PROTOCOL TITLE:

Clinical Trial Readiness for SCA1 and SCA3

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
Version 2	2/27/2018	CoC detailed in Section 16.1; condition to administer SARA (longer than 1 month between last clinical exam and MR scan) removed in Section 5.1.	Yes
Version 3	9/7/2018	Language on "Subset" of participants to undergo SARA exams removed in section 4.1; optional videotaping of SARA exams added in sections 4.1 and 5; up to three more scanning time points (with identical procedures) added in section 5; plans for sharing of de-identified data with external investigators added to consent form and data sharing process updated in section 6.3 (to replace Steering Committee review by NIH Data Access Committee review); typo corrected in section 15.4.	Yes

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ABBREVIATIONS/DEFINITIONS

- AD: axial diffusivity
- Ala: alanine
- Asc: ascorbate
- Asp: aspartate
- AUC: area under the curve
- BRP: Bioengineering Research Partnership
- COA: Clinical outcome assessment
- CRLB: Cramér-Rao lower bounds
- CTSI: Clinical and Translational Science Institute
- Cr: creatine
- CRC-SCA: Clinical Research Consortium for Studies of Cerebellar Ataxias
- CV: coefficient of variance
- EASG: European Ataxia Study Group
- FA: Fractional Anisotropy
- GABA: γ-aminobutyric acid
- Glc: glucose
- Glu: glutamate
- Gln: glutamine
- GPC: glycerophosphocholine
- GSH: glutathione
- HARDI: high angular resolution diffusion imaging
- mI: myo-Inositol
- Lac: lactate
- MD: mean diffusivity
- MRI: Magnetic Resonance Imaging
- MRS: Magnetic Resonance Spectroscopy
- NAA: *N*-acetylaspartate
- NAAG: N-acetylaspartylglutamate
- NAF: National Ataxia Foundation
- PC: phosphocholine
- PCr: phosphocreatine
- PE: phosphoethanolamine
- RD: radial diffusivity
- ROC: receiver operating characteristic
- RSN: resting-state network
- SARA: Scale for the Assessment and Rating of Ataxia
- SCA: spinocerebellar ataxia
- sIns: scyllo-inositol
- SNR: signal to noise ratio
- Tau: taurine
- tCr: total creatine, creatine + phosphocreatine
- UMN: University of Minnesota
- VOI: volume-of-interest

STUDY SUMMARY

Study Title	Clinical Trial Readiness for SCA1 and SCA3
Study Design	Observational, longitudinal
Primary Objective	To validate MR morphological (Volumetry/voxel based morphometry/diffusion), biochemical (MRS), and functional (resting-state fMRI) biomarkers in spinocerebellar ataxia 1 (SCA 1) and spinocerebellar ataxia 3 (SCA 3) at premanifest and early stage
Secondary Objective(s)	To study the relationship between these MRI/MRS measures and clinical status of subjects
Research Intervention(s)/Investigational Agents	• Longitudinal MRI/MRS scans at 3T • Clinical evaluation: Standardized ataxia scale (SARA)
Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Study Population	Patients with ataxias and healthy subjects, 18 years or older
Local Sample Size (number of participants recruited locally)	30

1.0 Objectives

1.1 Purpose: The **primary goal** of this study is to validate MR morphological (Volumetry/voxel based morphometry/diffusion), biochemical (magnetic resonance spectroscopy, MRS) and functional (resting-state fMRI) biomarkers in premanifest/early SCA1 and SCA3. The **secondary goal** is to evaluate the relationship of these MR measures with the clinical status of subjects with SCA1 and SCA3. Such morphological, biochemical and functional measurements can provide non-invasive biomarkers to monitor progression of the neurodegenerative pathology, as well as serve as secondary outcome measures in future clinical trials of ataxias.

2.0 Background

2.1 Significance of Research Question/Purpose:

SCAs are hereditary movement disorders in which cerebellar neurodegeneration results in progressive balance and coordination deficits (1). They are disabling, fatal and cause significant physical, psychological, social and economic burdens to patients and caregivers. While they are currently untreatable, neuronal and motor dysfunction is reversible in SCA mouse models (2, 3). Furthermore, advances in understanding of molecular mechanisms of common SCAs (1, 4) have raised a realistic hope for the development of effective therapeutic interventions (5). For example, therapies based on gene silencing show great promise for the polyglutamine (CAG repeat expansion) disorders SCA1, 2, 3 and 6 (3, 6, 7). Therefore, the need for establishing imaging biomarkers to monitor cerebral pathology is more pressing than ever.

SCAs 1, 2, 3, and 6 are the most prevalent SCAs in the US (8) and Europe (9). Of these, SCA1 progresses more rapidly than SCA2, 3 and 6 (8, 9), allowing shorter clinical trials, and SCA3 is the most prevalent SCA worldwide (8-10), allowing the recruitment of a large number of patients into clinical trials. SCA1 and SCA3 are relentlessly progressive, disabling, and eventually fatal neurodegenerative diseases with no efficacious treatments other than supportive therapy (11, 12). Importantly, several clinical trials for disease modifying therapies in SCA1 and SCA3 are anticipated within the next 5 years. Most clinical trials, thus far, have included SCA patients at all stages of disease and phenotypes, and may therefore have missed a therapeutic window. Mounting evidence argues for administration of therapies in the earliest, including *premanifest*, stages of neurodegeneration. Namely, inducible genetic mouse models of polyQ diseases including SCA1 (2, 13-15) show disease reversibility early on, which is lost as the disease progresses, with increasing cellular dysfunction and cell death in the brain. Consistent with this, efficacy of a novel antisense oligonucleotide (ASO) treatment doubled when administered in the pre-symptomatic vs. symptomatic phase in another hereditary neurodegenerative disease (16, 17). Hence, in this project we will focus on premanifest gene carriers who have no ataxia (score on the Scale for the Assessment and

Rating of Ataxia [SARA] <3; maximum score = 40) (18, 19) and early-stage patients (SARA 3-9).

