Please check all that are applicable:

☐ I am an adult participant in this study.

Print your name here:

Patient Information:

As the parent or guardian granting permission for a child's participation in this study the following information applies to the child or ward. The use of the word "you" refers to "your child" or "your ward".

☐ I am the parent or guardian granting permission for a child in this study (the use of "you" refers to "your child" or "your ward.")

Print child's name here:

_____

****

Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

This research study is being done to understand if high doses of vitamin D supplementation are safe in boys with the X-linked adrenoleukodystrophy (ALD) genotype who have not yet developed brain inflammation. This study will also examine whether or not vitamin D can reduce oxidative stress and inflammation in the blood and brains of ALD boys.

Research suggests that higher vitamin D levels in the blood are associated with reduced brain inflammation in patients with multiple sclerosis, a disease that is similar to the cerebral demyelinating form of ALD. Dr Van Haren's lab is the first to examine the relationship of vitamin D levels with brain inflammation in ALD. The results of that study showed that higher vitamin D levels in boys with the ALD genotype were associated with a lower risk of developing brain inflammation. This

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may suggest that increasing vitamin D levels could reduce brain inflammation; however, it is not certain.

Because no one is sure exactly how vitamin D improves outcomes in multiple sclerosis, it is also hard to know how vitamin D might help ALD boys at risk for developing brain inflammation. Scientists agree that the ALD gene defect leads to more oxidative stress, which can injure cells.

In this study, we will determine the safety of high dose oral vitamin D supplementation (1000IU-4000IU daily) and measure the effects of vitamin D supplementation on markers of oxidative stress within blood cells of study participants before, during, and after taking vitamin D supplements. This will allow us to determine if taking high dose vitamin D is safe for boys with ALD and if it helps reduce the oxidative stress that causes cell injury.

If you decide to terminate your participation in this study, you should notify Dr. Keith Van Haren at 650-723-0993.

This research study is looking for up to 25 boys with ALD from around the United States. Stanford University expects to enroll between 15-20 research study participants.

As part this study, we will collect genetic material from each participant that will be stored at Stanford University. This study is sponsored by the federal government (National Institutes of Health).

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

If you join the study, you will be asked to participate for a minimum of 12 months with the option to continue participation for up to 36 months

PROCEDURES

If you agree to be in this study, we will ask you to do the following things:

You may be asked to describe your symptoms in an interview and/or to permit your medical records to be reviewed by a member of the study team. The interview, lasting about fifteen minutes, consists of a series of questions related to your medical and family history as it pertains to ALD. Your medical records are used for study purposes only and will be reviewed only by the study doctors and the study coordinator.

You will be asked to provide contact information (address and phone numbers) and demographic information such as your date of birth and ethnicity.

You will be asked to provide a small sample of blood, about 6 tablespoons (30 milliliters), through a vein in your arm at the baseline visit, the 6month visit, and the 12month visit of the vitamin D research trial, as well as 3 tablespoons at the 3 month, 9month, 18month, and 24month visits. You will also need to provide a small sample of urine at baseline,, 6 months and 12months. This will take place either at your doctor's office or a blood drawing laboratory. The actual blood draw will take about five minutes.

Your samples will be analyzed at Stanford University. Biological materials obtained from your blood (cells, DNA, and RNA) will be stored in freezers at the Stanford University Department of Neurology's neuroimmunology research laboratory. The laboratory and the freezers are restricted to appropriate staff. If you take part in this study, samples you have already given as a part of this research trial may also be shared with other scientists at Stanford University and their collaborators.

A clinic visit and MRI of the brain with/without gadolinium must be performed every 6 months as per the routine standard of care for ALD boys aged 2-18 years in order to screen for early signs of brain inflammation. As part of this study, however, the MRI protocol will also include a magnetic resonance spectroscopy sequence in order to measure brain metabolites. This study will add 15-20 minutes to each MRI.

