Protocol Title	CreatineINFO Registry and Natural History Study
Date	January 29, 2025
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Co-Investigators	
Sponsor Name	Association for Creatine Deficiencies (ACD)
Sponsor Study Number	IRB Protocol: NB100007

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1. Objectives

The primary aim of the CreatineINFO Patient Registry and Natural History Study ("Registry") is to conduct a prospectively planned and efficient natural history study that will result in the most comprehensive understanding of the disease and its course and pace over time. Other registry objectives include the following:

- Provide a convenient online platform for participants (or caregivers) to self-report cases of Cerebral Creatine Deficiency Syndromes (CCDS).
- Develop a communications registry within the CreatineINFO Registry (e.g., to notify patients of research studies and clinical trials).
- Characterize and describe the CCDS population as a whole, enhancing the understanding of disease prevalence and phenotype as well as the rate of progression of disease characteristics.
- Help the CCDS community develop recommendations and standards of care.
- Be a resource for researchers who seek to study the pathophysiology of CCDS, retrospectively collate intervention outcomes, and design prospective trials of novel treatments.

2. Background and Introduction

Cerebral Creatine Deficiency Syndromes (CCDS) are a group of inborn metabolic disorders including Guanidinoacetate Methyltransferase (GAMT) Deficiency, Arginine-Glycine AmidinoTransferase (AGAT) and Creatine Transporter Deficiency (CTD). Individuals with CCDS have decreased creatine in their brains. Creatine supplies energy to all cells of the body. Therefore, a lack of creatine disrupts a person's typical development. Patients often develop complex symptoms such as developmental delays leading to intellectual disability, seizures, emotional dysregulation, expressive communication impairments, and impaired motor skills. Like many other rare neurodevelopmental conditions, symptoms often affect many domains and cascade over time.

CTD patients currently have no approved drug treatment. Caregivers struggle to address symptoms with medications and therapies such as speech, occupational, and motor therapies, and hope for small improvements, although none of these approaches deliver the creatine that is lacking in the brain. AGAT and GAMT deficiency patients can treat their conditions with diet modification and creatine supplementation; however, the diet is difficult and supplements are not well-tolerated. Additionally, GAMT deficiency patients experience a buildup of a neurotoxin called guanidinoacetate (GAA). While supplementation and diet modifications can help reduce GAA levels, normalization of GAA is never fully achieved. Continuing this treatment regimen for AGAT and GAMT requires dedicated caregivers and patients; compliance is a common issue. CCDS caregivers express a desire for better long-term solutions, ideally approved treatments that leads to improved symptoms and quality of life.

The CreatineINFO Registry is an online registry for patients with CCDS. It is hosted by the National Organization for Rare Disorders (NORD®), an independent non-profit patient advocacy organization dedicated to individuals with rare diseases and the organizations who serve them. NORD is committed to the identification, treatment, and cure of rare disorders through education, advocacy, research, and patient services. The Registry collects information about individuals who are affected by CCDS, heretofore referred to collectively as "participants". This information is entered into the Registry by the participant or their legally authorized representative (LAR).

3. Study Design

3.1 Survey Design

The CreatineINFO Registry is a prospective, longitudinal, web-based, and observational natural history study. Participants with CCDS will be followed throughout the course of their lives with either the participant or LAR contributing data at varying intervals throughout the course of the study. Each participant will be assigned a unique study identification number which will be linked with any personal information they provide. Data will be collected at the start of the study (baseline) and at various time points as needed. Data will be collected on demographics, quality of life, medical history, disease phenotypes, disease-related events, personal experience with CCDS, general health status, medications, diagnoses, and other relevant topics.

The Registry will also ask caregivers who are LARs to enter data about their experience as a caregiver for an individual affected by CCDS. This is explained in the appropriate consent document. An acknowledgement of this data collection will be required in the Authorization section.

To further the goal of having the Registry be a resource for researchers, study participants will be asked to establish and provide a CRID identifier (Clinical Research ID), though this is not required. CRID is a free service that enables patients involved in research the opportunity to create their own Unique Universal ID. Participants may establish a Clinical Research ID (CRID) at https://thecrid.org. 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 participant to provide limited identifying information, allowing the use of these identification numbers facilitates linking available clinical data and biological samples in a de-identified manner. CRID has been reviewed and approved by the Veritas Charitable Institutional Review Board. There is no affiliation between NORD, ACD, and theCRID.org.

