in children with NF1. It is important that you know:

- The study is voluntary - you do not have to join the study.
- You may change your mind and stop being in the study any time you want. However, as with any medication, you must discuss with your doctor if you decide to withdraw and stop taking the medication.
- You will be notified if any important changes are made to the study. In some cases we may need your signature on an updated consent form.

POTENTIAL BENEFITS: If you agree to take part in this study, there may or may not be direct benefit to you. It is possible that the medicine may improve your learning skills. However this may not occur. We hope that the information learned from this study will benefit you and other children with NF 1 and learning disabilities in the future. You will receive a summary of the neuropsychological testing before and after treatment. If there is any specific alteration that will need intervention, you will receive recommendations. The results of the neuropsychological testing will provide useful information about your cognitive profile. If you are one of the patients to receive the placebo drug on this study, you could benefit from a detailed, cognitive consultation to further understand your cognitive functions.

ALTERNATIVES TO PARTICIPATION: No alternative treatment is offered or recommended for participants in this study. We recommend that you please speak with your doctor regarding your individual treatment needs if you decide not to participate. If you decide not to participate it will not affect your regular health care. You should also discuss your decision to participate with your doctor prior to taking part in this trial.

QUESTIONS – WHO TO CALL: Please contact the Principal Investigator (PI), Dr. Bruce Korf, The University of Alabama at Birmingham, Genetics (Kaul Building), 205.934.1154 or 205.427.3818 (Emergency) of this study if:

- If you have questions about any part of this study or consent form either now or at any time in the future.
- If you believe you have been injured as a result of being in this study.
- If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the Office of the IRB (OIRB) at (205) 934-3789 or 1-800-822-8816. If calling the toll-free number, press the option for an operator/attendant and ask for extension 4-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

COST AND COMPENSATION: The University of Alabama at Birmingham cannot promise that the risks we have told you about or other unknown problems will not happen. If emergency treatment is deemed necessary as a result of this trial, it will be provided.

Additional costs to participants to take part: The University of Alabama at Birmingham will give you the medicine used in this study for free. You will not be charged for anything else we do that is part of the study. You will still have to pay for any medical care or costs (parking, etc.) that are not part of the study.

What compensation is available in case of injury: The University of Alabama has made no provision for monetary compensation in the event of injury from the research, and in the event of such injury, treatment will be provided, but is not free of charge.

The Principal Investigator or his/her designee will assist you and your child in obtaining appropriate medical treatment if it is required. If you have any questions, please discuss this issue thoroughly with the Principal Investigator or his/her designee prior to enrolling in this trial. This is not a waiver or release of any of your legal rights.

CONFIDENTIALITY: We will keep the records of this study confidential. Only the people working on the study will know your name. They will keep this information in case we have to find you later to let you know of any new information that may affect and/or benefit your health. The federal government can review the study records and medical records to make sure we are following the law and protecting the children in the study. Your medical record is confidential, but just like any medical record; there are some exceptions under state and federal law.

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI") consisting of name, address (including city and zip code), date of birth, telephone numbers, social security numbers, new and existing medical records, medical record numbers, health plan numbers, types, dates, and results of various tests and procedures, and blood and /or tissue sample analysis. Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

If you agree to participate in this research study, the research team, the research sponsor (when applicable) and the sponsor's representatives, may use Personally Unidentified Study Data. The Personally Unidentified Study Data does not include your name, address, telephone, or social security number. Instead, the researcher assigns a code to the Personally Unidentified Study Data. Personally Unidentified Study Data may include your date of birth, initials, and dates you received medical care. Personally Unidentified Study Data may also include the health information used, created, or collected in the research study.
The research team or the research sponsor may share the Personally Unidentified Study Data with others to perform additional research, place it into research databases, share it with researchers in the U.S. or other countries, or use it to improve the design of future studies. They

may also publish it in scientific journals, or share it with business partners of the sponsor and to file applications with U.S. or foreign government agencies to get approval for new drugs or health care products.

By signing this consent form you are giving permission for representatives of Bruce Korf, MD, the Investigator and UAB employees involved with the research study including the Institutional Review Board and the Office for Research Compliance, and any sponsoring company or their appointed agent as well as representatives and staff of: the NF Consortium Operations Center the Department of Defense (DOD), National Cancer Institute (NCI), the National Institutes of Health (NIH) and the Office for Human Research Protection (OHRP), the Federal Food and Drug Administration (FDA), the National Cancer Data Base (NCDB), the Medical Monitor and referring institutions involved with the research study, including participating labs and pharmacy personnel, to be allowed to inspect sections of your medical and research records related to this study. It should be noted that representatives of the U.S. Army Medical Research and Material Command are eligible to review research records as part of their responsibility to protect human participants in research.

A Data and Safety Monitoring Board and a site monitor will be reviewing the data from this research throughout the study. The investigator will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

The information from the research study may be published; however, you will not be identified in such publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without your authorization.

UAB and/or the Investigator will take the following precautionary measures to protect your privacy and confidentiality of your research and/or medical records:

Your individual identifiers (name, address, date of birth, etc.) will not be used in any publications or reports. All your study records will be kept in secure areas with limited access.

A copy of this consent form will be included in your medical research record.

Organizations that may inspect/or copy you medical and research records for quality assurance and data analysis include:

- The local Institutional Review Board
- Administration (FDA), involved in keeping research safe for people
- Department of Defense (USAMRMC)
- Office of the Congressionally Directed Medical Research Programs (CDMRP)

Names of participants or material identifying participants (except as described above) will not be released without written permission, unless required by law.

