Mitochondrial Disease Version 2.0 NINDS CDE Project
Imaging Subgroup Summary

The goal of the NINDS Mitochondrial Disease v2.0 Common Data Element (CDE) Imaging Subgroup (SG) was to establish a set of CDEs that would serve as a standard for mitochondrial disease clinical care and clinical research within the neurological and imaging community. To do so, the Imaging SG sought to make an inclusive set of data elements to allow researchers to be highly specific in their data collection.

Ideally the aims are to increase efficiency and effectiveness of clinical treatment and clinical research studies, increase data quality, facilitate data sharing, as well as help educate new clinical investigators. The CDEs created by the Imaging SG are designed to be applicable across a wide array of mitochondrial disease processes. As mentioned, the Imaging SG's goal is to establish data forms that would be all inclusive. Ideally, they should serve as a reference guide on what imaging data points might be useful to collect when researching mitochondrial disorders. It is not obligatory that each data point be entered, as some studies have more focused outcomes and are only concerned with specific variables. In addition, we recognize that some imaging centers are not able to perform every imaging study listed on the SG's Case Report Forms (CRFs).

The SG found many gaps in existing CDEs for Imaging in Mitochondrial Disease. While updating the guidance and definitions, reusing, and recommending many existing CDEs for Imaging in Mitochondrial Disease, the SG highlighted several variables on their CRFs that are unique to, though not exclusive to, mitochondrial disorders.

The guidance and definitions document reviews neuroanatomy terminology in addition to normal myelination patterns and is a useful resource complete with references.

The updated CRF for Magnetic Resonance Imaging (MRI) includes easy to mark check boxes for notations for T2 signal, edema/swelling, DWI, enhancement, atrophy/volume loss, cystic encephalomalacia/gliosis, calcification, iron, hemosiderin divided into the following sections: Cerebrum - Cortex (divided anatomically into frontal, parietal, temporal, occipital)(left vs right) and Cerebrum - White Matter (divided in to left vs right subcortical, periventricular); Deep Gray Nuclei (caudate, putamen, globus pallidus, thalamus); Cerebellum (cortex, white matter, vermis); Brainstem; White Matter Tracts (corpus callosum, anterior commissure, fornix, hippocampal commissure, central tegmental tracts); Miscellaneous neuroanatomy (dorsal columns, medullary pyramids, medial lemniscus, trigeminal tracts, superior/inferior cerebellar); Malformations of Development (each detailed anatomically: corpus callosum (partial agenesis, rostrum, splenium, posterior, body/anterior body, complete agenesis), cerebellum (vermian hypoplasia, hemispheric hypoplasia (right vs left)), polymicrogyria (left vs right: insula, frontal, parietal, temporal, occipital, cerebellum), heterotopia (left vs right: subependymal, periventricular, subcortical); Myelination (delayed myelination, hypomyelination, dysmyelination); with comment bars for detailing distribution of abnormal myelination and calculation age based on myelination pattern.

A separate CRF for Brain MRI is also included, which reviews number of studies, dates, age, location of exams, sedation, magnet strength, body part scanned, head circumference, total time in scanner, coils, sequences and orientation (T1, T2, FLAIR), whether contrast was given, MRI manufacturer, clinical read, if lesions were found and type, other incidental findings, malformations, white matter and gray matter findings, eye abnormalities found.

The updated CRF for Brain Perfusion Magnetic Resonance Imaging includes data typically recorded when collecting information on brain blood flow imaging. The CRF includes magnet field strength and manufacturer, model and software, and perfusion imaging method: Dynamic Susceptibility Contrast (DSC) or Arterial Spin Labelling (ASL). The remainder of the CRF is then detailed based on the perfusion imaging method. For DSC T2 perfusion, the CRF notes the name of the IV contrast agent, dosage, injection rate, sequence (gradient echo, spin echo, etc.), repetition time (TR),

echo time (TE), flip angle (degrees), number of volumes acquired over what time period (seconds), previous preload contrast injection (if yes, then amount), post processing and analysis software, parameter maps created (relative cerebral blood volume, relative cerebral flow, time to peak, relative mean transit time, time to maximum). For ASL perfusion, the CRF notes the ASL scheme, 2D or 3D acquisition, phase, crusher gradient, post processing and analysis software, parameter maps created (cerebral blood flow, blood arrival time).

