ASSESSING IMAGING ENDPOINTS FOR CNS CLINICAL TRIALS

Imaging-based endpoints are well established and have an increasingly valuable impact on CNS clinical trials. Accelerated understanding of a drug’s effect on safety and efficacy lays the foundation for a solid decision-making process.

**Key Benefits**

- Higher-quality endpoints through access to KOLs and ability to facilitate in-depth engagement of KOLs in approval of analysis design
- Ease and convenience of working with a single point of contact for both qualitative and specialized quantitative analyses
- Streamlined and accelerated imaging workflow by providing real-time neurology feedback to sites
- Clean and comprehensive data that is ready for regulatory review complete with full audit trails

**CNS Expertise**

As a leading imaging provider for clinical trials, PAREXEL Informatics offers multiple solutions to standardize CNS imaging endpoint assessments. With PAREXEL, you get the knowledge and expertise accumulated from our experience of supporting over 110 CNS imaging studies. When you work with us, you can be confident that you are working with a world leader in CNS imaging.

The structure and expertise of our global organization is aligned to adjust and scale imaging services to your needs. We have the specific scientific and operational expertise and flexibility that you should expect from your imaging partner for early phase, adaptive or exploratory imaging studies. In addition, we have the know-how to implement large, late phase submission trials effectively and efficiently with rigor.
Our Exploratory Imaging group is able to develop and validate imaging biomarkers for eventual clinical use, aid in the selection of an appropriate patient population, and provide early signals for efficacy and safety to accelerate go/no-go decision making. Our goal is to provide a flexible framework from which to incorporate cutting-edge technology, maintain data quality, satisfy regulatory requirements and minimize costs. This approach offers clients exceptional levels of quality and flexibility for both Proof-of-Concept and regulatory endpoint studies.

Experts
PAREXEL brings the world’s leading experts to your CNS imaging studies. Our in-house CNS imaging experts draw from their impressive clinical experience and imaging know-how to provide optimal medical support for your studies. Our team possesses intimate understanding of the regulatory requirements and includes George Mills, M.D.—Vice President of Early Phase Consulting.

Complementing our internal CNS imaging experts is a panel of renowned, independent scientific advisors including:

- Michael Greicius, M.D.
- Frederik Barkhof, M.D., Ph.D
- Jochen Fiebach, M.D.
- Barry Bedell, M.D., Ph.D.
- John Henson, M.D., FAAN
- Alan C. Evans, Ph.D
- Yair Safriel, M.D.
- J. James Frost, M.D., Ph.D., MBA

Standard CNS Endpoints
PAREXEL Informatics has proven capabilities for supporting all of the standard modalities used by investigative sites for routine imaging of CNS patients. With a team of experienced in-house medical imaging experts, including several radiologists, an MR physicist and a dedicated Advanced Imaging group, we are fully equipped and optimally positioned to support new and novel imaging methods.

Operational Excellence
Guiding your project through every step of the process, a dedicated team of experts focuses on meeting the specific requirements of your protocol. Consisting of a director of operations, project manager, imaging operations lead, medical director, medical writer and imaging specialists, and external scientific advisors when needed, the team is focused on delivering the highest levels of project rigor and quality service.