This study will define characteristics of the earliest disease progression measurable by MRI and MRS, with a goal to predict disease onset in premanifest individuals based on a multi-parametric model that incorporates imaging biomarkers. While we do have an existing predictive model to estimate the future age at onset for the major SCAs based on CAG repeat size and current age (20) there is great variability in onset ages between patients with the same CAG repeat, even within the same family. Therefore, measuring cerebral disease onset by noninvasive imaging is bound to substantially improve the estimation of onset age of manifest disease and allow recruitment of those premanifest patients who are closest to disease onset into future trials. Despite wide utility of brain MR biomarkers in neurological disorders, an advanced, 1-hour, 3T morphometric, biochemical and functional imaging marker protocol has not been validated in a multi-site trial setting and is likely to serve as a template in future neurodegenerative disease trials.

This protocol application is for local MRI/MRS acquisition and centralized data analysis under a recently funded multi-site U01 grant (U01NS104326-01, contact PI: Tetsuo Ashizawa, Houston Methodist Research Institute; Dr. Gulin Oz, MPI) for clinical trial readiness in SCA1 and SCA3. The Center for Magnetic Resonance Research (CMRR) is the lead imaging site for analysis of multi-site MRI data. Subjects will be identified by the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA) investigators, evaluated clinically and referred for MR scanning to select imaging sites. All imaging will be done under local IRB approval.

2.2 Preliminary Data:

Under a currently active IRB protocol (IRB# 0502M67488), we completed a study analyzing high angular resolution diffusion imaging (HARDI) data acquired from early-stage patients with SCA1, 2, 3, 6, and matched healthy controls (N=8-9 per group) at 3T. We demonstrated alterations in corticospinal tracts, cerebellar peduncles, pontine tract, cerebellar cortex, and thalamus in early stage SCA1 (SARA = 9 ± 5, mean ± SD) and localized differences in the cerebellar peduncles in early stage SCA3 (SARA = 6 ± 3, mean ± SD). Between-session test-retest CVs for fractional anisotropy (FA) obtained from HARDI data was <3%. Importantly, we found 11% lower FA in 3 premanifest SCA1 mutation carriers (SARA=0-1) vs. 9 controls ($p<0.05$, one-tailed two-sample unequal variance t-test) in the regions that demonstrated lower FA in the entire SCA1 cohort.

Under the same IRB protocol, we completed a single-site MRS study with 100 subjects (SCA1, 2, 3, 6 [58% of patients with SARA<10] and controls), including 9 premanifest mutation carriers (SARA=0-1). MRS data were acquired at 7T from 3 volumes of interest (VOIs). We utilized a distance weighted discrimination (DWD) approach (21) that combined data from the

3 VOI. DWD is a machine learning algorithm that finds an optimized hyperplane separating two or more groups. This analysis showed: **1)** subjects with SCA1 (SARA=8±4, mean±SD) and SCA3 (SARA=7±3) were distinguished from controls with 95-98% correct classification rate; **2)** classifications were driven strongly by metabolite levels in the cerebellar WM and pons, which showed that data collected from these 2 VOI will be sufficient for future trials; **3)** premanifest mutation carriers were distinguished from controls if the time-to-onset, estimated based on CAG repeat size and current age (20), was 10 years or less, which was the case for 6/9 cases in this cohort. These data indicate that neurochemical abnormalities can be detected up to 10 years from onset of ataxia. Even though these data were acquired at 7T, test-retest reproducibility for the neurochemicals that drive these classifications (NAA, *myo*-inositol, glutamate, creatine) is the same at 3T and 7T (22), and we have demonstrated the same classification accuracy at 3T and 7T for the SCA1 cohort that was scanned on both scanners (23), justifying the use of the 3T platform in future trials.

2.3 Existing Literature:

Conventional structural MRI has been the standard of care to monitor the characteristic cerebellar and brainstem atrophy in patients with SCA1 and SCA3. However, conventional MRI has limited sensitivity at the premanifest stage (24, 25) because macrostructural changes are the end point of a cascade of events that lead to neuronal death. Mounting evidence indicates that the underlying cellular changes start years before clinical onset and irreversible neurodegenerative damage detectable by conventional MRI (26). Therefore, we focus on imaging biomarkers that are sensitive to these early pathological changes, which are reliable, reproducible, and can gauge treatment effects objectively and quickly. Whereas a few Positron Emission Tomography (PET) studies have demonstrated hypometabolism in premanifest SCA (19), PET is significantly more expensive and less readily available than MRI and involves radiation exposure. Hence, we will utilize MRI modalities that have been widely validated in SCAs and are ready for use in a multi-site setting.

