

Session Title: Visionary Analytics: Advancing Ophthalmology with historical insights and advanced modeling methodologies

Submission Category: Symposium

Submitter: [REDACTED]

Description of session (include background & scientific importance)

Ophthalmology is a therapeutic area that presents unique challenges in disease treatment due to the delicate nature of the eye and its intricate physiology. Anti-VEGF treatments, for example, have significantly improved the prognosis for patients with retinal diseases, offering a transformative approach to manage conditions like neovascular age-related macular degeneration (nAMD). However, the necessity for regular intravitreal injections in clinical setting poses challenges for patients' adherence due to the cumbersome nature of frequent treatment visits. Moreover, variabilities in the response among patients and the duration of the responses highlight the need for optimized treatment. Despite the challenges posed by the dynamic nature of eye diseases, the field of ophthalmology also presents unparalleled opportunities, with a vast amount of longitudinal clinical, real world, and retinal imaging data available. Through integration of mathematical modeling and machine learning, the field of ophthalmology is being propelled forward by transforming this wealth of data into actionable insights. By leveraging the vast amount of data together with advanced analytics, we not only enhance our understanding of ocular pathophysiology but also pave the way for developing more effective treatments and optimizing treatment strategies. This symposium session is intended to highlight a few state-of-the-art pharmacometric, statistical, and ML approaches used to address critical questions in ophthalmology and provide significant impact during development. Following the presentations, a panel discussion is planned with the aim to provide different perspectives (industry and regulatory) and start a dialogue on how advanced analytics can be leveraged to bridge the new horizon for ophthalmology.

Primary Focus of Session

- Statistics oriented/AI/ML/Other

Learning Objectives

1. Upon completion, participant will be able to: - Understand unique challenges and opportunities in ophthalmology and how advanced analytics can help address critical questions and provide significant impact during drug development. - Provide a few examples of state-of-the-art pharmacometric, statistical, and ML approaches and their impact. - Provide industry and regulatory perspectives on the utilization and application of advanced analytics in ophthalmology.

ISoP Special Interest Group (SiG), Committee, Network or Community Affiliation

Clinical Pharmacometrics SIG, Mathematical and Computational Sciences SIG, and Statistics and Pharmacometrics SIG

Additional A/V Needs

N/A

Budget Request

We would like to request \$2500 to be split between Speakers 2 & 3 for their travel. Both of them are eligible based on the criteria set forth in the submission guideline.

Speaker/Chair(s)

[REDACTED]
[REDACTED]
[REDACTED]

Role: Chair-Speaker

Title of Speaker's Presentation

Bridging new horizons for ophthalmology: State of the art methodologies and outlook

Speaker's Presentation Summary

Developing ophthalmic drugs is challenging, in part due to limitations on sampling drug concentrations and biomarker levels at the site of action within the eye. Oftentimes, pre-clinical exposure-PD/efficacy/safety relationships do not necessarily translate into humans. Despite various challenges, there is a vast amount of longitudinal clinical data, real world data, and retinal imaging data available. Hence, there are many unique opportunities in ophthalmology, in which different tools can be used to address critical questions throughout different stages of drug development. In this talk, we will present a few examples on how knowledge, data and analytics can be seamlessly integrated throughout different development stages to help inform ophthalmic drug development. One of the examples is the ophthalmology PK-PD platform model developed to mechanistically describe drug PK and PD based on data from multiple therapeutic programs in nonclinical species and humans. There are also examples of disease progression models developed to describe and predict the natural progression of disease trajectories in the absence of treatment or with treatment. In addition, there are examples of exposure-efficacy models developed using longitudinal clinical data to predict clinical endpoints. We are optimistic that these state-of-the-art methodologies and tools can be integrated effectively and efficiently and offer a new horizon for ophthalmic drug development.

