OVERVIEW

CLARIO.

Multiple Sclerosis Studies

Medical Imaging Expertise

Magnetic Resonance Imaging (MRI) continues to play a major role in the evaluation of new therapeutic compounds for the treatment of Multiple Sclerosis (MS) due to regulatory agencies recognizing MRI as an objective method to evaluate MS lesion burden and activity as a primary or secondary efficacy endpoint. Additional quantitative endpoints such as brain atrophy, Diffusion-Tensor Imaging (DTI) and Magnetization Transfer Imaging (MTI) serve as markers of neurodegeneration and have shown tremendous value for investigating the long-term efficacy of new disease-modifying therapies. At Clario, we have deep imaging expertise drawn from our nearly 50-year history to help sponsors evaluate the efficacy of potential new MS treatments.

Accelerated decision making for patient safety and monitoring

Expedited regulatory review based upon credible, reliable trial data and processes

Abbreviated timelines through efficient workflow processes and engaged KOLs

Cost and time efficiencies through central imaging review

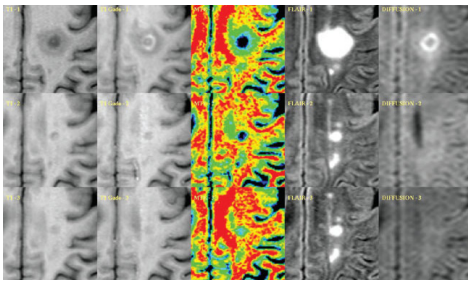
Expertise in Image Processing and Quantitative Analysis

- Semi-automated detection and quantification of MS lesions
  - Gadolinium-enhancing T1-weighted lesions
  - Hyperintense FLAIR/T2-weighted lesions
  - Hypointense T1-weighted lesions (“black holes”)
  - Fully automated 3D image registration
  - Facilitated detection of lesion changes using subtracted images
  - 4D Connectivity for automatic detection of new, enlarging and persisting lesions
  - Automatic detection of Combined Unique Lesions
- Automated brain volumetry using established methods (SIENAX, Freesurfer, multi-atlas segmentation)
  - Whole brain and ventricles
  - Hippocampus
  - Regional analysis (brain lobes, cerebellum, brainstem, corpus callosum, thalamus, etc.)
- Determination of atrophy using established methods
  - SIENAX
  - Boundary Shift Integral (BSI)
  - Tensor Based Morphometry (TBM)
- DTI
- MTI
- Functional MRI (fMRI)

Independent image review by expert neuroradiologists

Board-certified neuroradiologists highly specialized in MS and MR imaging independently evaluate native and processed MRI data for eligibility, safety and efficacy endpoints.

- Centralized image review significantly increases trial efficiency while minimizing trial costs.
- Image evaluations can be made available to the sponsor in real-time.



3D image registration using Mutual Information

Rows: Baseline, M12 & M24 MRI scans of one MS patient
Columns: T1, Post-Gadolinium T1, MTR, FLAIR & DWI MRI sequences

Lesion quantification and tracking

- MRI sequences and timepoints are spatially registered using an automated 3D mutual information-based algorithm.
- Subtracted images are generated in order to increase sensitivity to change while validating lesion contours (Moraal, Radiology 2009). Advanced editing tools are available to assist technicians.
- Gd-enhancing T1 lesions, hyperintense T2 lesions and hypointense T1 lesions (black-holes) can be assessed. Volume and number are evaluated by technicians and neuroradiologists. New or enlarging lesions and Cumulative Unique Active (CUA) lesions can be reported as needed, in agreement with study protocol.

Brain volume measurements and atrophy quantification

- Baseline brain volumes (whole brain and subregions) can be assessed using established techniques such as SIENAX, Freesurfer or multi-atlas segmentation.
- On follow-up visits, atrophy quantification can be carried out using SIENAX, TBM or BSI.

Exploratory assessments

- Regional volume changes (white matter, grey matter, thalamus, cerebellum, etc.) and cortical thickness can be assessed using TBM.
- Spinal cord assessments (lesions, cross-sectional area, and atrophy can be made using the Spinal Cord Toolbox (SCT) where possible.
- MTR can be assessed globally, over specified brain regions, or at individual lesion level.
- Additional exploratory endpoints include fMRI, myelin water fraction, etc.

Project management services

- Standardization of MRI protocol across vendors
- Development of imaging guidelines and charter
- Site qualification using test or phantom scans
- Image QC and interactions with sites for query resolution
- Data export in all standard formats (CSV, SAS, CDISC)
- Full regulatory compliance (FDA 21 CFR Part 11)

To learn more, go to clario.com or email info@clario.com