Consent to Participate in the CreatineINFO Registry and to Allow Data to be Shared for Future Research

Consent for a Person with a Legally Authorized Representative (LAR)

Title: CreatineINFO Registry

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Sponsor: Association for Creatine Deficiencies (ACD)

Key Information

You are invited to take part in a research study for individuals with cerebral creatine deficiency syndromes (CCDS) on behalf of the person in your care. We hope that this form will help you decide whether or not to participate, but you can also call or email the study staff at the contacts above if you have any other questions.

Things you should know:

We are doing this research to understand patient and caregiver experiences with CCDS, to help support the development of treatments.

If you choose to participate on behalf of the participant, you will be asked to:

1. Register the participant on the online CreatineINFO Patient Registry;
2. Complete surveys online; and
3. Upload medical documentation.

New surveys will be released a few times a year. Each survey will take approximately 15-20 minutes to complete.

You may experience the following risks, discomforts or inconveniences from participating:

1. The surveys may ask questions about the impact of CCDS on life-experiences, economic status, mood, and other topics that some individuals may find unpleasant;
2. The Registry collects and stores sensitive personal data about individuals. While we have safeguards in place to protect those data, there is always the possibility that those data may be compromised.

Participating in our study may not help the Study Participant directly, but your time and information may help others with CCDS in the future. There are no direct benefits of participation.

It is up to you whether to participate in this study, and you can stop at any time. Please take time to read this entire form and ask questions before deciding whether to take part in this research project on behalf of the person in your care. As the guardian or legally authorized representative (LAR) for the Study Participant, we encourage you to discuss the Registry with the Study Participant to the extent compatible with their understanding. Detailed information about your participation in this study follows.

Purpose of this Informed Consent Document

This document will give you the information so you can decide if you want to join this study on behalf of the Study Participant. This consent document is structured to follow the framework provided by federal regulations. While we hope the information we provide will answer most of your questions, it may not answer them all. If you have any remaining questions, please contact the Principal Investigator at the phone number or email listed above.

Definitions

For the purpose of enrolling in this Registry, a legal adult is defined as a person who is at least 18 years of age, the age of majority in their state, province or country, and able to consent for themselves or on behalf of a Study Participant.

On this form, "Study Participant" refers to the person with Cerebral Creatine Deficiency Syndromes (CCDS) who is not of legal age or is an adult who requires someone to act on their behalf. Registry information will be collected on patients who have CCDS.

"You" refers to the person reading this form and providing the information; in this case a family member or guardian who is legally responsible for the healthcare of the Study Participant.

"We" refers to the organization, Association for Creatine Deficiencies (ACD), who is doing the research

"The Registry" refers to the CreatineINFO Patient Registry and Natural History Study.

Institutional Review Board (IRB) is an independent group that reviews research proposals to make sure they properly protect participants.

Personally identifiable information (PII) is any data that could be used to identify the Study Participant. Examples may include but are not limited to name, date of birth, contact information, city, and postal code. In this form, "de-identified data" does not include PII.

Participation of Minors and Adults Unable to Consent

This study is for individuals who have a diagnosis of CCDS. Individuals may participate in the Registry if:

- They are a legal adult who is able to understand the consent form and able to legally provide their own consent.
- They are a minor or an adult needing assistance who has a legally authorized representative willing to consent on their behalf.

This consent is for those who need a legally authorized representative (LAR). During participation in this study, a Study Participant may become a legal adult. If this happens and they are able to consent on their own, a legally authorized representative is no longer permitted to enter data on their behalf. This individual must consent to the study directly and continue their participation in the Registry on their own. If the participant is still not able to consent, the LAR may continue to enter data on their behalf. A new consent will need to be signed.

Study Aims

The data collected in this Registry will be used by researchers to study CCDS with the following goals:

1. Describe the people who have CCDS and how CCDS may be different for different

people;
2. Understand the stages of CCDS and how it changes over a person's lifetime;
3. Learn how CCDS is treated and how people respond to those treatments;
4. Learn how to best care for and treat people with CCDS; and
5. Identify people with CCDS who might be willing to take part in other research studies or clinical trials. You will be able to choose whether you want to hear about these other studies on behalf of the Study Participant.