Macrostructural and microstructural MR measures are sensitive to progressive morphological alterations in SCA. Using MRI scanners of 1.5 Tesla (T) field strength, the European Ataxia Study Group (EASG), has established the sensitivity of volumetric MRI to morphometric alterations in the most common SCAs in both single- and multi-site investigations (27-29). Morphometric T_1-weighted MRI data analyzed with a 3D volumetric method and voxel based morphometry (VBM) reveal prominent reductions in gray (GM) and white matter (WM) in the cerebellum and brainstem in SCA1 and SCA3 (29). While these macrostructural changes correlate with

SARA (29), the volumetric measures were more sensitive to change than SARA in a longitudinal multi-site study (30), providing a strong rationale to supplement the clinical outcome assessments (COAs) with these objective, non-invasive MR markers in trials. Most importantly, a large multi-site EASG study of at-risk subjects (SARA<3) showed significant GM loss in the brainstem and cerebellum in SCA1 mutation carriers and subtle brainstem volume loss in SCA3 mutation carriers (18).

Regional damage to WM in SCA1 and SCA3 has been demonstrated by diffusion tensor imaging (DTI) by many groups (31-34). However, the standard DTI model may miss subtle WM alterations and does not resolve crossing fibers, limitations that are overcome by high angular resolution diffusion imaging (HARDI). Our preliminary data described in section 2.2, together with prior reports (31-34), warrant validation of diffusion MRI in large patient cohorts in a multi-site longitudinal setting.

MRS biomarkers reflect the clinical status, progression, and reversal of pathology in SCA. Over the past 7 years, the University of Minnesota (UMN) group has demonstrated the sensitivity of MRS-measured neurochemical levels to progression (35) and reversal (36, 37) of SCA pathology in animal models. Neurochemical abnormalities were detected at the presymptomatic stage (35) and prior to the appearance of gross histopathological changes (38). Importantly, MRS detected treatment effects in a conditional transgenic SCA1 mouse model with the same sensitivity/specificity (areas under the curve [AUC]=0.97-0.98 in receiver operating characteristic [ROC] analyses) as invasive outcome measures (histology and qPCR) and with much higher sensitivity/specificity than standard motor behavioral assessment (Rotarod, AUC=0.72) (37).

In human subject studies, we reported robust neurochemical alterations, reflecting neuronal loss or dysfunction (N-acetylaspartate [NAA], glutamate) and gliosis (myo-inositol) in the cerebella and brainstem of patients with SCAs, including SCA1 and SCA3 (39-41). Similar to morphometric measures, the neurochemical alterations measured by MRS correlated with SARA (39, 41), but were more sensitive to change than SARA in a longitudinal 3T study (42). We further showed excellent within- (22) and between-site (43, 44) reproducibility of MRS measures in healthy volunteers: Between session test-retest CV of ≤5% are obtained from a cerebellar volume-of-interest (VOI) for 5 major neurochemicals at 3T (22) and identical neurochemical profiles from the cerebellum and brainstem are obtained on different 3T scanners, allowing pooling of multi-site data (43).

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Primary endpoints are macro- and microstructural MR metrics, including cerebral, cerebellar and brainstem volumes, GM and WM loss metrics from VBM and diffusion MR metrics such as fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD) and mean diffusivity (MD), degree of co-activation within resting-state networks (RSNs) of interest and neurochemical levels measured by MRS, including alanine (Ala), aspartate (Asp), ascorbate (Asc), glycerophosphocholine (GPC), phosphocholine (PC), creatine (Cr), phosphocreatine (PCr), γ-aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glutathione (GSH), myo-inositol (mI), lactate (Lac), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), phosphoethanolamine (PE), scyllo-inositol (sIns) and taurine (Tau).

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Scale for the Assessment and Rating of Ataxia (SARA).

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

- Participants will undergo MRI/MRS scans at 3T.
- Participants will undergo SARA evaluation (videotaped).

4.2 Drug/Device Handling:

MR scans will be performed by CMRR personnel on this protocol trained and authorized to operate the scanners.

4.3 Biosafety:

N/A

4.4 Stem Cells:

N/A

5.0 Procedures Involved

5.1 Study Design:

Premanifest and early-phase subjects with the SCA1 or SCA3 mutation and healthy controls will be enrolled. Subjects will be scanned up to 6 times during the U01 period, at baseline, 6 months, 1 year, 18 months, 2 years and 3 years. With this scanning schedule, we aim to capture any imaging alterations as soon as they occur, and to obtain rich data for best trial readiness. We will enrich the SCA1 and 3 cohorts by inviting participants with an estimated time to onset (20) within 10 years. De-identified clinical data on the same subjects will be available from the multi-site U01 study for correlations with the MR measures. The main clinical assessment (SARA) will also be administered at UMN.

5.2 Study Procedures:

Screening: Subjects will be identified from among the enrollees of the multi-site U01 clinical study (performed under a central IRB and *not* covered under the current IRB protocol), screened clinically by the lead site of the U01 grant (Houston Methodist Research Institute) for disease stage and referred to UMN for MR safety screening prior to enrollment. For screening, the research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publicly available on the CMRR website (CMRR Policies / Procedures).

MRI Study: Subjects will undergo an MRI/MRS scan at 3T. Before the MRI scan, participants will be asked to remove all metallic objects and magnet-sensitive devices. The MR procedure involves lying on an imaging table which slides into an opening in a strong magnet. A radio antenna is placed around their head to transmit and receive radio signals from their brain. Subjects will need to remove any metallic objects (such as watches, keys, chains, hair pins, glasses, jewelry, coins, cell phones, etc.), items with magnetic data (credit cards), and other valuables, all of which will be safely stored in a secure locker during the procedure. The subject will then be taken to the magnet room, where ear plugs will be inserted for acoustic noise protection. The subject will be instructed to lie supine on the MRI table with their uppermost portion of the head and body inside the MR scanner. Blankets and pillows will be provided for their comfort. A "panic" alarm is provided (squeeze ball) should the subject wish to stop the study at any time and the subject is asked to squeeze the ball once for demonstration. Once inside the MR scanner, the subject will be asked to remain as still as possible because movement may affect the quality of the MR data. After the subjects are comfortably positioned, we will perform an MRI/MRS scan for 60-90 minutes. When the session is over, the subject will be escorted to the secure location where their personal items were stored.

