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

Adult Consent

Title: CreatineInfo Registry

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Sponsor: Association for Creatine Deficiencies (ACD)

This document is intended to give you the information you need to make an informed and voluntary decision whether or not to provide your personal and medical information to the CreatineInfo Registry. Much of the information in this form is required by the regulations designed to protect research participants, and the headings and structure of the document were chosen to be sure that all the required information was included. While this information is meant to answer most of the questions we anticipate, it may not answer all of *your* questions. If you have questions about anything you read, or other questions about the registry that are not answered here, please contact the Principal Investigator at the phone or email listed above.

Definitions

"Study Participant" refers to the person with Cerebral Creatine Deficiency Syndromes (CCDS). Registry information will be collected on patients who have CCDS. "You" refers to the person reading this form and providing the information. "We" refers to the organization, Association for Creatine Deficiencies.

Study Aims

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

1. To describe the people who have CCDS and to better understand the variability and stages of CCDS . To do this, we will ask you about your diagnosis, treatment, medical history, social and economic environment, and treatment outcomes.
2. To understand how CCDS changes over a person's lifetime and to learn about clinical practice patterns and variations over the course of treatment.
3. To help to develop best practices, management guidelines and recommendations so that clinicians can know how to give the best care to improve the quality of life and outcomes of people with CCDS.
4. To 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.

Research Data Sharing

A Registry collects and stores medical and personal information on patients, including their family history and other information that could be important for research. If you participate in

the Registry, you will be invited to provide personal and medical information by answering online surveys and uploading medical information. We will store the information you provide so that it can be used for future research projects.

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 data from the Registry community will not reveal participant identities.

How You Provide Your Data

We will ask you to enter your information using online surveys on a secure internet site. The specific information we ask for might include:

- name,
- date of birth,
- diagnosis,
- treatment,
- genetic mutations,
- lab results,
- other past and current medical information,
- school or job information.

You will be asked to update your registry information at least once per year, and you may be asked to update some surveys more frequently. We may contact you to:

- remind you to update surveys,
- finish incomplete surveys,
- complete outstanding surveys,
- complete new surveys,
- assist you with additional resources as needed,
- share registry updates.

The Registry Staff may also ask you to upload new test results or other medical information, and may contact you to clarify data you have entered.

You can update your information in the Registry whenever there is a change to your health, your treatment, or if you develop new symptoms.

We may contact you by telephone, email, through study-wide announcements or reminders automatically generated by the Registry, and by prompts on the organization's website and social media channels. You can view and revise your contact preferences at any time by logging into your registry account and changing your choices under edit/profile/contact preferences. Things you can decide you will allow or not allow us to contact you about include:

- reminders to update your surveys,
- clinical trials you might be eligible for,
- donating specimens or DNA for future research,
- Other research opportunities / Future research studies,
- ACD community events,
- New surveys and registry updates.

How We Use Your Data

The goal of the Registry is to let researchers, clinicians and industry partners use medical and other CCDS-related information to learn about Cerebral Creatine Deficiency Syndromes, while protecting the privacy of Study Participants.

The Registry is overseen by the ACD Oversight Board, a committee that may include scientists, doctors, and patients. The ACD Oversight Board reviews aggregated registry data (data that has been combined and from which things that might identify specific participants have been removed). The ACD Oversight Board also reviews ongoing research studies that use the Registry and evaluates new proposals for research that want to use the Registry's data. Lastly, the ACD Oversight Board reviews any reported problems or breaches of confidentiality to make sure they are appropriately reported and dealt with.

The ACD Oversight Board reviews three different kinds of research that use the Registry. First, the Principal Investigator and their colleagues who work with Association for Creatine Deficiencies can see all the data in the Registry and use it for research the ACD Oversight Board approves. The Principal Investigator will only be allowed to do research for which you have given your permission (by signing this form or another one in the future) and which has been reviewed by an Institutional Review Board (or IRB - an independent group that reviews research proposals to make sure they properly protect participants).