How You Provide Data

The Registry collects and stores medical and personal information about Study Participants. We will be asking you to give us information about the Study Participant by filling out surveys online and uploading medical documents related to their history and experience with CCDS. We will store the Study Participant's information so that it can be combined and compared with information from others and used for research. The Study Participant will be assigned a randomized unique study identification number. Only approved Registry staff can link the unique study identification numbers to the Study Participants' personal information.

You always have access to the data you enter in the Registry, via the participant dashboard. You can also view charts and graphs derived from the combined data contributed to the Registry by other Study Participants. This combined data will not reveal Study Participant identities.

We will ask you to enter the Study Participant's information using online surveys on a secure internet site.

At registration you were asked to provide basic information about the Study Participant such as name, date of birth, and residence. That information will also be considered research data.

One survey will ask you to create and provide a CRID (Clinical Research IDentifier) for the Study Participant. Providing this information is optional. The CRID is a unique identification number that allows participants to share their information with researchers while maintaining their privacy. While the creation of a CRID number requires the Study Participant to provide limited identifying information, allowing the use of a CRID helps to link available clinical data and biological samples in a de-identified manner. If you choose not to create a CRID, your data may not be able to be included in research that is relying on using the CRID for data linkage. For more information about thecrid.org security and privacy policies, visit https://thecrid.org/resources.php.

You will be asked about demographics such as the Study Participant's race, ethnicity, and education status.

We will ask for specific information related to the Study Participant's history with CCDS. This may include questions about diagnosis, treatment, genetic mutations, and lab results.

You will also be asked to attest that you are at least 18 years old, the age of majority in your state, province or country, and able to provide consent on behalf of the Study Participant.

You may also be asked to enter data about your experience as a caregiver related to CCDS.

You will be asked to update the Study Participant's Registry information at least once per year, and you may be asked to update some surveys more frequently. Periodically, ACD may add additional new surveys for you to complete. We may contact you to remind you to update surveys, finish incomplete surveys, or complete outstanding surveys.

In addition to reminding you about surveys, we may ask you to upload new test results or other medical information, and may contact you to clarify data you have entered. Registry staff may also notify you of major changes to the study or changes in the Institutional Review Board (IRB) of record. You can update information in the Registry whenever there is a change to the Study Participant's health, their treatment, or if they develop new symptoms.

We may contact you by phone or email, and the Registry may automatically generate some reminders that will be sent to you by email. After you agree to participate on the Study Participant's behalf, you will be able to choose what kind of contacts you want to receive, like notice of opportunities to donate some specimens or participate in other research studies. If you previously consented to receive updates about your genetic information from the Clinical Genome Resource (ClinGen), you will be asked if you would still like to receive those updates but those updates will now come from ACD. You will be able to change these preferences at any time by logging into your Registry account.

You can view and revise your study opt-ins at any time by logging into your Registry account. Select the Participant's name and the CreatineINFO Registry. Then, click the button labeled 'Consent/Opt-ins' followed by the button that says 'Opt-Ins'.

The Registry cannot provide medical advice or answer specific medical questions. For resources that support people with CCDS, please visit ACD's web site at creatineinfo.org. For medical assistance, contact your doctor's office.

How We Use the Data

While protecting the privacy of the Study Participant, the goal of the Registry is to help researchers, clinicians, and industry partners learn about CCDS.

As the sponsor, ACD is the owner of the data included in the Registry. Designated staff have full access to the entered data. Their approved activities include study management, contacting study participants as needed, and conducting analyses using the data in the Registry. These research activities will help to achieve the study aims listed above.

This Registry is maintained by the National Organization for Rare Disorders, Inc. (NORD®), a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. As owners of the IAMRARE platform, designated NORD staff will have access to all the data that you enter on the platform, including identifiable data. Identifiable data is any information that can link a participant to a research study and reveal their identity. Identifiable data may include information such as name, medical record numbers, and home address. It may also include indirect information that, when combined, may make it possible to identify a person. This would include information such as age, city, zip code, or gender. Some of this data will be used to set up a Global, Unique Identifier (GUID) for each Study Participant on the NORD platform. Information needed for this ID comes from the Participant profile that you provided on behalf of the Study Participant. The GUID will help to link data across studies, within and outside of the NORD platform, without sharing the Study Participant's identifying information. Linking of data by using the GUID will only be done with approval of the Registry Advisory Board where it is scientifically important to the research. Please read the paragraphs that follow for additional information on how your data might be shared and how your identity is protected. In addition to platform maintenance activities, after notifying ACD, NORD may conduct IRB-approved research across different rare diseases using Registry data. In all cases, your privacy and the

privacy of the Study Participant will be protected in any publications using data from the Registry.