Clinical evaluation: Subjects will meet the study physician Dr. Bushara or one of his research colleagues or associates. They will administer an ataxia scale that is based on inventories of gait, stance, sitting, speech disturbance, a finger-chase test, a nose–finger test, fast alternating movements and a heel–shin test (SARA, attached in Supporting Documents). The SARA exams will be videotaped using specified camera equipment, however subjects may opt out of the video recording.

5.3 Study Duration:

The study duration for participants is approximately 3 years, which will include up to 6 scanning visits separated by 6 months - 1 year. Each scanning visit is estimated to take about 1.5-2 hours, including consenting, preparation in the scanner, the MR scans and SARA. Subjects will be re-consented at every visit. We expect to complete enrollment over 2 years.

5.4 Individually Identifiable Health Information:

Personnel in the CMRR maintain a list of the names and contact information of all participants included in research at this facility. This information is required and will be used by CMRR to notify participants of significant new information about the effects of MR on human health that develop over the course of MRI research. Participant's identifying information is stored securely and it is maintained in a confidential manner by persons with oversight of research conducted at the CMRR.

Materials will be collected solely for research use. Subjects will provide medical information during neurological exams and MR images and spectra. Electronic records will be stored in a database that meets University standards for data encryption and data security, using Box. Identifiable private information will be stored in locked cabinets in locked rooms or electronically with password protection. A HIPAA authorization form is attached in Supporting Documents.

SARA videos recorded will be uploaded to a cloud storage website at Box.com. Houston Methodist Research Institute Coordinating Center (HMRICC) has an existing business associate agreement with Box.com, which will allow transfer of PHI from the covered entity to the business associate in compliance with HIPAA and HITECH regulations. Additionally, permissions are configured in such a way that links cannot be shared with persons outside the U01 consortium. Once videos have been uploaded to Box.com downloading capability will be restricted to the HMRICC. Furthermore, levels of access will be customized to individual site needs, such that viewing access is restricted to only videos uploaded by respective sites (in this case University of MN). Face recognizable video containing PHI will be restricted to local research site (University of MN), HMRICC and central raters.

5.5 Use of radiation*:*

N/A

5.6 Use of Center for Magnetic Resonance Research*:*

The research involves CMRR facilities. CMRR Pre-IRB approval letter for 3T is attached.

6.0 Data and Specimen Banking

6.1 Storage and Access:

N/A

6.2 Data:

MR images and spectra collected under this project are stored in secure CMRR servers. Associated clinical data are stored in a database that meets University standards for data encryption and data security, using Box.

6.3 Release/Sharing:

De-identified MR and clinical data will be shared with collaborating teams, namely site investigators of the U01 study, who will participate in data analysis. In addition, *de-identified* image data will be made publicly available, according to the terms of the cooperative agreement in the Rare Disease Clinical Trial Readiness U01 program with the NIH. Specifically, following QC, baseline MRI and MRS data will be released in year 3 and longitudinal MRI and MRS data will be released in year 5 of the U01 award. De-identified and defaced imaging data will be housed in an NIH funded archive and users will be bound to a Data Use Certificate (DUC), which prohibits attempts to identify subjects. U01 and external investigators interested in using the MR data for research will be asked to submit a formal application to the NIH Data Access Committee, which will ensure eligibility of the users before providing access to the data.

7.0 Sharing of Results with Participants

N/A.

8.0 Study Population

8.1 Inclusion Criteria:

1. Participants must be 18 years or older.

2. Participants must understand and cooperate with requirements of the study in the opinion of the investigators and must be able to provide written informed consent.

3. Individuals with ataxia and healthy volunteers who are medically stable for participation in study in the opinion of the investigators. [DNA testing will be performed for all individuals with ataxia and at-risk participants by the U01 team under a central IRB and is *not* included in this protocol]

8.2 Exclusion Criteria:

1. Known genotype consistent with other inherited ataxias.

2. Concomitant disorder(s) or condition(s) that affects assessment of ataxia or severity of ataxia during this study

3. Investigational drugs taken 2 months prior to participation in this study

4. Changes in coordinative physical and occupational therapy for ataxia 2 months prior to study participation

5. Medical conditions likely to interfere with the study, including neurologic conditions other than ataxia, restless leg syndrome, structural abnormalities such as subdural hematoma, intracranial neoplasms, concurrent illnesses or treatments interfering with cognitive function such as dementia, stroke or normal pressure hydrocephalus. A SARA score above 2 will be exclusion criterion for healthy control participants.

6. Pregnant or lactating or those women of child-bearing age who are not using acceptable forms of contraception.
7. Inability to undergo MRI scanning, including but not limited to claustrophobia, unable to remain still in an MRI scanner for more than 30 minutes, presence of paramagnetic substances or pacemakers in body, weight over 300 lbs.
8. Inability to adhere to study protocol for whatever reason.

8.3 Screening:

Subjects will be screened clinically by the lead site of the U01 grant (Houston Methodist Research Institute) for disease stage under the central IRB for the U01 grant.

For MR safety screening, the research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publicly available on the CMRR website (CMRR Policies / Procedures).