The SG discussed the role of MRS, spinal cord imaging, and CT scan, and added these as new CRFs as discussed below:

The new CRF for Spinal Cord Imaging includes: whether MRI brain was completed at same time, if spine has been completed prior and number, what segments are available for review (cervical, thoracic, lumbar), magnetic field strength, name of manufacturer, sequences used, parameters for T1, T2, gradient echo, DWI, post contrast T1 (slice orientation, thickness, gap, repetition time, echo time), overall assessment of MRIs (was reader blinded to clinical data, were quality of images technically satisfactory), if lesions were found and location (cervical thoracic, conus medullaris). Anatomical details for Cervical, Thoracic, Lumbosacral MRI: review normal vs abnormal study, cord swelling or expansion, cord atrophy, cord lesions, cord lesion levels, enhancement, diffusion restriction, nerve root enhancement (yes, no, equivocal, ventral, dorsal), primary cord lesion pattern (gray, white, both, entire cross section, indeterminate), white matter (lateral column, posterior column), gray matter involvement (anterior horn, posterior cord, central gray, all gray), bright spots, comparison to prior (unchanged, improved, worsened), presence of cervicomedullary junction lesion, conus lesion, conus enhancement, conus restricted diffusion, cauda equina root enhancement, and other incidental findings (low lying conus, malformation, dysraphism, Chiari, tumor, etc.).

The new CRF for Magnetic Resonance Spectroscopy (MRS) includes: scanner manufacturer and model, field strength, software version, raw data format saved and available, was study done during acute metabolic crisis, single voxel spectroscopy (SVS)(Voxel 1 and Voxel 2 selections): PRESS< STEAM, LASER, repetition (TR) time, Echo (TE) time, number of averages, shimming procedure, voxel size, location (basal ganglia, occipitoparietal gray, parietal white, frontal white, other), voxel within signal abnormality or restricted diffusion, visual spectral quality assessment. With multivoxel spectroscopy, similar selections are queried with the addition of slab/slice thickness and level. The final question is whether an absolute metabolite quantification procedure was performed, and if so, which software quantification tool was used, followed by Table 1: MRS Metabolites. Here can be noted NAA< choline, Creatine, Lipid/lactate (short TE), Lactate (intermediate/long TE), Myo-inositol (short TE) and whether these are normal, elevated or decreased (for age).

The new CRF for Head Computed Tomography (CT) includes; whether multiple studies have been performed, scanner manufacturer, model name, software version number, image acquisition mode, pitch, parameters, slice thickness, orientation, if contrast was used, clinical read. Findings (presence of lesions) are described as: hypodensity, calcification, infarct, hemorrhage and location (cortical, white matter, caudate, putamen, globus pallidus, thalamic, brainstem, cerebellum, other), presence of white matter involvement and location, presence of cavitation and location, acute infarct presence and number and location with a detailed table included, chronic infarct presence and number and location with a detailed table included. Malformations with location, atrophy with location, abnormal enhancement with location, eye abnormalities (optic nerve, microphthalmia, cataract).

The SG created the Mitochondrial Disease Imaging CDEs as a reference guide for future research and have also created a definitions guidance to accompany their CRFs which details all the elements included in their CRFs as an aid for future research.

As the recommendations are mainly focused on clinical and clinical research purposes at this time, we have not included diffusion tensor imaging (DTI), functional MRI (fMRI), PET, and others. As these modalities continue to be used and expand into the mitochondrial medicine space, we hope to include these in future iterations of the NINDS CDE project.

Summary of Recommendations

Subdomain	CRF/Guidance Document Name	Classification
Imaging Diagnostics	Brain Magnetic Resonance Imaging (MRI)	Core
	Brain Perfusion Magnetic Resonance Imaging (MRI)	Supplemental – Highly Recommended
	Head Computed Tomography (CT)	Core
	Imaging Guidance and Definitions	N/A
	Imaging - Mitochondrial Disease	Core
	Magnetic Resonance Spectroscopy (MRS)	Supplemental – Highly Recommended
	Spine Magnetic Resonance Imaging (MRI)	Core