The Registry is overseen by the ACD's Registry Advisory Board (RAB), Family Advisory Board (FAB), and Registry Oversight Board (ROB). These boards, which include scientists, doctors, patients, and caregivers, have been involved since the early planning of the Registry and continue to advise on the development of surveys.

Specifically, the RAB oversees the direction and goals of the Registry. The FAB reviews content, family-friendly language, and translations of surveys and materials. The ROB advises on surveys, reviews de-identified Registry data, and reviews reported problems or breaches of confidentiality to make sure they are appropriately reported and resolved.

The ROB is responsible for reviewing all requests for Registry data to be sure that the proposed project has scientific merit and will be valuable to the community. They will also be responsible for deciding what specific data will be given to researchers. This will be limited to only the data needed to answer their research question(s).

The ROB will only ever release de-identified data. This means that any information that could be used to identify the Study Participant will be removed. This may include but is not limited to name, date of birth, contact information, city, and postal code. Maximum security and privacy practices will be followed. The IRB will determine the need for additional consent.

Any researcher who applies to receive Registry data will need to have their project approved by an IRB. The application requires that the researcher describes things such as the aims of the research, how the data will be analyzed, who the Principal Investigator is, and how they will protect the confidentiality of the data. They will need to sign a Data Confidentiality Agreement. They must agree not to try and identify participants or share information in a way that people could be identified.

Outside researchers may ask the ROB to advertise their study to Registry participants for recruitment purposes. The Registry staff will not give outside researchers your contact information. If this request is approved, the Registry staff will provide you with study details and how to contact the researcher. It will be up to you if you decide to participate in this study or not. You can also decide not to receive information about outside studies by editing your opt-ins.

The ROB may determine that it would be valuable to include the Registry data on a data sharing platform. An example of this is the U.S. Food and Drug Administration (FDA)-sponsored Rare Disease Cure Accelerator – Data and Analytics Platform (RDCA-DAP). Any data shared with a data sharing platform will be de-identified. Additionally, outside researchers who request de-identified Registry data may also share those data with other databases and repositories. One example of a database is ClinVar, a database of genetic changes and their relationship to health.

A member of the ROB may conduct their own research outside of the Registry. They may wish to have access to the data or inform participants of a clinical trial or research study in which they are personally involved. They are required to apply for access as an independent researcher. They will remove themselves from the discussion and voting process concerning their own research.

Risks and Inconveniences

Putting the Study Participant's data in the Registry does not put you or them at any risk of physical harm. As with any information you provide electronically, there is a risk that their privacy could be compromised if the data is inappropriately disclosed or misused. The Registry is designed to make the chance of this happening very small.

ACD's ROB reviews ongoing and new research to help prevent misuse (see How We Use the Data, above). We have technical and administrative protections in place to reduce the risk of inappropriate disclosure (see Privacy Rights and Confidentiality, below).

The Registry surveys may ask questions that you or the Study Participant find unpleasant or uncomfortable, such as the impact of CCDS on the Study Participant's daily life, their economic status, or mood. While some questions (marked with a red asterisk [*]) require responses, where the information may be sensitive, you can choose 'Prefer not to answer. While these are the risks we can foresee, it is possible that other risks may arise in the future.

Benefits

Participation in this Registry is voluntary and unlikely to lead to direct medical or financial benefits for you or the Study Participant. We hope the results from research we make possible will help people with CCDS in the future.

Cost and Payment

It should not cost you or the Study Participant anything to participate in the Registry, other than the costs of internet access, and you will not be paid for the information you provide.

On behalf of the Study Participant, you may elect to receive gifts of nominal value (for example, T-shirts or gift cards) which may be offered periodically.

The information will only be used for research, but it is possible that the research could lead to the development of a commercial medical product. Should this happen, neither you nor the Study Participant should not expect to be paid.

