

**CROCTINO:** Collaborative Retrospective Study on Retinal OCT in Neuromyelitis Optica

**PAMRINO:** Parallel Study on MRI in Neuromyelitis Optica

Dear NMOSD Colleagues,

It has been a productive new year so far, and we hope this newsletter finds you all well! The CROCTINO/PAMRINO Study Team recently sent out an update email regarding our CROCTINO data upload timeline, which was extended to the end of April 2017. We received a great response to our update email and there was a large push by all participating centers to sign up and upload their clinical data and OCT images. None-the-less, we welcome additional centers to participate in CROCTINO, and of course, the deadline for data upload will accommodate this expansion. We would be happy to discuss any further participation and timelines with new centers directly.

As the analysis of PAMRINO datasets will begin in the coming weeks, we invite all of you working with MRI data to participate in this international study as well. Please contact us at [croctino@neurodial.de](mailto:croctino@neurodial.de) or [pamrino@neurodial.de](mailto:pamrino@neurodial.de) for more information on these international studies. Those centers who are already participating in CROCTINO, can use the same account to share PAMRINO data, as well.

We sincerely thank you all for your hard work and time. Your efforts, to date, have allowed us to begin analyzing the OCT data for this report! We presented some of the preliminary analyses from this collaborative project in greater detail at the Guthy-Jackson Charitable Foundation Roundtable Conference in Los Angeles in March.

In our last report, we announced that the CROCTINO study had successfully started its image analysis program, and that we are working hard to launch the corresponding PAMRINO MRI study. Since PAMRINO will be in operation shortly, we would like to take this opportunity to remind you of the consensus vision for this project.

## **PAMRINO**

### Background & Objectives

Much research into NMOSD, including MRI studies in this field, has been limited by small sample sizes, and thus has yielded limited analyses and results. In some cases, ambiguous findings may result from cohort heterogeneity in terms of diagnosis, scanning protocols, as well as variations in analytical and statistical methods. One key goal of PAMRINO is to evaluate optimal MRI protocols and analysis methods for the identification of imaging biomarkers in NMOSD and related disorders, by integrating data from a large multicenter cohort.

### Methodology

Within the PAMRINO study we will collect a broad range of MRI data acquired during normal clinical visits of NMOSD patients. Consequently, this dataset will be representative of real world sample MRI data with substantial heterogeneity in terms of MR scanners, MR sequences, and data quality. A main goal for PAMRINO is to investigate this real world data in anticipation of gaining an overview of what MRI data are acquired in everyday practices. This assessment will inform the research community of the extent of heterogeneity in MRI protocols as utilized in the diagnostic workup of NMOSD patients. With this information, optimization of protocols and standard methods may be introduced in prospective clinical trials as well as in MRI scanning conducted in routine clinical practice and for NMOSD studies. Insights from such studies may ultimately allow for large-scale standardized analyses of MRI data to elucidate comparable differences in the brain and spinal cord of NMOSD patients.

## Status & Next Steps

Based on consensus achieved among the Imaging Solution Team and ICC, we will evaluate these protocols with respect to the fulfillment of international recommendations for imaging protocols in terms of completeness and data quality.

This evaluation will be performed using quantitative and qualitative assessments:

- 1) on a quantitative level (e.g. sequence parameters, slice thickness, voxel sizes, etc.)
- 2) on a qualitative level (e.g. image quality, movement or pulsation artifacts, etc.)

In a second step after assessing heterogeneity, we will perform quantitative structural analysis on a subset of the data. Each subset needs to be suitable for analysis, as detailed below, and to share a minimum comparability across the included datasets.

The quantitative analyses will include:

- 1) T2- lesion load measurements (count and volume) on FLAIR/T2/PDw images (min. 3 mm slice thickness)
- 2) Cerebral atrophy (if non-enhanced MPRAGE is available)
- 3) Cervical myelon atrophy (if MPRAGE including cervical spine is available)
- 4) Total myelon atrophy (if full spine imaging is available)

As always, complete methods, data and draft interpretations from the above preliminary evaluations will be circulated to the entire ICC for review and feedback prior to any recommendations being drafted.

## Next Steps

The IT infrastructure (REDCap archive) for sharing demographic, clinical and visual function data is fully operational, as the CROCTINO platform will be shared by the PAMRINO platform. This structure affords all centers a facilitated means of adding MRI data to existing patient records, if they have already uploaded their information for CROCTINO.