Second, outside researchers may apply to the ACD Oversight Board to see aggregated data. In most cases, such researchers will describe what they want to see, and the data will be assembled by Registry Staff, ensuring that no identifying information is shared. In rare cases, the ACD Oversight Board may allow outside researchers to see individual data, but only after anything that can identify an individual participant has been removed. In these cases, the outside researchers will have to agree not to try and identify individuals from the data they receive.

Third, outside researchers may be looking for individuals to participate in their own research study, not directly related to the Registry, and may ask the ACD Oversight Board to use the Registry for this purpose. In this case, the Registry will not give outside researchers your contact information but will instead contact you with details of the planned study and tell you how to contact the researchers if you are interested. You can also decide that you are not interested in receiving information on outside studies.

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. To further that mission, everyone who participates in *this* Registry is enrolled in NORD's Natural History Study Program (NHS). Information that specifically identifies participants is removed and their information combined with information from other rare diseases for cross disease analysis, cross disease research, and to facilitate advocacy. NORD may

also share information from the NHS that doesn't identify individuals with other databases that further rare disease research and the interests of the rare disease community, such as the Rare Disease Cures Accelerator – Data and Analytics Platform (RDCA-DAP) of the Critical Path Institute.

The ACD is also working with the Clinical Genome Resource (ClinGen) Patient Data Sharing Program to give you the choice to share your pseudonymized genetic and health data with others who will use it to improve patient care and genetic testing. ClinGen is a National Institutes of Health (NIH)-funded project aiming to build a resource that defines the impact of genes and genetic changes on health. This effort relies on data sharing.

In a separate consent survey within this study, you will have the option to give the ClinGen Patient Data Sharing Program access to your individual genetic and health information that you share with the Registry. With your permission, your genetic and health data will be pseudonymized (removing all personal identifying information) and shared with approved users and open and controlled-access databases. If you choose to give the ClinGen Patient Data Sharing Program access to your individual genetic and health information, you will have the option to receive updates about your genetic test results from the ClinGen Patient Data Sharing Program team.

Please note that granting consent here does not mean that ClinGen will have access to your individual genetic and health information. If you are willing to share your individual genetic and health information with ClinGen, you will need to grant ClinGen consent ("ClinGen Data Sharing Informed Consent") in a separate survey inside the registry.

Risks and Inconveniences

Putting your data in the registry does not put you at any risk of physical harm but, like any information you provide electronically, there is a risk that your privacy could be compromised if your data is inappropriately disclosed or misused.

The registry is designed to make the chance of this happening very small. The ACD Oversight Board reviews ongoing and new research to help prevent misuse (see How We Use Your Data, above). And 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 about the impact of CCDS on your daily life, your economic status, mood, and other topics that you may find unpleasant or disquieting.

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 is unlikely to lead to direct medical or financial benefits for you, but 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 anything to participate in the Registry, other than the costs of internet access, and you will not be paid for the information you provide.

Your 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, you should not expect to be paid.

Privacy Rights

The information we collect in the Registry is personal, and where that information relates to your health and medical records, it is considered Protected Health Information (PHI) and protected by a law called the Health Insurance Portability and Accessibility Act (HIPAA). This law only protects information when it is held by certain recognized parties, like doctors, hospitals, insurance companies, and some researchers. All reasonable efforts will be made to protect your PHI, which may be shared with others to support this research, but it is possible that your information could be used or disclosed in a way that leaves it no longer protected by law. We have taken steps to make that unlikely, described below.

Confidentiality

All identifiable information that is obtained in connection with this Registry will remain confidential. This Registry will share detailed medical and other information with researchers. We will protect your privacy by removing your name, address, and other identifying information before it is shared. It is important that the information you provide can all be kept together, as belonging to a single person, when it is used for research. To make this possible we will identify your information with an arbitrary code, which *will* be shared, but researchers will not be able to link the code back to you. This process is called “pseudonymizing” and the coded information is considered “pseudonymized.”

