Protocol Title	CreatineInfo Registry and Natural History Study
Date	2/21/2023
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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 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.
- Assist the CCDS community with the development of recommendations and standards of care.
- Be a case-finding resource to be used 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 group of inherited metabolic disorders including Guanidinoacetate Methyltransferase Deficiency (GAMT), Arginine-Glycine AmidinoTransferase (AGAT) and Creatine Transporter Deficiency (CTD). Creatine is an essential energy shuttle in the brain. 50% of creatine is synthesized in the kidney and liver and the remaining is from diet.

Parents of children with CCDS share similar stories: around one year of age, an affected child's life is marked by difficulties in feeding, failure to thrive and failure to achieve developmental milestones. Common clinical symptoms in CCDS include severely impacted speech, language and motor skills, intellectual disability, behavioral problems, hypotonia and in half of cases, seizures.

Onset of symptoms ranges from the first few months of life up to two years of age. There is a lag between onset of symptoms and confirmation of diagnosis up to 5-7 years. CCDS are severely under-diagnosed due to lack of awareness and availability of clinical diagnostic tests in every center. It is estimated that nearly 1% of all X-linked intellectual disability is due to creatine transporter deficiency, one of the three CCDS.

The CreatineInfo Registry is an online registry for patients with CCDS. It will be 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 and as such is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services. The registry will collect information from participants, (or their authorized respondents, heretofore referred to collectively as "participants"), who are affected by CCDS.

- What is CCDS?
- How are CCDS diagnosed?

- Who is affected by CCDS?
- How are CCDS treated/managed?

3. Study Design

The CreatineInfo Registry is a prospective longitudinal web-based observational natural history study. Participants with CCDS will be followed throughout the course of their lives with either the participant or authorized respondents contributing data at varying intervals throughout the course of the study. Data will be collected at the start of the study (baseline), at least once per year and ad-hoc with participants updating information as needed. Data will be collected on demographics, quality of life, medical history, disease phenotypes, event episodic data, retrospective data, participant review of systems and medication and diagnostic data. The driving components to the study include provisions for a convenient online platform for participants; developing a communications registry within the CreatineInfo registry; characterizing and describing the CCDS population as a whole; assisting the CCDS community with the development of recommendations and standards of care and; being a case-finding resource to be used for researchers who seek to study the pathophysiology of CCDS.

A Registry Oversight Board that may include scientists, doctors, and patient advocates, will be assembled to oversee the conduct of the study. The ACD Oversight Board will review aggregate registry data and the use of this registry, ensure proper evaluation of protocols requesting to use registry data and/or contact registry participants, and review any protocol or confidentiality deviations on a case-by-case basis and ensure that any such deviations are reported to the IRB.

Table 1

Questionnaire	Longitudinal(y/n)	Updateable(y/n)	Schedule of data collection
A.Getting Started	N	N	As needed
B. Caregiver Contact Information	N	Y	As needed
C. Participant Profile	N	N	Baseline
D. Diagnosis	N	N	Baseline
E. Clingen Informed Consent	N	Y	As needed
F. Clingen Survey	N	Y	Baseline

(Back-End)			
G. Patient Meaningful Outcomes	Y	N	Every year
H. Seizure	N	Y	Baseline
I. Cardiovascular Health	N	N	Baseline
J. Medication	N	Y	As needed
K. CCDS Disease Management	N	Y	Baseline
L.Medical Notes and Documents	N	Y	As needed

The registry will utilize a web-based interface to maximize accessibility to participants and clinicians worldwide. No experimental intervention is involved in participation in the CreatineInfo registry study. Following informed consent, participants will be invited to input their data and information that will be stored indefinitely or until a participant revokes consent from participation in the study. Any de-identified data collected prior to withdrawal of consent may be used for research purposes.

Annual maintenance will be funded by Association for Creatine Deficiencies (ACD). Registry participants will be automatically enrolled in NORD's Natural History Study Program (NHS), and their pseudonymized information aggregated with information from other rare diseases may be used for the purposes of cross disease analysis and cross-disease research to facilitate advocacy and further NORD's mission. Pseudonymized information may be shared with other databases such as the Rare Disease Cures Accelerator – Data and Analytics Platform (RDCA-DAP). This will allow more researchers to use the information to do research.

The ACD will work with the Clinical Genome Resource (ClinGen) Patient Data Sharing Program to give the participants the choice to share their deidentified and 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.

