Bayesian Hierarchical Linear Model: Application towards Patients with Wet Age-related Macular Degeneration

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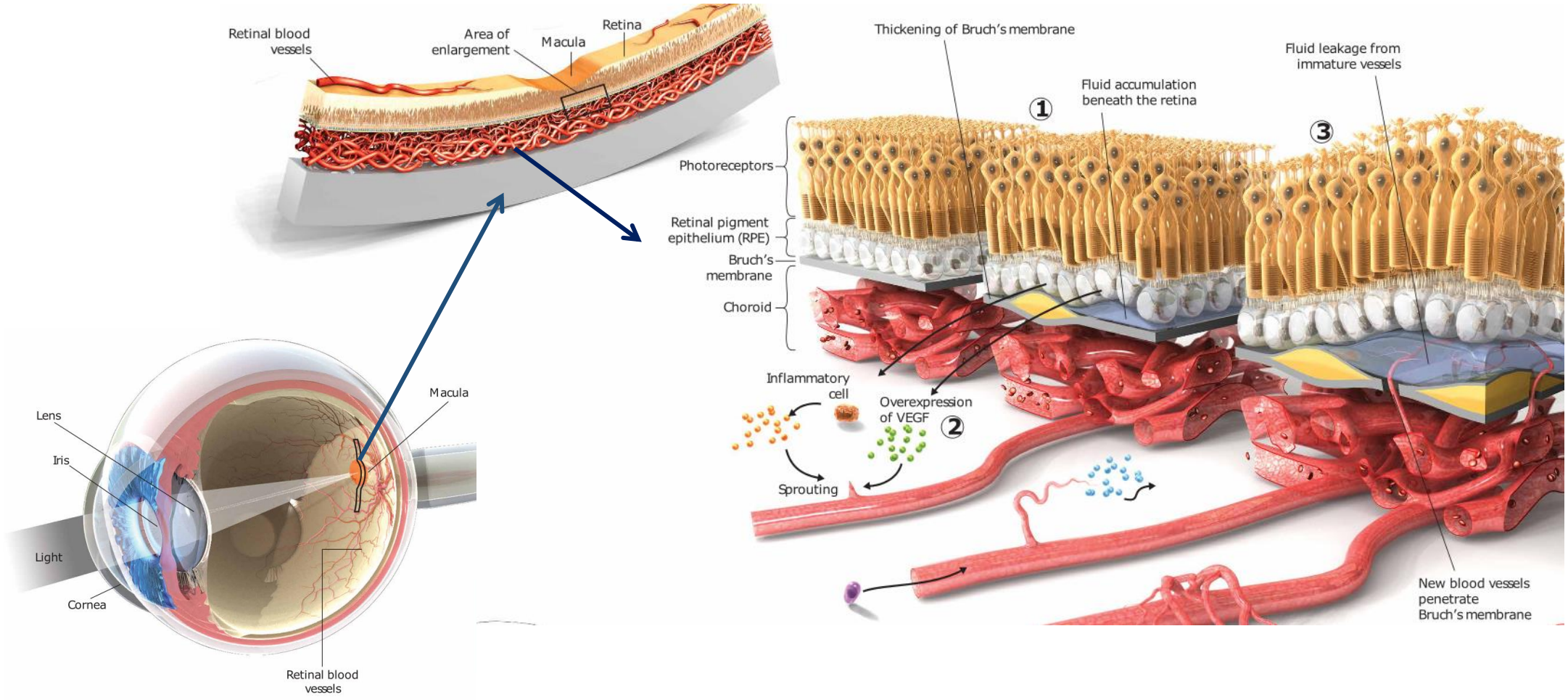
Wet Age-related Macular Degeneration

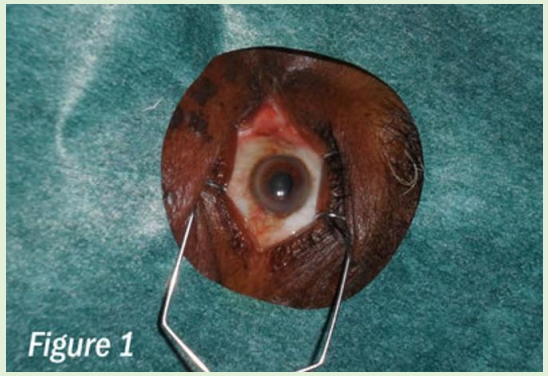
WetAMD is known to be caused by an over-expression of **vascular endothelial growth factors (VEGF)** which induces

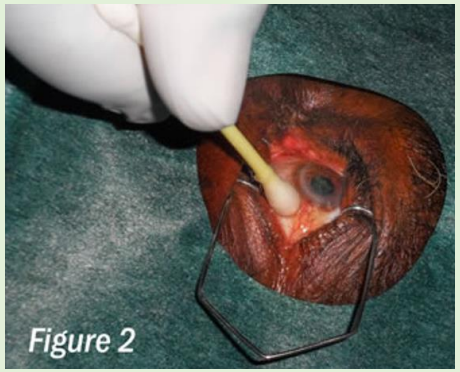
choroidal neovascularization (CNV), the formation of abnormal blood vessels leaking fluid, eventually resulting in a rapid vision loss.