Privacy Rights

Your participation in the Registry on behalf of the Study Participant is private. ACD will not inform unauthorized individuals that you and the Study Participant are participating in this study. They will only contact you using the contact methods and information that you provide.

Confidentiality

You will be asked to provide two types of information in the Registry. The first type of information includes details that can be used to identify you and the Study Participant, such as name, address, birthdate, and sex. The other type of information includes details about the Study Participant's health and wellbeing that by themselves cannot be used to identify them. For example, questions may be asked about a symptom or a treatment received.

All identifiable information that is provided to the Registry will remain confidential. ACD and NORD staff will have access to this data, as needed to provide Registry support and maintenance.

Data may be provided to approved researchers. The goal is to provide these researchers with the minimum data necessary to accomplish their research study. Potentially identifiable information

will only be shared if the research cannot be done without it. For example, the Study Participant's "country of residence" may be requested by a researcher that wishes to understand the methods used to diagnose CCDS patients in different areas of the world. When a small number of patients live in a country, this information may be considered identifiable and will be considered carefully prior to release. The researchers will need to sign a Confidentiality Agreement in which they promise to keep the Study Participant's information safe. When the results of research conducted with data from the Registry are published or reported, no information that could identify them will be disclosed.

Representatives from NORD and from North Star Review Board, the IRB that oversees this Registry, may inspect study records during auditing procedures. This is to ensure that the Registry is protected according to regulations and policies. NORD staff may access this Registry to provide technical support. These representatives must keep all information confidential.

Voluntary Participation, Withdrawal, and Alternatives to Participating

It is up to you whether or not you want to participate in this Registry on behalf of the Study Participant. If you choose not to, neither you nor they will be penalized in any way. Neither of you will lose any benefits you might otherwise be entitled to, and the Study Participant's health care will not be affected. If you decide not to participate on behalf of the Study Participant, or choose to withdraw them from the Registry, that decision will not harm their relationship with their doctors, even if they are involved with the Registry or with ACD.

There may be other registries that serve patients with CCDS. You are free to provide data to any such registry instead of, or in addition to, working with the CreatineINFO Registry. There may be other research opportunities, including clinical trials, for patients with CCDS. You may choose to have the Study Participant participate in any research project whether or not they participate in this Registry.

If you choose to participate in the Registry on behalf of the Study Participant, that permission will not expire, but you can change your mind at any time. To withdraw from the Registry, log into your account. Select the Participant's name and the CreatineINFO Registry. Then, click the button labeled 'Consent/Opt-ins' followed by the button that says 'Revoke'. You may also withdraw by contacting the Registry staff directly by email or phone (Emily at registry@creatineinfo.org).

Withdrawing your consent means that the Registry will no longer contact you and that you will not be asked to submit new information. However, researchers may continue to use data that has already been shared by the Registry and the Registry will continue to share data that you provided before you withdrew. If you no longer want the data to be shared, even in a form that does not identify the Study Participant, you should contact the Registry directly by phone or email, as described above, and request that the data be removed from the Registry.

If You Live Outside the United States

The Registry is maintained on servers that are physically present in Canada. For persons living outside the United States who choose to share information about themselves and about a person for whom they serve as a Legally Authorized Representative (LAR), the same protections for privacy and confidentiality are offered as in the United States; in addition, as explained below, residents of the European Union and Switzerland have additional particular rights related to personal information. By signing this consent, you acknowledge that you are disclosing information that would otherwise be private. Privacy laws in your country may have different

protections than those provided in the United States.

For persons who are residents of the European Union and Switzerland, transfers of your and the Participant's personal information outside of the European Union and/or Switzerland, will comply with the General Data Protection Regulation under an appropriate transfer mechanism provided for by that regulation, including the use of standard data protection clauses adopted by the European Commission. Please be aware that, under the General Data Protection Regulation, the European Commission is permitted to issue a decision that the data protection laws of a third country are adequate to the protection of personal information and that, to date, the European Commission has not done so with respect to the United States.

For persons who are residents of the European Union and Switzerland, processing of personal information will also be undertaken in such a manner as to ensure the rights of data subjects provided for by the General Data Protection Regulation or other applicable laws and regulations. Specifically, Registry participants who are residents of the European Union and Switzerland are entitled to:

- Request to obtain access to and rectification or erasure of personal data;
- Receive personal data in a portable, readily-accessible format;
- Restrict or withdraw permission for the processing of personal information; or
- Lodge a complaint with an appropriate supervisory authority.