If the participant chooses to give the ClinGen Patient Data Sharing Program access to their individual genetic and health information shared with the Registry, the ClinGen Patient Data Sharing Program team members, will have access to the Study Participant's identifiable information including the genetic testing report that will be uploaded in the registry surveys and health information shared in the surveys. If participants no longer have a copy of their testing, the ClinGen team can help them to request one. Once participant's report is uploaded, a ClinGen Patient Data Sharing Program team member will collect information about the

genetic change(s) that were found from the report, and the participant genetic and health data will be pseudonymized (removing all personal identifying information) and shared with approved users and open and controlled-access databases including:

- ClinVar, a National Center for Biotechnology Information database of genetic changes and their relationship to human health.
- Pseudonymized information from the Registry will also be available to inform other ClinGen activities to understand the relationship between genes and health. Although the ClinGen Patient Data Sharing Program team that is included on the IRB will have access to identifiable data, no identifiable data will be available for other ClinGen efforts besides the authorized staff.
- To learn more about where data would be shared, click here.

4. Duration

This registry will be open for five years with the option to extend beyond that time. There is no date of termination or closure.

5. Eligibility and Recruitment of Participants

5.1 Inclusion Criteria

All patients with a confirmed diagnosis of CCDS are eligible for inclusion. The registry is open to recruiting patients of all ages who have a diagnosis consistent with CCDS.

Eligibility for participation in the CreatineInfo registry is based on the following criteria:

- AGAT Deficiency, GAMT Deficiency, or Creatine Transporter Deficiency as defined by genetic testing or lab value
- Disease defining characteristics (2 or more of the following):
  - o Low serum creatine and guanidinoacetate (AGAT deficiency) or low serum creatine and elevated guanidinoacetate (GAMT deficiency) or increased urine creatine/creatinine ratio (creatine transporter deficiency)
  - o Biallelic pathogenic or likely pathogenic variants in the GATM gene (AGAT deficiency) or GAMT gene (GAMT deficiency) or hemizygous or heterozygous pathogenic or likely pathogenic variant in the SLC6A8 gene (creatine transporter deficiency)
  - o Decreased creatine peak on brain magnetic resonance spectroscopy o Reduced creatine reuptake in human fibroblasts (creatine transporter deficiency)
  - o Reduced enzymatic activity of AGAT or GAMT
- Willing and able to provide informed consent

● Able to comply with web-based study procedures and data collections

5.2 Exclusion Criteria

Patients will be excluded from the registry if they do not meet inclusion criteria.

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 interested members of the CreatineInfo community including patients, physicians and researchers. In addition, information about the registry will be disseminated through clinical, professional, research, patient foundations and support groups including but not limited to:

- Child Neurology Foundation
- ClinGen
- Child Neurology Society
- National Organization for Rare Disorders

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

Submission of information by participant or their representative/respondent: Registry participants or their legally authorized representative/respondent 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 also explain that pseudonymized information will be shared with the NORD Natural History Study program and the Rare Disease Cures Accelerator-Data Analytics Platform (RDCA-DAP). Individuals giving consent will be asked to confirm that they are the participant or a legally authorized representative of the participant. Consent from a legally authorized representative is required for participants who are minors or who are adults unable to provide legal informed consent for themselves. When consent is given by a legally authorized representative, every effort will be made to explain the study to the participant within their ability to understand. Participants will also be asked if they consent to future contact by the registry staff to clarify data entries or to provide them with contact information for researchers seeking participants for future research studies outside the registry. They will be informed that by participating in the registry and/or consenting to be contacted they are in no way obligated to participate in such future studies.

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. Study Participants can view and revise their contact preferences at any time by logging into their registry account and editing their preferences under edit/ profile/ contact preferences. Permission for contact includes the following statements:

- Reminders to update my survey responses
- Clinical trials I may be eligible for
- Potentially donating biospecimens and or DNA for future research studies
- Other research opportunities / Future research studies
- ACD community events
- New surveys and registry updates

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 authorized representative 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. However, if potential participants have questions, they can contact the study staff by email or telephone; contact information will be provided with the consent form. Unless required by the IRB, the consent of one parent or legally authorized representative 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 investigators, staff, and third parties granted access to pseudonymized data by the Registry Oversight Board (ACD). In addition, participants will be explicitly asked to provide additional permission if they are willing to allow registry administrators and staff to contact them to see if they are interested in participating in future research studies and/or clinical trials. This permission will only be for contact; participants will be asked to provide separate informed consent for each such research study.