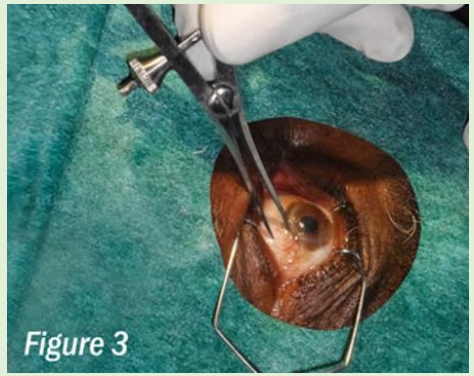


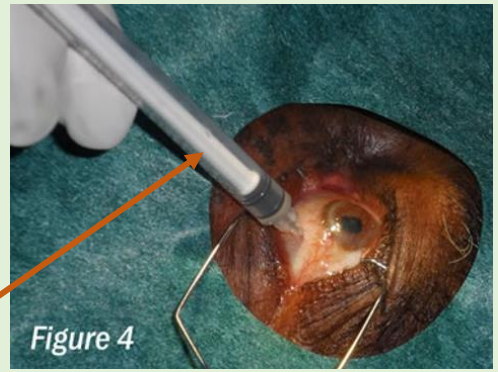
Source credit: Angiogenesis Foundation VIDEO 1 VIDEO 2

Intravitreal (IVT) injection and anti-VEGF drugs

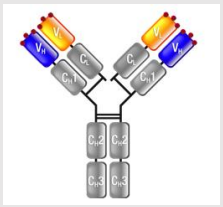
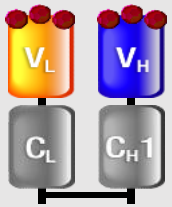
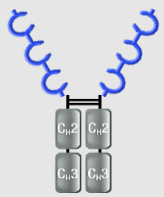
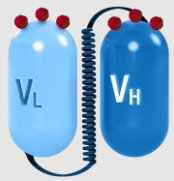








FDA approved anti-VEFG drugs

	Bevacizumab (Avastin®)	**Ranibizumab** (Lucentis®)	**Aflibercept** (Eylea®)	**Brolucizumab** (Beovu®)
Molecular structure				
FDA Approved	**2004** (for chemotherapy)	**2006**	**2011**	**2019**
Administration interval	**every 4 weeks (q4w)**	**=** **every 4 weeks (q4w)**	**<** **every 8 weeks (q8w)**	**<** **every 12 weeks (q12w)**

Source credit: https://www.cehjournal.org/article/intravitreal-injection-technique/

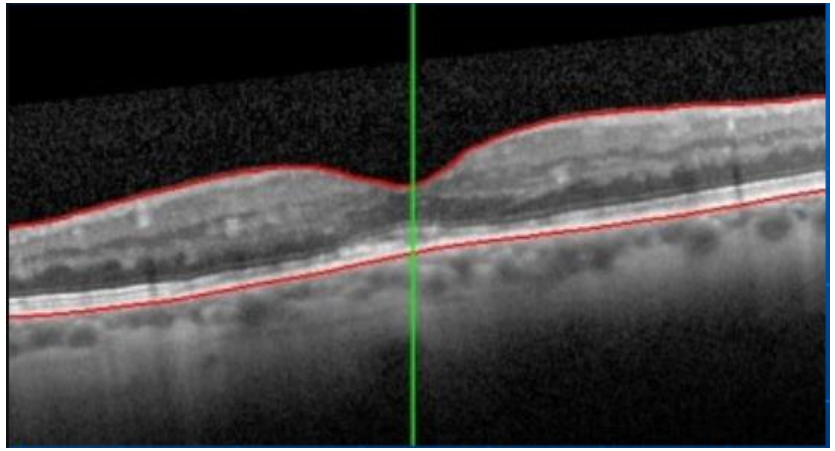
Two efficacy endpoints in treating patients' data with wetAMD

- **Best corrected visual acuity (BCVA) (0 ~ 100 letters)** measured by early treatment diabetic retinopathy study (ETDRS) testing.
- **Central sub-field thickness (CSFT) (μm)** measured by optical coherent tomography (OCT).