Our in-house medical imaging experts provide consultation on developing the imaging component of your protocol and the analysis design. We ensure a standardization of image acquisition, as well as collection and processing of all images in a central digital repository. Rigorous training and testing of reviewers is performed prior to the independent review. Independent reviewers will complete our training academy, a comprehensive three-step program that ensures effective medical quality control for the selection and management of reviewers for the independent review process. Our medical experts will also conduct ongoing quality checks of the reviewers’ case assessments and reports. These practices enable the independent and
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<th>Indication</th>
<th>Modality</th>
<th>Read Type</th>
<th>Assessment</th>
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<tr>
<td>Cerebrovascular Disease (Stroke)</td>
<td>• CT&lt;br&gt;• Perfusion CT&lt;br&gt;• MRI&lt;br&gt; - Conventional&lt;br&gt; - DWI/PWI</td>
<td>• Eligibility&lt;br&gt;• Efficacy&lt;br&gt;• Safety</td>
<td>• Confirmation In-/Exclusion criteria&lt;br&gt;• Infarct size (volume), penumbra in ischemic stroke, vessel assessment (MORI scale, TIMI scale)&lt;br&gt;• Hemorrhage, mass effects, edema</td>
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<td>Neuro-Oncology</td>
<td>• CT&lt;br&gt;• MRI&lt;br&gt; - Conventional&lt;br&gt; - DWI&lt;br&gt; - DTI</td>
<td>• Eligibility&lt;br&gt;• Efficacy&lt;br&gt;• Safety</td>
<td>• Confirmation In-/Exclusion criteria&lt;br&gt;• Tumor size [bi-dimensional (Macdonald criteria), volumetric measurements]&lt;br&gt;• Hemorrhage, mass effects, edema&lt;br&gt;• Oncology review for pseudoprogression</td>
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<td>Demyelinating Disease (MS)</td>
<td>• MRI&lt;br&gt; - Conventional&lt;br&gt; - 3D&lt;br&gt; - DTI&lt;br&gt; - MTR&lt;br&gt; - MRS&lt;br&gt; - OCT</td>
<td>• Eligibility&lt;br&gt;• Efficacy&lt;br&gt;• Exploratory&lt;br&gt;• Safety</td>
<td>• Confirmation In-/Exclusion criteria [McDonald criteria]&lt;br&gt;• Lesion counts [McDonald criteria]&lt;br&gt;• Lesion volume, brain volume (normalized brain volume, percent brain volume change, gray matter and white matter volume, CSF volume)&lt;br&gt;• Lesion prediction&lt;br&gt;• Changes in optical nerve&lt;br&gt;• Extra-CNS safety assessments&lt;br&gt;• Unexpected non-MS related findings&lt;br&gt;• Analysis of functional MRI such as DTI and MRS</td>
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<td>Neurodegenerative Disease (Alzheimer’s/Dementia, Parkinson’s)</td>
<td>• MRI&lt;br&gt; - Conventional&lt;br&gt; - 3D&lt;br&gt; - PWI&lt;br&gt; - BOLD&lt;br&gt; • PET&lt;br&gt; - FDG and beta-amyloid imaging&lt;br&gt; - Novel tracers</td>
<td>• Eligibility&lt;br&gt;• Efficacy&lt;br&gt;• Exploratory&lt;br&gt;• Safety</td>
<td>• Confirmation In-/Exclusion criteria&lt;br&gt;• Any types of measurements including volumetric measurements&lt;br&gt;• Hemorrhages, edema, mass effects, etc.</td>
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<td>Other Neurological Disorders (Acromegaly, Brain Injury)</td>
<td>• CT&lt;br&gt;• MRI&lt;br&gt; - Conventional&lt;br&gt; - Functional&lt;br&gt; • X-ray&lt;br&gt; • PET&lt;br&gt; • DSA</td>
<td>• Eligibility&lt;br&gt;• Efficacy&lt;br&gt;• Exploratory&lt;br&gt;• Safety</td>
<td>• Confirmation In-/Exclusion criteria&lt;br&gt;• Any types of measurements including volumetric measurements&lt;br&gt;• Hemorrhages, edema, mass effects, etc.&lt;br&gt;• Detection of asymptomatic pathology&lt;br&gt;• Change in carotid atherosclerotic plaque</td>
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unbiased evaluation of images and ensure high-quality image analysis data.

Partnering with PAREXEL means access to our worldwide network of reviewers. Our Global Reviewer Operations group is focused on the management of both our on-staff and independent reviewers. The flexible reviewer model allows the freedom to choose between our in-house staff and independent reviewer network as well as experts identified by our client. To supplement training provided at investigator meetings, our seasoned experts can provide advanced on-site training customized to individual customer requirements. We also offer international training via webcasts for radiology and trial staff. Training materials such as CD-ROMs with content required for your investigator sites can also be produced. PAREXEL Informatics can qualify the radiology departments of your investigator sites and confirm that all sites are able to
acquire the images according to mutually developed standardized image acquisition guidelines.

**Biospective’s PIANO™ software for fully-automated, quantitative analysis of CNS imaging data**

PAREXEL works with Biospective, Inc. to provide cutting-edge image processing and analysis capabilities for CNS studies. This synergistic relationship allows us to offer sponsors scientifically validated and fully automated software, which provides quantitative imaging outcome measures from MRI and PET data. The sophisticated automated PIANO™ analysis pipeline from Biospective allows for the following types of analyses:

- Structural analysis including whole brain volume, hippocampal volume, ventricular volume and cortical thickness
- Functional analysis such as ASL perfusion MRI and resting-state and task-based fMRI
- Molecular and Metabolic analysis such as Amyloid and FDG PET

The scientific and technological expertise of Biospective, combined with the operational and site management capabilities of our Advanced Imaging group, offers sponsors a unique, efficient and cost-effective single solution for their early and late phase CNS imaging studies. Biospective and PAREXEL are committed to working closely with sponsors to bring their agents from discovery to market.

**Advanced Technology Tools**

Our CNS solution is underpinned by an integrated suite of proprietary technology tools specifically designed to provide built-in expertise and rigor and are configurable to support the specific requirements of your protocol. With embedded analysis workflows and criteria rules to streamline the entire process, the combined applications provide superior, intuitive user experiences while enabling data quality:

- Advanced technologies to enable imaging visualization, analysis, tracking, reporting and export including viewer application for SUV of FDG, FLT, F-18 amyloid compounds
- Tight integration of electronic case forms and image analysis application to simplify review workflow
- Qualitative and quantitative analysis of PET images with SUV computations. Core analysis applications with capabilities for PET image analysis
- Three-panel display with grid-based image display
- Measurement recording and updating to allow automatic calculations for the reviewer, as well as unidimensional, bidimensional and volumetric measurements
- Multiple review platforms including single radiology review, double reads with adjudication, global radiology review, combined radiology-oncology, consensus and triple read review
- Single-click lesion detection and 3D propagation
- "Coregistration" superimposition of sequences for more rapid, accurate assessment of different pathologies in the same exam
- Integration with ClinPhone® RTSM (Randomization and Trial Supply Management) to facilitate real-time queries on patient statuses, enabling proactive patient management and swift reporting of screening confirmation
- Advanced reporting solution for real-time access to imaging and trial data including Metrics Consortium Champion (MCC) report card metrics

Part of the Perceptive MyTrials® framework, enabling integration with clinical trial software applications to help users plan, design and conduct clinical trial programs in a single place.