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. Their identifiable information will be stored but not used for further research. Any information that was aggregated before their withdrawal may be used to complete research that has already started. It may not be possible to retrieve or remove all pseudonymized data that was aggregated or shared with a participant's consent prior to their withdrawal.

In addition to the "revoke consent" option on the website, a participant or their legally authorized representative can withdraw by notifying the study team in writing.

7. Facilities and Performance Sites

The CreatineInfo Registry data will be stored on secure severs located at the National Organization for Rare Disorders, Inc. (www.rarediseases.org). Data may be entered 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 will 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 that result from the registry and for which separate informed consent will be obtained.

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, as 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 the 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) replacement of direct participant identifiers in the registry with codes, and storage of the information that links the codes to the identifiers in a separate physical database or separate database tables; (2) restricting access to this linking information to authorized members of the registry staff and authorized registry researchers; (3) requiring that non-registry researchers be approved by the ACD, and do not have access to linking information. Further details are provided below.

Participants' privacy and the confidentiality of their information will be safeguarded by using modern database management techniques and informed consent. Participants will be able to choose whether or not to be contacted by the registry for information or opportunities not directly related to the study and how they would prefer that contact take place (e.g., mail, email, phone.) Registry staff may contact participants to clarify entered data. Confidentiality will be protected by limiting access to data and keeping PHI (protected health information) data password protected on a secure server. Access to PHI in the database will be limited to members of the sponsor's registry research team, who will use password-based security measures. Best practice will be followed for password selection and maintenance, and administrative controls will minimize password exposure or password sharing. NORD staff may also access PHI in cases where technical support is needed and will only do so with the permission of registry staff. The informed consent will state these terms for access to PHI.

Data will be maintained on the NORD Natural History Studies platform, which meets or exceeds current guidelines for maintaining security of PHI.

Aggregate data will be shared with the public as general descriptive statistics regarding database contents. Pseudonymized data will be shared with NORD. Identifying information in the data will be replaced with a unique identifier that is assigned by registry staff, and the file linking the unique identifier with the PHI will be kept in a separate password protected database.

Third parties may seek access to data in the CreatineInfo Registry. Third parties may include, but are not limited to, researchers or companies conducting retrospective studies or conducting research and/or clinical trials on new therapies. Third parties will only be granted access to registry information after review and approval of this study's Advisory Board (ACD). Such approval must be obtained before pseudonymized data is shared and will be based on the scientific impact of proposals and the validity of their design. Decisions regarding access, and their rationales, will be documented, and access will only be considered for research related to CCDS. Any third party given access to pseudonymized data must agree not to attempt to reidentify individual participants. Third parties seeking access to registry information for the purpose of determining eligibility for participation in a research study or clinical trial must provide IRB approval of the research study for which access is being requested. Such third parties will not be given contact information for participants; registry staff will contact the participants who have agreed to receive such contact and give participants the researcher's contact information, so that participants can decide whether they would like to participate in the new research.

The protected health information (PHI) associated with this study will be retained indefinitely. There is no plan to destroy data or the key since this is an open-ended registry with no planned completion date. If a participant uses the "remove consent" option on the website or contacts the registry staff or investigators and requests in writing that they be withdrawn from the registry, their data will be stored and not used for future research. However, any research use of participant information prior to the date that consent is formally withdrawn cannot be retrieved or archived.

Personal information that has been withdrawn will be stored rather than destroyed to preserve the opportunity for a participant to re-enter the study in the future.

8.4 Privacy and Confidentiality Protections for International Users of the Platform

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, 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, 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.

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 impact 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. Such assessment is particularly important given the technical requirements (i.e., internet access) for participation.

9. Data Analysis and Reporting

Statistical analyses will focus on simple characterization of the data in the registry. Basic descriptive statistical measures will be calculated to summarize registry information. Specifically, frequencies, percentages, means, medians, ranges, etc. will be generated. Subgroup analyses may also be performed to further delineate registry data. These analyses may include t-tests / Wilcoxon rank-sum tests and Pearson correlation / Spearman correlation for continuous measures; for categorical variables, chi-square and Fisher exact tests may also be performed. Third party individuals or organizations with a focus on data analytics may be consulted to assist with data interpretation.