An embedded link to XNAT allows convenient upload of MRI image data for each subject.

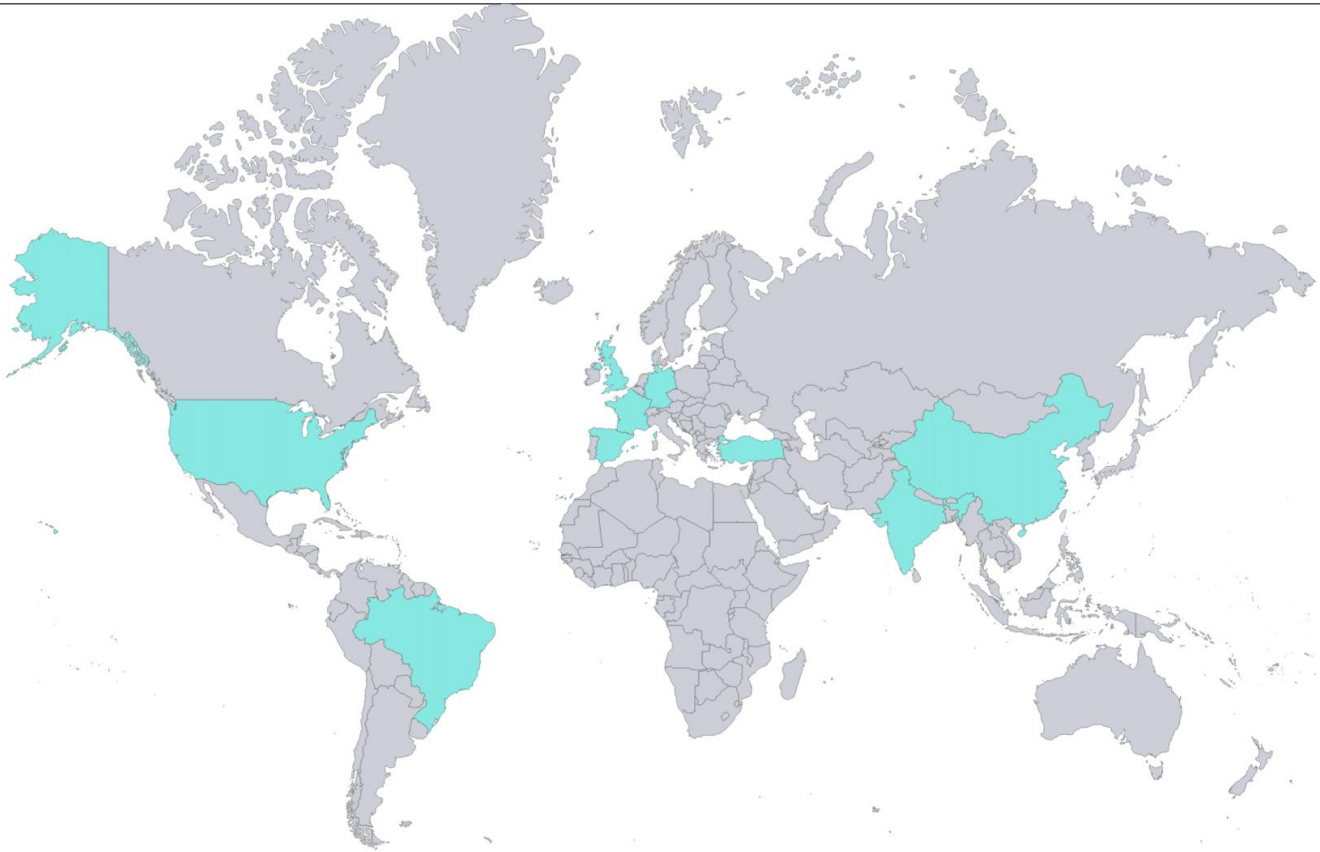
To date, 24 academic centers from Asia, Europe, and North & South America have agreed to contribute MRI images and related data to PAMRINO. Thus, we hope to meet the goal of obtaining, curating, and uploading 350 MRI datasets from NMOSD patients, and 100 matched healthy control subjects by July 1, 2017.

We are currently recruiting centers to contribute MRI datasets for PAMRINO. If desired, it is possible to participate in only PAMRINO or CROCTINO. We are happy to have your participation in either study or both, depending on the data available for you to share with all of your collaborators in this exciting project.