[REDACTED]
[REDACTED]
[REDACTED]

Role: Chair

Title of Speaker's Presentation N/A

Speaker's Presentation Summary

For the proposed session on "Visionary Analytics: Advancing Ophthalmology with historical insights and advanced modeling methodologies", Hao will be co-chairing the session with Joy Hsu. He will also join the panel discussion planned after the presentations. However, Hao will not present in the session as a speaker.

[REDACTED]

Role: Speaker

Title of Speaker's Presentation

Historical borrowing in nAMD: the present as a "prior" for designing more efficient future trials

Speaker's Presentation Summary

Anti-vascular endothelial growth factor (aVEGF) treatment has been the standard of care for the treatment of nAMD since the approval of ranibizumab in 2006. A wealth of clinical historical data on aVEGF is now available and by utilizing that appropriately, the efficiency of future clinical trials could be improved by reducing the sample size needed or improving their statistical power. While virtual trials and model-based simulations are increasingly recognized within modeling and simulation discussions, the statistical nuances of employing virtual patients have not been thoroughly explored. In this talk, we will discuss how to incorporate historical knowledge on standard of care ranibizumab in the analysis of a new trial, blending modeling and Bayesian statistics. Historical data of ranibizumab treatment arms from 6 Phase 2, 3, and 4 clinical trials were used to develop a non-linear mixed effect model that relates the clinical endpoint (i.e. Best Corrected Visual Acuity, BCVA) with ranibizumab exposure over time. Relevant patient characteristics at baseline were incorporated. The model was validated and could thus be used to simulate the clinical endpoint in a new trial design. These simulations represent our current knowledge on ranibizumab before a new trial starts. Using the Bayesian paradigm, this prior knowledge is integrated and updated based on emerging ranibizumab data collected as part of the new trial. We found that, through our borrowing approach, the sample size of a future trial can be reduced to two thirds with a minimal loss of power and bias in the estimation of the treatment effect.

[REDACTED]

Role: Speaker

Title of Speaker's Presentation

Charting New Paths in Ophthalmology with DeepNLME-Powered Predictive Modeling

Speaker's Presentation Summary

Large potential gains from understanding and predicting the heterogeneous treatment needs of

patients undergoing Anti-vascular endothelial growth factor (aVEGF) treatment for neovascular age-related macular degeneration (nAMD) has prompted a quest for robust and accurate precision medicine. In this study, we introduce the application of DeepNLME (neural-embedded nonlinear mixed effects) for developing semi-mechanistic, semi data-driven longitudinal predictive models for key ophthalmic biomarkers measured in the HARBOR trial, including Best Corrected Visual Acuity (BCVA), Central Foveal Thickness (CFT), Subretinal Hyperreflective Material (SHRM), Pigment Epithelial Detachment (PED), Intraretinal Fluid (IRF), and Subretinal Fluid (SRF). Our findings reveal that the DeepNLME model for BCVA slightly surpasses state-of-the-art models in making individualized longitudinal BCVA predictions based on early observations, showcasing its unique capability to handle inter-subject variability and capture patient-specific trends. Furthermore, we investigate the predictive power of longitudinal biomarkers (CFT, SHRM, PED, IRF, and SRF) on the primary endpoint, BCVA, demonstrating a modest improvement in predictive accuracy (finding a maximal reduction of predictive error by 1.4 ETDRS letters from a baseline of 12.4). This enhancement, although slight, underscores the potential of incorporating multiple ancillary longitudinal biomarkers to refine predictions of key clinical outcomes. The application of DeepNLME not only advances the methodological toolkit available for ophthalmic research but also for pharmacometrics modelling in general. This lays the groundwork for broader applications in healthcare. By effectively integrating mechanistic insights with data-driven identification of diagnostic and prognostic patterns hidden in complex clinical data, our approach promises to contribute significantly to the development of more personalized, effective treatment strategies. The methodology and principles underlying our analysis of the HARBOR trial data are anticipated to have wide applicability, offering a new horizon for predictive modeling across pharmacometrics and beyond.