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☒ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)

☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

9.2 Additional Safeguards:

We have to include participants with a rare neurodegenerative condition for which there are no satisfactory standard treatments because there is a great need to identify and validate imaging biomarkers to facilitate development of effective therapies for these diseases. We expect that the information gained in this investigation will be important in developing robust biomarkers to monitor treatment effects in spinocerebellar ataxias. Therefore, we believe that the insights gained from this project will ultimately have a significant impact on reducing the morbidity and early mortality associated with these diseases. Given the enormous personal and public health burden of neurodegenerative diseases, we believe the limited risks our subjects will be asked to incur are significantly out-weighed by the new knowledge we will gain for all people with neurodegenerative diseases. While the discomforts of traveling to CMRR and lying still in the scanner may be greater for this population than healthy volunteers, we find that patients with ataxias are eager to volunteer for our studies and highly value the research effort that is focused on their rare condition. In these studies, we focus on early stage disease, with no or limited motor impairment, because such patients are the most likely participants in future trials and we are interested in detecting early structural, neurochemical and functional changes in the brain.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

We expect to enroll up to 30 subjects locally under this protocol.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

Subjects will be recruited from the clinical practices of U01 site investigators, which in the US is comprised of sites of the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA), under central IRB for the U01 study. Patients will also be recruited to the U01 study by notices in ataxia newsletters, e.g. the NAF newsletter, and through flyers. In addition, patients who have previously participated in our ataxia study may be contacted by our study coordinator, as stated in the consent form they signed when they participated in our earlier ataxia studies (under protocol # 0502M67488). Control participants will be recruited through the CMRR volunteer mailing list or in person.

A phone screening interview will be conducted by the study coordinator for MR safety and other inclusion/exclusion criteria using the CMRR safety

screening form. A phone script for this purpose is attached in Supporting Documents.

11.2 Identification of Potential Participants:

Subjects will be identified from among the enrollees of the multi-site U01 clinical study (performed under a central IRB and *not* covered under the current IRB protocol), screened clinically by the lead site of the U01 grant (Houston Methodist Research Institute) for disease stage and referred to UMN for MR safety screening prior to enrollment.

In addition, the research team will utilize the CMRR Center's volunteer pool for recruitment of healthy research volunteers in this protocol. The CMRR Center's volunteer pool is IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding volunteers is publicly available on the CMRR website (CMRR Policies / Procedures). The control group will also likely include spouses and friends of patient participants who find out about the study through their relation with the patient.

11.3 Recruitment Materials:

Recruitment will be done by the multi-site U01 clinical study under a central IRB. In addition, healthy volunteers will be recruited through the CMRR Center's volunteer pool (IRB approved under the CMRR Center Grant, HSC# 1406M51205).

11.4 Payment:

Subjects will not be responsible for the cost of any study procedure. They will be compensated $50 for each MRI scan visit. If they need to stop any testing for any reason, they will receive partial payment for their time.

In addition, participants who are from out of the Twin Cities will be reimbursed for travel, hotel and meals by the lead site of the U01 study. Reimbursement will not exceed $1,500 per participant. Subjects will be reimbursed up to $50 for ground transportation and up to $100 for meals that incur during the visit.

Compensation and reimbursement will be sent within 4-6 weeks of their visit to CMRR in the form of a check to their home address.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants can withdraw or terminate the study at any time and for any reason without impacting their current or future relations with the University or the CMRR. If they decide to withdraw or terminate the study data collected up to the point of their withdrawal will be maintained in a confidential manner for the remainder of the study.

Moreover, the researcher may withdraw the participant if they appear to be unduly distressed, uncomfortable, e.g. due to muscle twitching, or are unable to adhere to study protocol, e.g. if the subject is unable to lay still in the scanner. The researcher will have extensive experience with scanning human participants and will be thus in an ideal position to judge the level of distress and discomfort of the participants. Finally, subjects may be withdrawn from the study in case of incidental findings. The CMRR Research Scan Review System gives the researcher a way to request a high-level radiologist review if they observe something in a scan that may need medical attention. The reviewing radiologist indicates whether or not the subject should be seen for further tests. If the recommendation is to further investigate the unusual MRI results with their own physician, the investigator will contact and inform the subject of the need for follow-up. Further medical follow-up is not a part of this study.

12.2 Withdrawal Procedures:

Subjects who choose to withdraw will be asked about the rationale for making this decision. We will inform them that this is to make sure if it has something to do with the study or its design so that we can take that into consideration for future projects.

If the investigator withdraws a subject due to undue distress or discomfort, the participant will be informed that we are ending the study because we are not able to get suitable images. If the withdrawal is due to incidental findings, i.e. the radiologist recommendation from the Research Scan Review System is to follow-up the incidental finding, the investigator will instruct the subject to do so.

All study activities will be stopped at the point of withdrawal. No further data will be collected.

12.3 Termination Procedures:

The participant will be explained the rationale for withdrawal, if it was without their consent, and provide reimbursement as described in Section 11.4. If sufficient data were collected, these data will be used for analysis.

13.0 Risks to Participants

13.1 Foreseeable Risks:

- **Risks of Study Participation:** Subjects may experience stress, fatigue, or frustration while participating in the study. They can refuse to answer any questions that make them feel uncomfortable. They may take a break, discontinue the testing, or withdraw from the study at any time.
- **Risk of loss of confidentiality:** Subjects will be asked to provide medical information documenting their condition. This information will be stored in a secured access database. All attempts will be made to preserve confidentiality of participants, including the following:

1. Any paper records obtained, reviewed, or generated as part of the study will be kept in locked cabinets.
2. Study information will be stored in password protected files on a computer in a locked office and in a secured access database (Box), and can only be accessed by research staff.
3. Any information included in publications will not include identifying information.
4. If health information is released to an outside institution, it will be in the form of a limited dataset that does not include participant identifiers (see Section 6.3).