10. Data Requests and Release

It is anticipated that the CreatineInfo Registry will be a valuable resource for current and future research. The Association for Creatine Deficiencies (ACD) board of directors is the oversight board entity for the CreatineInfo registry and will ensure proper evaluation of protocols to use registry data and/or contact registry participants. To promote use of the repository, aggregate information about database contents will be updated quarterly or semi-annually and made available to the public. Such information may include number of registrants, prevalence of common diagnoses of registrants, demographic information, and percent willing to be contacted for future research. Investigators wanting to use the registry or contact participants will need to apply to the ACD. The application will require information

concerning: Principal Investigator, aims and hypotheses of the proposed research, where the research will be performed, and how the research will be funded.

After the ACD approves the scientific/technical merit of a registry use request, the following approach will be applied:

Scenario 1: Study Principal and Co-investigators. Study Principal Investigator and Co-investigators outlined in the protocol cover page will have access to all database elements for analysis and publication; any publication of data will be done so as to protect the confidentiality and the identity of individual registrants. PHI (protected health information) will not be shared with others outside of the registry study staff. Registry investigators may not contact registry participants for new research (work that goes beyond the data collection specified in this protocol) without project-specific IRB approval for the new research project.

Scenario 2 - Pseudonymized and coded data requested. This scenario addresses the need of outside collaborative researchers to scan the registry and view aggregate data on the registered population. The researcher will provide as part of the application process the types of research or preparation for research that will be conducted with the data. The registry research team may enter specific search criteria into the CreatineInfo Registry and provide aggregated or pseudonymized data to researchers. Alternatively, upon unanimous ACD approval, researchers may be granted direct access to pseudonymized registry data. No information that would directly link the data to the registrants will be included in the output data. This data could be used for publication, or as preliminary data for a grant or IRB proposal.

Oversight Requirement - No project-specific IRB submission is needed. The ACD will review the request, and if needed, obtain clarifying information during the approval process. 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.

Scenario 3: An outside investigator would like to contact registry participants to recruit them for other research. The general mechanism by which this contact can be made is that the registry staff would contact the participants on behalf of the outside researcher, and give the participant contact information about the researcher, so that the participant can decide whether they would like to participate in the new research. Thus, after ACD approval of the application for registry use, an IRB approved recruitment flyer will be requested from the researcher offering details about their planned study. This flyer will be reviewed by ACD for appropriateness and then distributed to all registry participants who have agreed to receive such contacts, along with contact information for the researcher.

Oversight Requirement - Requests for recruitment from the registry will only be fulfilled after ACD approval of the application. A project-specific IRB approval must also be provided.

Note: there is no scenario in which third parties can be given access to personally identified information or to the code linking database unique identifiers to participant identities.

11. Data Safety Monitoring Plan

The ACD Oversight Board will meet at least once per year and review aggregate registry data and the utilization of this registry. No stopping rules apply. TheACD Oversight Board will also review any protocol or confidentiality deviations 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

12. Cost of Participation

There is no cost to participants of the registry. Initial design and implementation of the registry will be funded by Association for Creatine Deficiencies and NORD. Expenses for cost of data retrieval and analyses may be passed on to future investigators as deemed appropriate by the Advisory Board.

13. Payment for Participation

While there will not be direct compensation for completing surveys, we will incentivize participation in the registry and completion of surveys by providing discounted rates to attend conferences, meetings, webinars, and other ACD events. Respondents may earn a one-time 25% discount off event registration fees for the completion of the Patient Meaningful Outcomes (PMO) survey. To receive the PMO discount, respondents must answer at least 75% of questions in the PMO survey AND submit the survey. They can earn an additional one-time 25% discount off event registration fees for uploading their genetic report as part of the ClinGen Patient Data Sharing Program. These two discounts can be earned independent of one another, but can be used in combination for a total of 50% off registration fees. The eligibility of these discounts may also be given on a case-by-case basis, depending upon the accessibility of surveys for non-English speaking respondents.

14. References

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15. Signature Page

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

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

For and on behalf of the ACD:

Signature: Date:

Heidi Wallis 02/21/23

Name (please print):

Heidi Wallis.....

Position:

Executive Director, Association for Creatine Deficiencies

Signature: Date:

..../...../.....

Name: (please print):

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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	3	02/21/2023	Emily Reinhardt	Changed Principle Investigator (P.I.) from Laura Trutoiu to Heidi Wallis. The nature of the study has not changed.

16.3 Appendix C: Data Dictionary