Please note that the rights to erase personal data or restrict or withdraw permission for the processing of personal information are subject to limitations provided for by Article 17 of the General Data Protection Regulation, namely, that such rights may be limited as necessary to protect the public interest in the area of public health or for archiving purposes in the public and scientific interest.

Getting Answers to Your Questions about the CreatineINFO Registry

We have used some technical terms in this form and talked about issues in research and data sharing with which you may not have been familiar. Take as long as you need to consider this information and decide if you want to share the Study Participant's personal and medical information with the Registry. If you have any questions or want anything explained further, please contact the Registry Staff at: registry@creatineinfo.org. It is our responsibility to answer your questions.

An IRB has reviewed this Registry to ensure that it meets ethical and regulatory standards for protecting your rights. An IRB is an independent group that reviews research proposals to make sure they properly protect participants. To discuss study-related concerns or complaints with someone who is not part of this Registry team, please contact North Star Review Board at 877-673-8439 (toll free) or info@northstarreviewboard.org. You may want to contact the IRB if:

- You have questions about your rights and those of the Study Participant in this Registry;
- You have questions, concerns, or complaints that are not being answered by the research team;
- You are not getting answers from the research team;
- You cannot reach the research team; or
- You want to talk to someone else about the research.

Please do not sign this form unless you have had all your questions answered.

Authorization

The following statements are intended to:

- Make sure that you have had the time and opportunity to consider whether you and the Study Participant want to participate in this Registry;
- Have had your questions answered; and
- Agree to participate in the study as described.

You will be asked to acknowledge that:

- You have read the consent form and have no further questions about the Registry and the Study Participant's participation;
- You wish to provide the Study Participant's personal data to the Registry for the purposes of the Study;
- You allow for this data to be used for future research;
- You have explained the study to the Study Participant to the extent they are able to understand; and
- You are of legal age.

This is a web-based form. Your digital signature is the same as if you had signed your name to a paper document. By answering "Yes" to all of the following statements, you are giving your consent to participate in the CreatineINFO Registry on behalf of the Study Participant. After signing, a copy of the consent form will be emailed to you. If you cannot comfortably answer "Yes" to these statements, please do not check the consent boxes in the following section.

1. I have read this Consent and Authorization Form to provide the Study Participant's personal and medical data to be shared for the purpose of research. All my questions about the CreatineINFO Registry have been answered to my satisfaction, and I understand the purpose of the Registry and the risks of participation.

   Yes ___ No ___

2. I wish to provide the Study Participant's research data to the CreatineINFO Registry for the purposes described above under "Study Aims".

   Yes ___ No ___

3. I wish to provide the Study Participant's research data to the CreatineINFO Registry for future research within recognized ethical standards for scientific research, as described under "How We Use the Data".

   Yes ___ No ___

4. I have explained the study to the Study Participant to the extent they are able to understand, and the Study Participant has given their assent to participate in this study.

   Yes ___ No ___

5. I wish to provide research data about myself as described under “How You Provide Data”, where applicable, to the CreatineINFO Registry only for the purposes described under “How We Use the Data”.

   Yes ___ No ___

6. [Programmer Note: only show the following for U.S. residents] I acknowledge that I am at least 18 years of age and the age of majority in my State, and able to provide consent on behalf of the Study Participant. For validation purposes, I am providing my date of birth. This is requested to abide by good research practices and will be used for no other purpose than to confirm legal age. [Programmer Note: Insert Date of birth field to follow.]

   Yes ___ No ___

7. [Programmer Note: only show the following for non-U.S. residents] I acknowledge that I am at least 18 years of age and the age of majority in my State, Province or Country, and able to provide consent on behalf of the Study Participant.

   Yes ___ No ___

Permission for contact includes the following statements:

- Interest in hearing about other studies from ACD
- Interest in hearing about relevant clinical trials
- Interest in donating specimens or DNA (biobanking) for future research
- Interest in genetic testing
- Interest in receiving updates about uploaded genetic information
- Interest in learning more about ACD
- Interest in signing up for an ACD newsletter
- Interest in regional family support groups
- Interest in relevant volunteer opportunities