If you have already agreed on participating in CROCTINO and have MRI data to contribute as well, the PAMRINO Study Team is going to contact you shortly. All other centers, please contact the CROCTINO/PAMRINO Study Team when you are interested in contributing MRI and/or OCT data.

## Current CROCTINO Site Participant Map

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*Figure 1: This world map shows all countries marked in blue belonging to centers which are currently participating in the CROCTINO study: Brazil, China, France, Germany, India, Spain, Turkey, United Kingdom and United States of America.*

We are proud to report that 10 participating centers in 9 different countries are currently participating in the CROCTINO effort to date, and we encourage other collaborating sites to join as well. An additional 3 centers have agreed to participate in both CROCTINO and PAMRINO. Upload of OCT images and clinical data through the REDCap and XNAT systems managed by the University of Utah DCC are ongoing, and we anticipate a finish date in this first phase of collection by the end of April 2017. Thus, we are happy **that more than half of our collective goal of 350 OCT datasets has been achieved, and includes 210 datasets from NMOSD patients! Excellent teamwork!**

As you recall, a central reading center for this collaborative project has been established in Berlin. Its initial focus has been on manual quality control checks of the uploaded OCT image data. After extracting OCT images from XNAT, we check for scan quality, perform segmentations and identify abnormalities. These findings will enrich our understanding of how typical NMO research centers conduct their OCT imaging. At the moment, the Reading Center is in the process of analyzing demographic data from REDCap, and will begin image analysis in conjunction with our collaborators and the GJCF team as soon as we have received datasets from all participating centers.

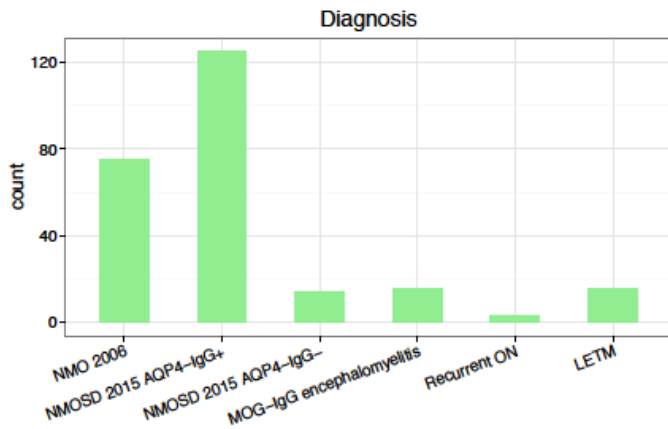


Figure 2: Preliminary CROCTINO results: distribution of the diagnosis of all patients which are currently shared in the REDCap platform (status February 2017).

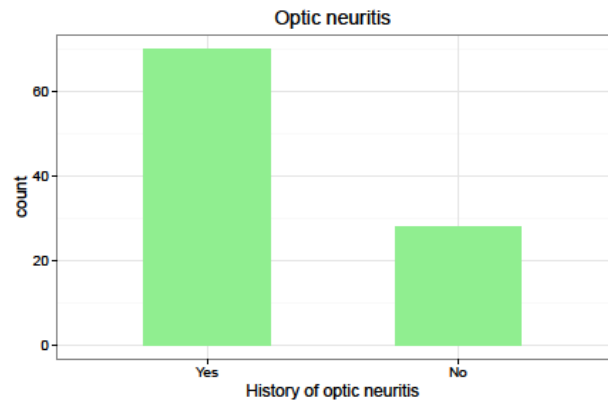


Figure 3: Preliminary CROCTINO results: History of optic neuritis of the patients shared in the REDCap platform (status February 2017)

### Access to the CROCTINO/PAMRINO database

The PAMRINO and CROCTINO projects are supported in-part by the GJCF. Access is available to all members of the ICC. As is established practice in this collaboration, studies using data from this program follow the standard process of circulating manuscript drafts to the entire ICC and Imaging Solution Core Team. Feedback will be integrated into the manuscript and a final manuscript will be prepared for review of all ICC members to accept or decline affiliated co-authorship. If you have any operational or academic questions or suggestions for additional scientific analyses, please feel free to contact us or the GJCF.

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On behalf of NMOSD patients and families, we thank you for your time and effort in joining us in these exciting projects. We are excited to continue this worldwide collaboration on the journey to a cure!