- **Risks associated with MR scanning:** The risks associated with MR scanning and exposure to strong magnetic fields are well known and widely published. The FDA considers exposure to magnetic fields as high as 8 tesla to represent a non-significant risk (NSR) medical device study. The images created during this study are for research purposes only and are not intended to provide health care to the participants. However, if the results from the MR scanning show something unusual, a Radiologist trained in reading the scans will review them. The study investigator will contact the participant if the recommendation of the Radiologist is to further investigate the unusual results of the scans with the participant's own physician. The following are the risks associated with having an MR exam:

1. **Mild Effects.** While there are no known health risks associated with these strong magnetic fields, some people report dizziness, mild nausea, headache, a metallic taste in their mouth, or sensations of flashing lights. These effects have been associated with movement of the head in a strong magnetic field. These symptoms, if present, usually go away shortly after leaving the magnet. However, the long-term risks of spending time in high magnetic fields are as of yet unknown. To avoid any discomfort in moving the subject into the scanner too quickly, the subject will be moved into and out of the scanner at a slow speed.
2. **Projectile Objects.** Some metallic objects (e.g. pens, keys, metal chairs, etc.) are attracted by the magnet and can be dangerous if they are brought into the magnet room. Participants will be closely screened to make sure that no one brings such hazardous objects into the room.
3. **Claustrophobia**. Some patients may experience claustrophobia (fear of being in closed spaces) during MR scanning. Subjects will be screened for claustrophobia prior to the scan and if claustrophobia occurs during the scan, it will be discontinued immediately. MR operators communicate with subjects while in the scanner through a speaker system.
4. **Loud Sounds**. The MR scanner makes loud banging noises during operation. Subjects will be given earplugs and/or headphones to reduce the noise level.
5. **Radio Waves**. Radio waves are used for MR scanning, but these are well below the strength that causes harm. The radio waves used for MR scanning are similar to the radio waves used to broadcast AM and FM radio stations.

6. **Muscle twitches**. Although rare, some people experience involuntary muscle twitching during the MR procedure. If this occurs, we will stop the study as a precaution.
7. **Metal on or in the body.** MR may not be appropriate in the presence of the following conditions: cardiac pacemaker; mechanical heart valve replacement; brain clips; venous umbrella; aneurysm surgery; intracranial bypass; renal, aortic clips; middle ear, eye, or penile implants; hearing aid; some dental implants; joint replacements; neurostimulator; insulin pump; intrauterine device (IUD); shunts/stents anywhere in the body; metal mesh/coil implants; metal plate/pin/screws/wires anywhere in the body, any other metal implants; metal fragments in eye, skin, or body; worked as a sheet-metal worker or welder; tattoos, permanent eyeliner or permanent artificial eyebrows; or foil medication patches. There is also a risk of skin heating from radiofrequency imaging coils, button response boxes, and their associated cables. The power of the radio waves is well below the strength needed to heat the tissue in the body and cause harm, but any metal in contact with the skin could heat up. We administer a questionnaire to each potential subject to assess for any metal in the body, as well as on their clothing. We have procedures to remove all jewelry for safekeeping during the MR exam. Finally, RF power deposition is monitored with the software and hardware protection systems and kept below the FDA limit.
8. **Mild Stiffness or Soreness**. It may be uncomfortable lying still in the magnet for the length of the study and some subjects may experience some mild stiffness and soreness in their muscles for being still. We will try to make the subject as comfortable as possible during the MR scan by providing soft pads to support the subject's neck, back and legs.

13.2 Reproduction Risks:

Although there are no known risks associated with MR scanning during pregnancy, we will not scan someone who is or may be pregnant.

13.3 Risks to Others:

N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

There will be no personal or immediate benefit of participating for our subjects.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

De-identified MRI and MRS data will be analyzed in a blind fashion at UMN, as described previously for volumetric, VBM (18, 45) and MRS (22, 43) analyses. Diffusion MRI data will be analyzed using tract-based spatial statistics (TBSS) (46), which is part of the FMRIB's Software Library (FSL (47)), and tractography to delineate particular WM pathways (e.g.,

cerebellar peduncles). Functional (rs fMRI data) will be pre-processed using FSL, followed by between-group analyses using seed-based connectivity analysis for particular regions of interest, and ICA/dual regression (MELODIC/FIX)) (48, 49) for RSNs. Outcome measures will consist of cerebellar and brainstem volumes, GM, and WM loss metrics from VBM, metabolite concentrations, FA, MD, RD and AD, as well as degree of co-activation within RSNs of interest (e.g., motor function).