The Registry will use a web-based interface to allow participants and caregivers to participate worldwide. Once they document their voluntary and informed consent, participants will be invited to enter their data and information which will be stored indefinitely or until a participant revokes consent to participate in the study and requests that their data be removed. No experimental intervention is involved in participation in the CreatineINFO Registry.

3.2 Internal Oversight

The Registry Advisory Board (RAB) oversees the direction and goals of the Registry, and recommends possible surveys. Members include: ACD's board, executive director, scientific advisor, and Registry coordinator; clinical and academic representatives; industry partners; CCDS representatives. The Registry Oversight Board (ROB) advises on the development of surveys, reviews de-identified Registry data and the use of the Registry, ensures proper evaluation and oversight of protocols requesting to use Registry data, and reviews any protocol or confidentiality deviations on a case-by-case basis and ensures that any such deviations are reported to the Institutional Review Board (IRB). Members include: ACD's board, executive director, scientific advisor, and Registry coordinator; clinical and academic representatives; CCDS representatives. The Family Advisory Board (FAB) reviews content, family-friendly language, and translations of surveys and materials. Members include CCDS patients and caregivers.

4. Duration

This registry will be open for five years with the option to extend beyond that time. Annual maintenance will be funded by the ACD.

5. Eligibility and Recruitment of Participants

5.1 Inclusion Criteria

For the purposes of the Registry, CCDS is defined as a diagnosis of one of the following:

- Arginine:glycine amidinotransferase (AGAT) deficiency; or
- Guanidinoacetate methyltransferase (GAMT) deficiency; or
- Creatine transporter deficiency (CTD).

A CCDS diagnosis may be confirmed by genetic testing, lab value, and/or clinician diagnosis.
For the purposes of the 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 an individual in their care.

Eligibility for participation in the CreatineINFO Registry is based on the following criteria:

- Individuals of any age with a confirmed diagnosis or diagnosis consistent with CCDS are eligible to enroll as a Study Participant.
- Individuals must be willing to provide informed consent. Study participants can be:
    - Legal adult individuals who are able to provide their own consent
    - Children and adults unable to provide their own consent, for whom consent must be provided by a Legally Authorized Representative (LAR) who is a legal adult. The role of the LAR is defined as a person who is authorized under applicable law to consent and enter data in the Registry on behalf of another individual. The LAR may be a parent, grandparent, spouse, caregiver, or guardian as long as they have this legal authority.
- Individuals must have at least periodic access to the internet and be able to comply with web-based study procedures and data collections.
- Employees of and volunteers working with ACD are eligible to enroll as a Study Participant or LAR and contribute data to the CreatineINFO Registry.
- Study Participants or LARs who are pregnant may enroll in the Registry and contribute data; Study Participants and LARs who become pregnant while participating in the CreatineINFO Registry may remain in the Registry and contribute data.

5.2 Exclusion Criteria

- Individual is unable to read and understand English, French, or Spanish (as available and applicable)
- CreatineINFO Registry will not knowingly enroll Study Participants or LARs who are incarcerated. If this occurs in error, the IRB will be notified as soon as possible.

5.3 Sample Size

There is no upper limit for the number of participants in this study.

5.4 Recruitment of Participants

Information about the existence of the Registry will be communicated by NORD and ACD via mass media (email, website advertisements, flyers, patient foundations and other means of mass communication) to members of the CCDS community including patients, physicians, and researchers. In addition, information about the Registry will be disseminated through clinical, professional, research, patient foundations, and support groups.

Study contact may occur through auto-generated reminders within the Registry platform, by telephone calls, email, study-wide announcements, and prompts using the organization's website and social media channels.

6. Process of Obtaining Consent

Registry participants or their LAR will be asked to read an online consent form explaining the purpose of the CreatineINFO Registry and must agree to allow the use of their personal and medical information, including information that identifies them. The consent form will outline how and to whom data reported to the Registry can be shared. Individuals giving consent will be asked to confirm that they are the participant or an LAR of the participant. These individuals will be asked to attest that they are a legal adult. Consent from an LAR is required for participants who are minors or who are adults unable to provide legal informed consent for themselves. When consent is given by an LAR, every effort will be made to explain the study to the participant within their ability to understand.