If enrolled and eligible for drug initiation, the parents or patient (if >18yo) will be responsible for administering the tablets. The medication will be dispensed every 3 to 6 months at clinic visits, which perform laboratory and clinical screening for toxicity. Dosing will be dependent on age and weight at the of enrollment as described below

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Weight	0-6mo	6-12mo
10-15kg	1000IU	2000IU
15-20kg	1000IU	2000IU
20-25kg	2000IU	3000IU
25-30kg	2000IU	3000IU
30-40kg	2000IU	3000IU
>40kg	2000IU	4000IU

A numeric code will be used in place of your name for all specimens and all other information related to you. Only Dr Keith Van Haren and a small number of study staff will have access to the link between each person's identifiers (name and date of birth) and code; this link will be kept in a secure place. Coded means that your medical information, your sample and all information obtained from your sample will be assigned a number. Your coded medical information and any results will be put on a computer and stored in a secure, encrypted electronic database. The purpose of this database is to capture and store data for neurological clinical research. The repository will allow the combination of data from multiple studies. We will share combined datasets with researchers who want to advance understanding of neurological disease. Your data will be used to study illnesses and conditions affecting, or related to, the brain and nerves.

For this research project, some identifiable information may be collected and stored in the database. Clinical information recorded will include, but is not limited to, diagnosis, disease presentation, and age. This information, along with your specimen, may be shared in the future with other qualified researchers although your identity will remain hidden using the numeric code; your identity will not be revealed to other researchers. These researchers will include Stanford University researchers, other academic collaborators, or those in industry.
At the end of this project, all data will be deidentified, (all identifying information including dates will be removed). The deidentified dataset combined with information from other projects will then become available for sharing with other researchers.

Global Unique Identifier (GUID):
In this study, each participant will be assigned a unique patient identifier called a Global Unique Identifier (GUID). If you are participating in another clinical study that uses this GUID, it is hoped that data for this current study can be linked to data from other projects. Linking data to other projects makes it more useful.

The Global Unique Identifier (GUID) is created on a secure website by a specialized computer program that uses 12 pieces of information about you (e.g. first and last name, gender, birthday, etc.) The website and computer program used to create the GUID does not store any personal information, but if the same information is entered again in the future, the program will return the same GUID every time. Once generated, this GUID will be used to uniquely identify you. This is how data from this study might be linked to data from another study you participate in that uses the GUID. As the GUID is generated randomly, it is impossible to identify you from the GUID string.

The GUID and any identifiable information will be removed from your record before your data are shared.

Do you agree to the sharing of your data as described above?
Yes ___ No __
Initials____

In addition to the electronic data, your biological materials will be used for research to help understand the biology of ALD as well as other disorders. These materials, along with your clinical information (again, both coded), may be used indefinitely.

Any of your samples which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of samples do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Tissue Sampling for Research

Research using tissues is an important way to try to understand human disease. You have been given this information because the investigators want to include your tissues in a research project and because they want to save the samples for future research. There are several things you should know before allowing your tissues to be studied.

You have the right to refuse to allow your tissues to be studied now or saved for future study. You may withdraw from this study at any time. The investigators might retain the identified samples, e.g., as part of your routine clinical care, but not for additional research.

The results of the study of your samples will be used for research purposes only. You will not be told the results.

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_____ I consent to my samples being saved for future research

_____ I do not consent to my samples being saved for future research

Tissue Sampling for Genetic Testing

As part of the analysis on your samples, the investigators plan to do genetic testing on your sample. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Some individuals have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

The results of the study of your samples from this project will be used for research purposes only, and you will not be told the results of the tests.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

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WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Keith Van Haren at 650-723-0993.

Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Stanford University may continue to use the health information that it has already collected if the information is needed for this study or any follow-up activities.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

Blood draw risks

Likely

Taking blood may cause discomfort, bleeding or bruising where the needle enters the body.

Rare

You may get tired or bored when we are asking you questions. You do not have to answer any question you do not want to answer. In rare cases, taking blood may result in fainting. Some patients experience anxiety while in the enclosed space of an MRI machine.

Rare, but serious

Blood draws could cause infection at the puncture site. Extremely high doses of vitamin D can cause elevated calcium levels in the blood which can result in abdominal pain, headaches, lethargy, confusion, and/or kidney stones; as a result, calcium levels will be closely monitored every 3 months during this study.

MRI risks

You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

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Risks of Gadolinium based contrast agents:
It has been observed that deposits of Gadolinium-based contrast agent (GBCA) remain in the brains of some people who undergo four or more contrast enhanced MRI scans, long after the last administration. It is not yet known whether these Gadolinium deposits are harmful or can lead to adverse health effects. You should talk to the study doctor if you have any questions about the use of GBCAs with MRIs

Participation in research may cause a loss of confidentiality, but at all times, your records and other information that you share with the investigators will be handled in a confidential manner. Your blood donation will be coded with a number and your initials.