15.2 Power Analysis:

The sample size calculation for this study is based on imaging data that will be acquired at 6 imaging sites, for a total sample size of 100 subjects, namely a 30 (20 premanifest and 10 early-phase) subjects with the SCA1 mutation, 40 (27 premanifest and 13 early-phase) subjects with the SCA3 mutation and 30 controls. The at-risk subject study by the EASG group, which included imaging data from 26 SCA1 mutation carriers and 9 SCA3 mutation carriers, reported significant VBM alterations in SCA1 and trends in SCA3 (18). Based on these data, a Wilcoxon rank sum test will have 95% power to show a difference between controls (mean = 0.018, SD = 0.019) and SCA (mean = 0.016, SD = 0.0019) with 30 subjects per group (α = 0.025 to take into account the two comparisons of SCA1 and SCA3 versus controls, two-tailed test). Note that this power computation is conservative since the EASG study included only at-risk subjects, whereas the current study will include both premanifest and early manifest patients. In addition, based on our MRS preliminary data described above, a Wilcoxon-Mann-Whitney test will have 94% power to show a difference in NAA at baseline between premanifest subjects who have disease onset within the 5 years of the U01 (conservatively estimated at 1/3 of the patients i.e. n=7, mean = 1.2) and those patients who remain in the premanifest stage (n=14, mean = 2) for the SCA1 group (standard deviation of 0.4, α =0.05, two-tailed test). We will recruit a larger sample size for the SCA3 cohort because: 1) imaging alterations did not reach significance for SCA3 mutation carriers in the at-risk EASG study; 2) the diffusion MRI abnormalities in our preliminary data (see section 2.2) were less pronounced in SCA3 than those in SCA1; and 3) SCA3 is the most common SCA, enabling recruitment of a larger cohort.

15.3 Statistical Analysis:

To compare the imaging biomarkers between SCA1, SCA3 and control cohorts, globally and in a pairwise fashion, we will use Wilcoxon rank sum test. In addition, premanifest carriers and early-stage patients will be compared using Wilcoxon rank sum test. Within each SCA group, premanifest and manifest patients will be compared regarding the biomarkers at baseline and during follow-up. If this approach is not conclusive, cluster approaches will be carried out. Sex will be considered as a biological variable to assess potential sex-based differences in imaging results.

15.4 Data Integrity:

Non-biological sources of data variation due to MR hardware and software will be minimized by procedures for quality assurance (QA), which prospectively aims to avoid production of poor quality data, and retrospective quality control (QC) to identify poor quality data. All participating MR sites of the U01 project routinely verify scanner stability with regular QA tests on their 3T scanners, e.g. with a weekly American College of Radiology (ACR) phantom protocol. In addition, we will follow the guidelines put forth by the MRS Consensus Group for quality management in clinical MR spectroscopy (50), including regular MRS-specific tests with a dedicated phantom that has a composition of the most concentrated neurochemicals in the brain at appropriate proportions (GE MRS-HD-Sphere). The imaging sites of the U01 will be required to meet consistent performance metrics prior to subject accrual. QC criteria will be applied uniformly to all data prior to inclusion in final analyses. The assessment will be based on quantitative quality metrics (signal-to-noise ratio, contrast-to-noise ratio, identification of image and spectral artifacts and, in addition, for MRS, linewidth, % water suppression and Cramér-Rao lower bounds). To accomplish these QC procedures, all MRI and MRS data will be sent by U01 imaging sites to UMN monthly, using the data management software Flywheel (https://flywheel.io/).

16.0 Confidentiality

16.1 Data Security:

Participants will be assigned a unique subject code (determined by the U01 clinical study) and this subject code will be used for all procedures and data collection.
All identifying data and PHI will be kept in the UofM Box Secure Storage. Videotaped SARA exams will be kept at Box.com. Face recognizable video containing PHI will be restricted to local research site (University of MN), HMRICC and central raters of the U01 study. Paper records will be kept in locked file cabinets in the study coordinator's office. Any information included in publications will not include identifying information. If health information is released to an outside institution, it will be in the form of a limited dataset that does not include participant identifiers. A copy of the consent form or other research study information will *not* be placed in the participants' medical, employment, or educational records.
A Certificate of Confidentiality (CoC) was issued automatically for this research; effective October 1, 2017 CoCs are issued automatically for any NIH-funded project using identifiable, sensitive information that was on-going on/after December 13, 2016. The CoC was issued as a term and condition of the U01 award and there will be no physical certificate issued.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

The PI will supervise the progress of the study, and ensure that data are collected and reported in accordance to protocol. Study progress will be reviewed monthly, as well as on as-needed basis. The PI will utilize reports provided by the study coordinator to ensure continuing enrollment and data summaries provided by the study team members responsible for MRI and MRS data acquisitions.

For independent monitoring, we will utilize the Clinical Monitoring Service of the Clinical and Translational Science Institute (CTSI). The service is provided every 6 months and includes a review of the case report forms, medical records, and regulatory documents by the CTSI Clinical Research Monitor. A summary report that details the study progress, regulatory and subject records that were monitored, and any findings identified during the visit is provided to the PI. Upon addressing any findings, the PI will submit the report together with a description of how the findings were addressed to IRB within 5 days of receipt of the report.

17.2 Data Safety Monitoring

The research team will utilize the CMRR Center's Subject Information Form and adhere to the SOP during enrollment of all research participants in this protocol. The CMRR Center's Subject Information Form and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding these procedures is publicly available on the CMRR website (CMRR Policies / Procedures).

This is not a clinical trial, therefore a data and safety monitoring board is not required. The PI will review each study with the study staff on a monthly basis to determine if unexpected adverse events have occurred. Serious adverse events will be reported as soon as they occur to the IRB. All adverse events will be reported annually to the IRB.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy:

Participants will interact with limited study staff. Demographic information, personal health information and clinical assessments will be obtained by the study physician and/or coordinator, ensuring one or two investigators will be interacting with participants most of the time. Other than the study physician and research coordinator, other staff on this protocol will interact with the subjects only to the extent necessary for MR scans. The consenting process and clinical assessments will take place in a private room with only the study staff, the subject and their caretaker if they desire. We will explain to the subject that they can stop participation at any time if they do not wish to interact or provide requested information. The subject will be told why information is necessary. They can refuse to answer any questions that make them feel uncomfortable. They may take a break, discontinue the testing, or withdraw from the study at any time.