The informed consent document will inform study participants or their LAR that the Registry cannot provide medical advice or answer specific medical questions. They will be provided information as to where they may find resources to support people with CCDS and will be referred to consult their medical provider for further questions.

Voluntary and informed consent to participate will be documented by an electronic signature. The informed consent form will be presented online; potential participants must read it and answer a list of questions that demonstrate or attest their understanding and that all their questions have been answered to their satisfaction. Once all questions are answered "yes," they can signal their consent to participate by checking a consent box.

By consenting to participate in the Registry, participants or their LAR are consenting to allow the Registry staff to contact them as it relates to study procedures. Staff may contact participants to ask them to upload new test results or other medical information, update their surveys or clarify data they have entered. Registry staff may also notify participants of major changes to the Registry or IRB of record.

Participants will also be asked if they wish to be provided with contact information for researchers seeking participants for future research studies outside the Registry. If participants opt-in to receiving information about such studies, they will have to contact those study investigators and provide separate informed consent. The Registry consent does not obligate individuals to participate in any outside studies, nor does it allow the Registry staff to share participants' contact information with outside researchers.

Study Participants or their LAR can view and revise their study opt-ins at any time by logging into their Registry account. They will select [their] / [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 individual may edit their selections at any time.

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

For those Study Participants who previously consented to receive updates regarding their uploaded genetic information from the Clinical Genome Resource (ClinGen) will now receive those updates from ACD, if they “Opt-in”.

There will be no hard-copy informed consent with a written signature associated with this online Registry, but an electronic version of a participant’s signed informed consent form will be available and can be downloaded from their Registry account at any time. In addition, a copy of the electronically signed consent form will be e-mailed to the study participant or their LAR when they first enroll. Since consent for this minimal risk Registry study will be provided online at the convenience of potential participants, no real-time discussion of the information in the consent form will routinely be provided. If potential participants have questions, they can contact the study staff by email or telephone; contact information will be provided with the consent form. The consent of one LAR will be considered sufficient for participation of a minor in this Registry.

Consent to participate in the Registry will allow Registry information to be used by Registry staff. Third parties may also be granted access after careful review and approval by ACD’s Registry Oversight Board (e.g., ClinGen).

Participants will be able to withdraw from the study at any time through the website’s “revoke consent” option. When a participant revokes consent, they withdraw from the registry. Any ongoing research using data collected by the registry before a participant formally withdraws their consent will continue, but no new information will be collected. In addition to the “revoke consent” option on the website, a participant or their LAR can withdraw by notifying the study team in writing. To revoke consent, study participants or their LAR should log in to their Registry account. Select [their] /[the Participant’s] name and the CreatineINFO Registry. Then, click the button labeled “Consent/Opt-ins” followed by the button that says “Revoke”.

7. Facilities and Performance Sites

NORD will store CreatineINFO data on NORD encrypted servers and/or encrypted servers of third-party vendors hosted in Canada, providing regular back-up at commercially acceptable intervals. Servers are compliant with United States and international regulations, including General Data Protection Regulation (GDPR).

Data may be entered into the registry world-wide through a web-interface.

8. **Ethical Considerations**

8.1 Potential Benefits

There are no direct benefits to participating in the CreatineINFO Registry. The CreatineINFO Registry may facilitate collaboration between clinicians at multiple sites and may assist in recruitment of participants for clinical trials. Indirect or future benefits could include the knowledge gained from the Registry or other studies it makes possible, knowledge that may increase understanding and the availability of therapeutic options for CCDS patients. In addition, if they opt to do so, participants in the CreatineINFO Registry will be informed of future research studies involving CCDS for which they may be eligible. Some participants may directly benefit from inclusion in future treatment studies .

8.2 Potential Harms

There are no foreseeable risks of physical harm to participating in the study. The Registry surveys may ask questions about the impact of CCDS on life-experience, economic status, mood, and other topics that some participants may find unpleasant or disquieting.

The Registry is a repository of sensitive personal data about individuals. With any such repository, there is always the possibility that a participant's confidentiality could be breached, either through unauthorized release of information or through unauthorized access to the data. This risk will be reduced as far as practically possible by following applicable data security regulations and standards, as described below.