POTENTIAL BENEFITS

There is no direct benefit to you from being in this study. However, the knowledge that is gained from the study will help the investigators learn more about vitamin D and its potential benefits for ALD patients, which could include reducing oxidative stress and preventing brain inflammation. This may help to develop improved treatments for the disease in the future. We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You do not have to join this study. If you do not join, your care at Lucile Packard Children's Hospital/Stanford University Medical Center will not be affected.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.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.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Your personal health information related to this study may be disclosed as authorized by you. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number that will hide your identity. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.
Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of vitamin D; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Information from analyses of your coded samples and your coded medical information will be put into one of the National Institutes of Health (NIH) databases along with information from the other research participants and will be used for future research. These databases will be accessible by the Internet. Only anonymous information from the analyses will be put in a completely public database, available to anyone on the Internet.

No traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will be put into the public database. While the public database will not contain information that is traditionally used to identify you, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to

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identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

However, your privacy is very important to us and we will use safety measures to protect it. Despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as Information from analyses of your coded samples and your coded medical information will be put into one of the National Institutes of Health (NIH) databases along with information from the other research participants and will be used for future research.

Authorization To Use Your Health Information For Research Purposes

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Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The primary purpose of this trial is (1) To determine the safety of high dose oral vitamin D3 supplementation in boys with X-linked adrenoleukodystrophy who do not yet have cerebral demyelination on MRI and (2) to determine if oral vitamin D3 supplementation reduces laboratory measures of oxidative stress.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study.

Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to Dr. Keith Van Haren.

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1201 Welch Rd, P213
Palo Alto, CA 94305
Phone: 650-723-0993
Fax: 650-723-7299

What Personal Information Will Be Obtained, Used or Disclosed?

The people working on the study will collect information about you. This includes things learned from the procedures described in this consent form (medical history, family history, physical exams, radiographic images, questionnaires, race, ethnicity etc.). They may collect other information including your name, telephone number, address, date of birth, medical record number, study identification number and other details. The information collected will be limited to the least amount of information needed to accomplish the purpose of the research.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. Keith Van Haren
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Kennedy Krieger Institute, a partner institution for this study.
- The Food and Drug Administration

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When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on 01/01/2100 or when the research project ends, whichever is earlier. You can cancel your permission to use and disclose your information at any time by contacting the Principal Investigator of this study. The Principal Investigator can be reached by phone at 650-723-0993 or by sending a letter to:

Keith Van Haren, MD
1201 Welch Rd, P213
Palo Alto, CA 94305
Phone: 650-723-0993
Fax: 650-723-7299

If you send a letter, please be sure to include the study number and your contact information.

If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

_____ _____
Signature of Participant Date

_____
Print Name of Participant

_____ _____

Signature of Adult Participant) Date

_____
Print Name of Adult Participant

_____ _____
Signature of LAR (Parent, Guardian or Conservator) Date

_____
Print Name of LAR

_____
Authority to act for participant

Participant ID:

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FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor
The National Institutes of Health are providing some financial support for the facility and staff where part or all of the study is taking place.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.** If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Keith Van Haren, MD. You may contact him now or later at 650-723-0993.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Keith Van Haren, MD. (650-723-0993).

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306. Appointment Contact: If you need to change your appointment, please contact the Protocol Director.
Alternate Contact: If you cannot reach the Protocol Director, please contact the clinical research coordinator assigned to the study.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;

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- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of LAR (Parent, Guardian or Conservator) Date

_____
Print Name of LAR

_____
Authority to Act for Participant

_____ _____
(If available) Signature of Other Parent or Guardian Date

_____
Print Name of Other Parent or Guardian

_____
Authority to Act for Participant

Participant ID:

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_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

The IRB determined that the permission of one parent is sufficient for research in accordance with 21 CFR 50.55.

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of witness for interpreter Date

_____
Print Name of Witness

(e.g. staff, interpreter, family member, or other person who speaks both English and the participant's language)

- Translated short form must be signed and dated by both the participant (or LAR) and witness.
- The English consent form (summary form) must be signed by the witness and the POC.
- The non-English speaking participant does not sign the English consent.
- The non-English speaking participant should not sign the HIPAA participant line