18.2 Access to Participants:

The research team needs to access private information about the participants, such as ataxia diagnosis, disease duration and triplet repeat length in the affected ataxia gene, to be able to evaluate clinical correlates of the MR measures under investigation. In addition, members of the MR professionals committee may need to see information on implants and devices to consult on MR safety and the administrative staff will need to see name and address information to be able to process remuneration.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the participant or their insurance company.

19.2 Contract Language:

N/A

20.0 Consent Process

20.1 Consent Process (when consent will be obtained):

Subjects who decide to participate based on the phone interview described in section 11 will be mailed a consent form to review. The consent process usually occurs over time through several conversations and discussion of written descriptions of the study between the study coordinator and the potential participant. All applicable potential risks will be discussed with each subject and the subjects will be asked to describe the study in their own words and explain the risks to which they will be exposed to ensure that they have understood the procedures before the consent form can be signed. The IRB-approved consent form will be reviewed and signed on the day of study before any investigation is begun. Written consent will be obtained by the study coordinator or the MR operator, if the study coordinator is not available, in a private room. The forms will be held by the investigators and the subjects will be offered a copy to keep.

20.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

N/A

20.3 Non-English Speaking Participants:

N/A

20.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

N/A

20.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

N/A

20.6 Adults Unable to Consent:

- Permission: N/A
- Assent: N/A
- Dissent: N/A

21.0 Setting

21.1 Research Sites:

All procedures will be performed at the CMRR located on the Twin Cities campus at the University of Minnesota.

21.2 International Research:

N/A

22.0 Multi-Site Research

N/A (While the U01 study includes sharing of de-identified data between sites and analysis of multi-site data, each site will obtain their own IRB approvals for MR scanning of subjects with the U01 protocol. Therefore, this study is not classified as multi-site research).

23.0 Resources Available

23.1 Resources Available:

- **Feasibility of recruitment**: The UMN group and the CRC-SCA consortium have extensive experience with recruitment of subjects with ataxias. Even though most of our patient participants are from out of the Twin Cities area, 200 subjects have been successfully enrolled as of the 2017 continuing review of our existing MRS in ataxias protocol (#0502M67488). Under the current protocol, we will continue to collaborate with the CRC-SCA and the NAF headquartered in Minneapolis for recruitment, see section 11.
- **Study Team**: The PI will devote approximately 20% of her time to this project. The local study team includes two study coordinators, two research associates who are responsible of MR data acquisition and analysis and a clinical collaborator who is responsible of the clinical aspects of the project.
- **Training process**: The PI will have an interview with each new study staff member to describe the protocol and research procedures, and clarify the duties of each member. In addition, the protocol will be shared with all study team members.

- **CMRR facilities**: The CMRR is an interdepartmental and interdisciplinary laboratory that provides unique instrumentation, expertise, and infrastructure to enable the faculty, trainees and staff at U Minnesota and other institutions to carry out basic biomedical, translational and clinical research utilizing the capabilities of high magnetic fields. The CMRR is a NIH funded BioTechnology Resource Center (BTRC) through the P41 mechanism and is equipped with an array of high end instruments: Three 3T (Siemens), a 4T (Agilent), two 7T (Siemens) and a recently installed 10.5T system for human studies and a 9.4T (Agilent) and a 16.4T (Agilent) system for animal studies. The 3 Tesla Siemens system will be used for this project.

  Clinical: To support translational clinical research CMRR has extensive patient/subject handling facilities with over a 1000 sq. ft of space for Waiting/Reception area and allocated rooms for subject interview and staging rooms adjacent to each magnet suite. There is 3000 sq. ft. dedicated to Clinical Research for human subject preparation and nursing support. This space will be utilized for consenting and administration of the clinical scales and questionnaires.

  Computing resources: Each of the MR instruments at the CMRR has a console host workstation along with physiologic monitoring and paradigm presentation computers. The scanners with Siemens consoles (3T, 7T) use Windows based PCs. Each console host is connected by a 10 gigabit per second Ethernet network link for rapid transfer of image data to the data center for post- processing, analysis and storage.

  The data center in the CMRR has 59 servers. To handle the amount of image data generated by the MR scanners, twenty four (24) of these servers provide NFS file sharing with a total of 80 Terabytes of RAID data storage. Six (6) of the servers are dedicated to backups for disaster recovery contingency and long term archive and each has an LTO tape auto-loader library attached. Twenty (20) of the CMRR servers are compute nodes, most configured with 8 CPU cores and over 32 gigabytes of RAM memory each.

  In addition, as an fBIRN (functional Biomedical Informatics Research Network) grid point-of-presence, the CMRR houses a BIRN node, consisting of a gridftp server, HID (Human Imaging Database), and HID GUI interface server. The BIRN node includes 1TB of RAID storage and four Linux hosts to support distributed high-performance computing and data sharing between institutions at gigabit speeds over a nationwide network of Internet-2 connected computer systems.

  Office Space: The PI has an office in the CMRR building. The nursing professional/study coordinator and the research associates also have offices in the CMRR building.

  Machine Shops/Electronics Shop: A machine shops and a 1500 sq. ft. full electronics shop is located within the CMRR and is used for

building RF probes, and developing physiological monitoring and recording systems for use in the MR scanner.

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