Note that, since CCDS are rare disorders, it may be possible to identify participants from the data they provide, even without direct identifiers. Any non-Registry researchers granted access to the Registry data by ACD's Registry Oversight Board will be required to agree not to attempt to identify participants from the data to which they are given access.

8.3 Privacy and Confidentiality

Risks will be minimized by ensuring adherence to applicable regulations and through the following measures: (1) use of random numeric codes as unique participant identification numbers in place of direct identifiers; (2) restricting access to direct identifiers and the link between codes and identifiers to authorized members of the Registry staff; (3) requiring that non-Registry researchers be approved by the ACD's Registry Oversight Board, and not providing links between codes and identifiers.

In addition to these design measures, participants' privacy and the confidentiality of their information will be safeguarded by using appropriate technical measures. Confidentiality will be protected by limiting access to data and keeping protected health information (PHI) data on a password-protected secure server. Access to PHI in the database will be limited to members of the Registry staff and NORD staff, who will use password-based security measures. Best practice will be followed for password selection and maintenance, and administrative controls will minimize password exposure and prohibit password sharing. NORD staff may access PHI in cases where technical support is needed and will only do so with the permission of Registry staff. The informed consent will describe these terms for access to PHI. The PHI associated with this study will be retained indefinitely. There is no plan to destroy data or the key that links a participant's identifying information to their random code. If a participant uses the "revoke consent" option on the website or contacts the Registry staff or investigators and requests in writing that they be withdrawn from the Registry, their coded data will be retained and may be used for future research, unless they explicitly contact NORD and request that their data be removed from the platform.

8.4 Privacy and Confidentiality Protections for International Users of the Platform

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, 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, Participants acknowledge that they are disclosing information that would otherwise be private. Privacy laws in the Participant's 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 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. 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.

8.5 Diversity, Equity, and Inclusion

The Registry will allow participants to voluntarily provide data on their race and ethnic identification, as well as on relevant social determinants of health. Such data will allow researchers to look for differential impacts of CCDS based on social determinants, and to ensure that, to the extent practically possible, the data in the Registry appropriately represents the population affected by CCDS.

9. **Data Analysis and Reporting**

Statistical analyses will focus on specific research objectives such as understanding CCDS symptoms and interventions. Data analysis will begin with simple characterization of the demographic, clinical, and quality-of-life data reported in the Registry. Longitudinal data may be assessed to investigate disease progression over time. Third party individuals or organizations with a focus on data analytics may be consulted to assist with data analysis and/or interpretation.

10. **Data Requests and Release**

It is anticipated that the CreatineINFO Registry will be a valuable resource for current and future research. ACD's Registry Oversight Board (ROB) will evaluate protocols that request

to use Registry data. To promote use of the Registry and to keep study participants and the community updated on the progress of the registry, de-identified information about database contents may be updated annually and made available to the public. Such information may include number of participants, prevalence of common genetic variants of participants, group demographic information, and other highlights.

Investigators wanting to obtain a report of registry data will need to apply to the ACD. The application will require information concerning: principal investigator, institution, aims and hypotheses of the proposed research, how the research will be funded, and where the data will be shared.

After the ROB approves the scientific/technical merit of a Registry use request, the requested data will be de-identified and provided by Registry staff. De-identified means personally identifiable information (PII) has been removed. Examples of PII include but are not limited to name, date of birth, contact information, city, and postal code. A data transfer agreement will be distributed along with the data specifying the agreed upon scope of research to be performed with the Registry data and specifying that no attempt may be made to identify the Registry participants.

ACD may share de-identified participant data with other ACD approved external research studies and databases (e.g., Clinical Genome Resource [ClinGen]), who may in turn provide this data to databases and repositories (e.g., ClinVar).

For registry maintenance and support purposes, NORD registry and IT staff will have access to all entered data, including identifiable data. NORD is collecting detailed information about names, sex and place of birth in order to use algorithms to establish Global, Unique Identifiers (GUID). These data were collected prior to the signing of the consent form; however, the intent is that these data elements are included as part of the research data. These identifiers will allow for de-duplication across the IAMRARE platform. It will provide opportunities to conduct data linkages using the GUID, thus removing the need to share identifiers and promoting privacy protections. In addition to platform maintenance activities, after notifying the study sponsor, NORD may choose to conduct IRB-approved, cross-disease research using record-level data.