I. ADDITIONAL ELEMENTS

By signing this form you are authorizing Dr. Bruce Korf, and his/her research staff to create, access, use, and disclose my PHI for the purposes described below.

Protected Health Information that may be used and shared includes:

☒ Information that identifies you such as name, address, telephone number, date of birth, Social Security number and other details about you.

☒ Information that relates to your health or medical condition from your medical records

☒ Information obtained from the study procedures outlined in this consent form, for example: things done to see if you can join the study such as physical exams, blood and urine tests, x-rays and other tests, and any other medical information we learn from you about your health history and family history

☒ Laboratory results obtained on specimens collected from you (blood, urine, tissue)

☒ Questionnaires or surveys you complete

☒ Interviews conducted with you by members of the research team

The Researchers may use and share my Protected Health Information with:

♦ The Principal Investigator, other Investigators, Study Coordinators, and all administrative staff in charge of doing work for the study;

♦ Government agencies that have the right to see or review your PHI, including but not limited to the Office of Human Research Protections and the Food and Drug Administration;

♦ The University of Alabama at Birmingham, includes, but not limited to pharmacy, IRB and regulatory governing groups, and clinical staff.

♦ Audit Committee of The University of Alabama at Birmingham.

♦ Quality Improvement Program Coordinator and other staff in the Office for the Protection of Human Subjects of the University of Alabama at Birmingham.

In addition to the above people and organizations, the Researchers may also use and share my Protected Health Information with:

☒ Doctors and staff at other places that are participating in the study. The name(s) of the other place(s) that are participating in this study are: National Institutes of Health (NIH), National Cancer Institute (NCI), The University of Alabama at Birmingham, University of Chicago, University of Utah, and Washington University.

☒ Laboratories and other people or organizations that look at your health information in connection with this study.

☒ The Sponsor of the study and people that the Sponsor may contract with for the study.

☒ The Contract Research Organization (an organization that helps the Sponsor run the study).

☒ The Data Safety Monitoring Board (a group of people who examine the medical information during the study)

☒ The Medical Monitor for the Study (a person who reviews medical information during the study)

☒ The Patient Advocates (person(s) who watches out for your best interest)

☒ Any other outside entity who will receive health information deemed necessary, i.e. the drug distribution facility, your primary physician, etc.

Note: should your health information be disclosed to anyone outside of the study by you, your information may no longer be protected by HIPAA and this Authorization. However, the use of your health information will still be regulated by applicable federal and state laws.

Storage of PHI in a Database: Your PHI (Personal Health Information) will be stored in a database for this research and future research. Please indicate your approval of any or all of the following by initialing next to the statement:

My PHI may be stored in the above-named database for future analysis related to this study

Yes No _____Initials

My PHI may be stored in the above-named database. Researchers may contact me to request my authorization for future studies that are not related to this study

Yes No _____Initials

My PHI may be stored without any of my identifying information for use in other studies of other diseases

Yes No _____Initials

You do not have to sign this Consent/Authorization. If you decide not to sign the Authorization, you will not be allowed to participate in the research study. **After signing the Consent / Authorization, you can change your mind and:**

- Revoke this Authorization. After withdrawal you will not be allowed to participate in the study.
- If you revoke this Authorization, researchers may only use and disclose the PHI that was collected for this research study before you revoked the Authorization.
- If you revoke this Authorization your information/data may still be used and disclosed if you should have an adverse event (unexpected side effect).

You will not be allowed to review the information collected for this research study until after the study is completed. If you are not allowed to review your information during participation in the study, when the study is over you will have the right to access the information.

If you have not already received a Notice of Privacy Practices, you may request a copy and will be given one. If you have any questions or concerns about your privacy rights, you may contact Dr. Bruce Korf's office or the IRB. It is necessary for you to understand that by signing this form you are not giving up any legal rights.

CONSENT/AUTHORIZATION: I am the participant or I am authorized to act on behalf of the participant. I have read this information and will receive a copy of this form after it is signed. By signing this form, you agree that you have talked to your doctor about the study and understand it, and you want to be in the study. You agree that we have talked to you about the risks and benefits of the study, and about other choices. You may decide to stop being in this study at any time and no one will mind and nothing will change about your medical care other than not being in the study. Copies of this form will be:

(1) Kept in the study file by the Principal Investigator;
(2) Put in your medical record; and
(3) Given to you to keep.

Printed Name of Participant:_____

Printed Name of Parent(s)/Guardian(s): _____

Signature of Parent(s)/Guardian(s): _____Date:_____

[Signature of one parent required]

[Note: Legal authorization in this order: (1) Parent for child/minor under 19 years of age; (2) Judicially Appointed guardian or individual named in a durable power of attorney; (3) Spouse; (4) Son or daughter over 19 years of age; (5) Either parent; (6) Brother or sister over 19 years of age; (7) Other nearest kin over 19 years of age].

Witness (to signatures): _____Date:_____
(may be investigator)

I certify that I have explained to the above individual(s) the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised.

Printed Name of Individual Obtaining Consent: _____

Title: _____ Signature: _____ Date: _____

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant name: _____
Research Protocol: A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1 (STARS)

UAB IRB Protocol Number: F090202002
Principal Investigator: Dr. Bruce Korf
Sponsor: The US Army – Depart. Of Defense

What health information do the researchers want to use? All medical information and personal identifiers including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date:_____
or
participant's legally authorized representative: _____ Date:_____

Printed Name of participant's representative: _____

Relationship to the participant:_____