The Registry itself will maintain a database that links these arbitrary codes to the information that identifies Participants. We need to do this so that we can associate new information you give us with the pseudonymized information that we already have and to maintain the integrity of the database. Only trained and authorized people who work for the Registry will be able to see the information in this linking database.

When the results of research conducted with data from the Registry are published or reported, no information that could identify you will be disclosed unless you have explicitly given your consent for such disclosure. You are **not** giving that consent if you sign this form.

Representatives from NORD and from North Star Review Board, the IRB that oversees this Registry, may inspect study records during auditing procedures to be sure that the Registry is being protected according to regulations and policies. Additionally, NORD staff may access this registry in cases where technical support has been requested. However, these organizations and the individuals acting on their behalf are required to 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. If you choose not to, you won’t be penalized in any way, you won’t lose any benefits you might otherwise be entitled to, and your health care will not be affected. If you decide not to participate, or choose to withdraw, that decision won’t harm your relationship with your doctors, even if they are involved with the Registry or with Association for Creatine Deficiencies.

There may be other Registries that serve patients with CCDS, and you are free to provide data to any such registry instead of, or in addition to, working with us, or not to share your data at all. There may be other research opportunities, including clinical trials, for patients with CCDS, and

you may choose to participate in that research whether or not you participate in this Registry.

If you do choose to share your information with us, you can change your mind at any time. If, after joining the Registry, you decide you no longer want to participate, the Registry researchers may still use data that was submitted before you changed your mind in order to complete research that has already started, however, the data you shared with us will no longer be available for future research, and will not be shared further by Association for Creatine Deficiencies, even if it has been pseudonymized. It may not be possible for us to recover or destroy pseudonymized data that has already been shared with other researchers, who may still use your information to complete the research they have started. Similarly, pseudonymized data that has already been shared with NORD's NHS or The Critical Path Institute's RDCA-DAP cannot be removed from those databases.

If you choose to participate in the Registry, that permission will not expire. If you change your mind and want to withdraw from the Registry, you can do so through the website or by contacting the Registry staff directly by email at: registry@creatineinfo.org.

If You Live Outside the United States

The Registry is maintained on servers that are physically present in the United States. For persons living outside the United States who choose to share information about themselves, 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 personal information outside of the European Union and/or Switzerland, if any, will be undertaken in compliance with the General Data Protection Regulation under an appropriate transfer mechanism provided for by the General Data Protection 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. 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;
- To receive personal data in a portable, readily-accessible format;
- To restrict or withdraw permission for the processing of personal information;
- To 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 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 or want to consider what was presented here and whether you want to share your 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 Institutional Review Board (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. For questions about those protections and your rights as a Study Participant in this Registry, or to discuss other 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, 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.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

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

Authorization

The following statements are intended to ensure that you have had the time and opportunity to consider whether you 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 your participation
- That you wish to provide personal data to the registry for the purposes of the Study
- And that you wish to provide your pseudonymized data for future research

This is a web-based form and by answering Yes to all of the following statements, you are giving your consent to participate in the CreatineInfo Registry, just as if you had signed your name to a paper document. After signing, a copy of the consent form will be emailed to you. If you cannot comfortably answer “Yes” or have further questions, please do not check the consent boxes in the following section.

1. I have read (or someone has read to me) this Consent and Authorization Form to provide my personal and medical data to be shared for the purpose of research. All my questions about the 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 my research data to the CreatineInfo Registry for the purposes described above under Study Aims (page 1).

   Yes ___ No ___

3. I wish to provide my research data that has been pseudonymized to the CreatineInfo Registry for future research within recognized ethical standards for scientific research, as described under How We Use Your Data (page 3).

   Yes ___ No ___

4. I understand that by providing my consent to participate in this study now, I am not automatically sharing my individual genetic and health information with the ClinGen Patient Data Sharing Program. If I am willing to share my individual genetic and health information, I will need to grant ClinGen consent in a separate survey inside the registry.
   Yes___ No___