11. Data Safety Monitoring Plan

The ACD Registry Oversight Board will meet at least once per year and review use of Registry data. Because this is a low risk study and does not include any interventions, no stopping rules apply. The ROB will review any protocol or confidentiality deviations throughout the year on a case-by-case basis and report any such deviations to the IRB for their consideration. Protocol violations or unanticipated problems will be handled per: 45 CFR part 46 HHS Regulations for the Protection of Human Subjects; 45 CFR parts 160 and 164 Health Insurance Portability and Accountability Act (HIPAA) Regulations for Standards for Privacy of Individually Identifiable Health Information; and 21 CFR part 56 FDA Regulations for the Protection of Human Subjects.

This study will be submitted to an Institutional Review Board (IRB), which is a board formally designated by an institution or investigator to review, approve the initiation of, and conduct periodic review of research involving people. The primary purpose of such an assessment is to assure the protection of the rights and welfare of the participants in the study. The protocol, informed consent form(s), survey questions (data dictionary), recruitment, and all other participant-facing materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol, data dictionary, and other documents will require review and approval by the IRB before the changes are implemented to the study. In addition,

all changes to the consent form will be IRB-approved and a determination will be made by the IRB regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

12. Cost of Participation

There is no cost to participants of the registry. Initial design and implementation of the registry will be funded by ACD and NORD. Expenses for cost for survey development, data retrieval, and analyses may be passed on to future investigators as deemed appropriate by ACD's Registry Oversight Board.

13. Payment for Participation

While there will not be direct compensation to enroll in the Registry, we may provide incentives for completion of surveys. Incentives may include discounted rates to attend ACD events, and small material incentives such as t-shirts or gift cards etc. Notifications of incentives and eligibility will be reviewed by the IRB.

14. References

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15. Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that ACD and the Principal Investigator agrees to conduct the research in compliance with the approved protocol.

Each signatory agrees to ensure that the confidential information contained in this document will not be used without the prior written consent of ACD for any other purpose other than the evaluation or conduct of the research.

Principal Investigator, as authorized by ACD:

Signature: Date:

Name (please print):

Heidi Wallis

Position:

Executive Director, Association for Creatine Deficiencies

16. Appendices

16.1. Appendix A: Consent Form

16.2. Appendix B: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2	08/27/21	Sofia Balog	Replace the existing approved CreatineINFO Registry Protocol V1 with the new IRB-approved Protocol template. Include additional contact preferences (also included in the consent forms.) The nature of the study has not changed.
2	3	02/25/22	Emily Reinhardt	Adding participation incentives to the study protocol to allow for discounts to be given for registration fees for conferences and other ACD events. The nature of the study has not changed.
3	4	02/21/2023	Emily Reinhardt	Changed Principle Investigator (P.I.) from Laura Trutoiu to Heidi Wallis. The nature of the study has not changed.
4	5	12/6/2024	Emily Reinhardt	1. Incorporated edits from NORD's "NORD Protocol Template_Migration _ANNOTATED" document (to migrate our registry to the new NORD platform) 2. Section 3 - added information about Clinical Research ID (CRID) 3. Section 3 - updated information about ACD's registry boards 4. Section 3 - updated information about ClinGen's Data Sharing Program 5. Section 10 - updated information about data requests 6. Section 13 - updated information about participant incentives
4	5.1	1/23/2025	Emily Reinhardt	1. Added language clarifying that each Study Participant would be assigned a randomized unique study identification and who would have access to the code. 2. More clearly defined what de-identified data means. 3. Removed explicit details about ClinGen partnership, specifically we removed any

				language suggesting that we would share identifiable information with ClinGen. That is no longer the case. We have changed our partnership with ClinGen so they will no longer have direct access to Registry data and will now only ever receive de-identified data from the registry. 4. Included language indicating that external research partners may share de-identified Registry data with other databases and repositories. 5. Removed language indicating that we would only ever share aggregate data with the ROB or external partners. In some cases, we will share aggregate data. But in other cases, we may share participant level data which has been coded and de-identified.

16.3 Appendix C: Data Dictionary