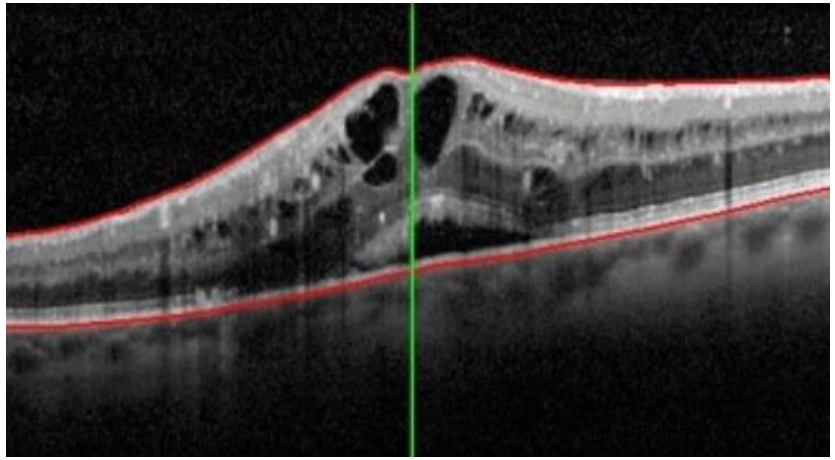
ETDRS

OCT

Normal macula, CSFT ≤ 250 μm

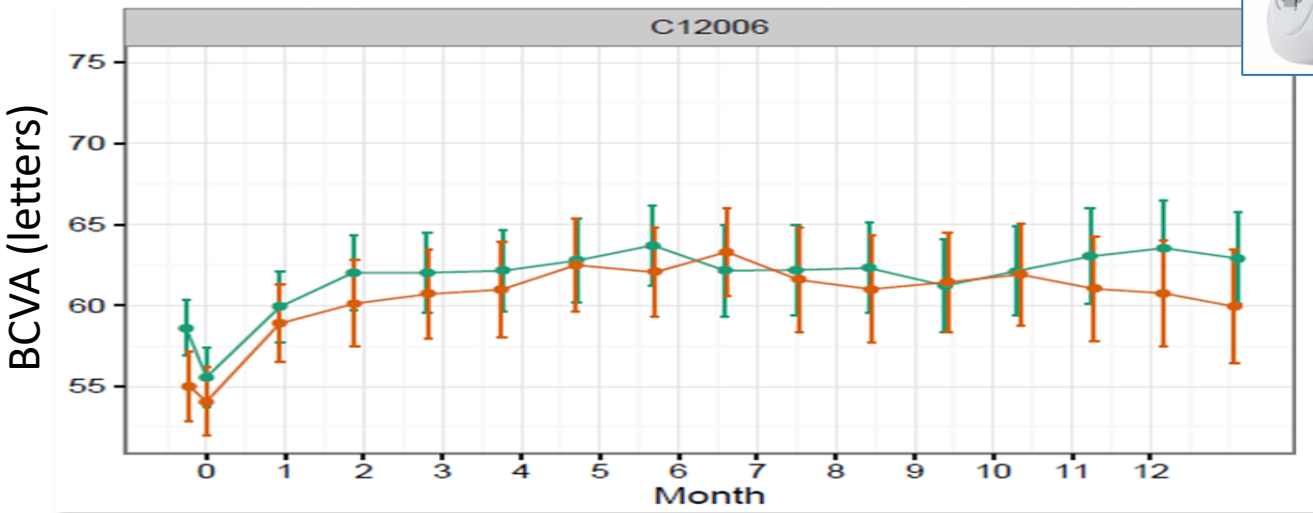


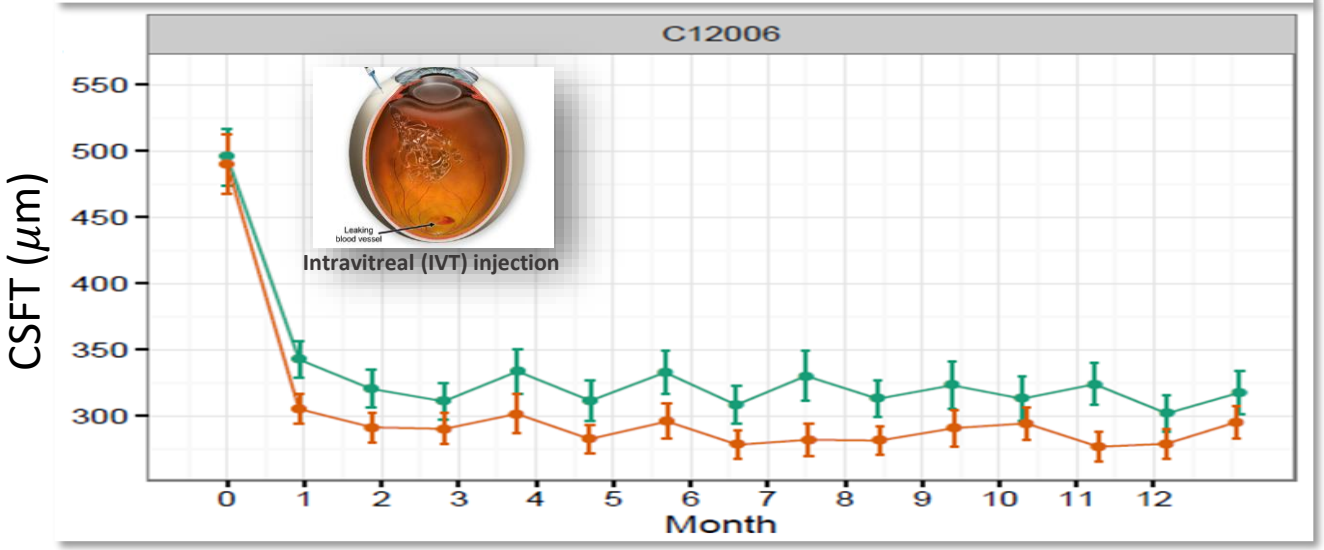
Increased CSFT due to intraretinal fluid



Example plot showing a treatment effect due to anti-VEGF

(Bimonthly injections of Brolucizumab (orange) and Aflibercept (green))

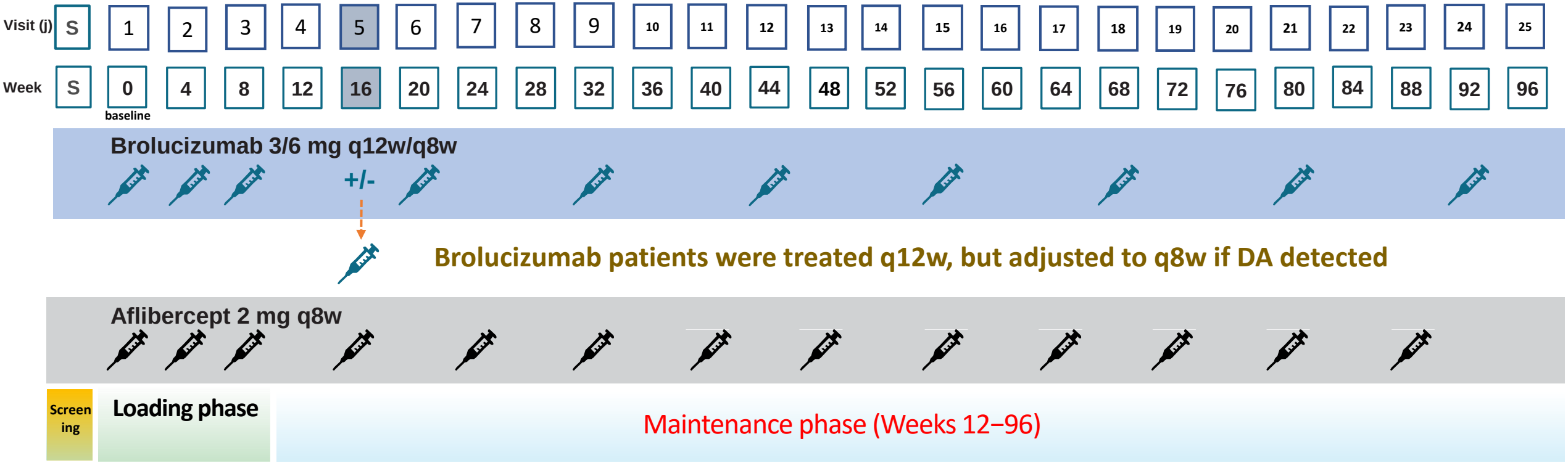




HAWK and HARRIER

	HAWK and HARRIER
Purpose of study	Comparison between two anti-VEGFs, **Brolucizumab** (3mg/6mg; Beovu®) versus **Aflibercept** (2mg; Eylea®)  
Status of trials	FDA Approved (Oct 7, 2019)
Number of patients	1,817 patients
Common study design	Double-masked, Randomized, Phase 3, Multi-center, and Intravitreal (IVT) injection
Study Duration	2-Year (96 weeks)
Randomization of Patients	• 1 (Afl 2mg) : 1 (Bro 3mg) : 1 (Bro 6mg) in HAWK • 1 (Afl 2mg) : 1 (Bro 6mg) in HARRIER
Interventions	• **Aflibercept treated patients:** after loading with 3 monthly injections, patients are treated with every 8 weeks (q8w) • **Brolucizumab treated patients:** after loading with 3 monthly injections, patients are treated with every 12 weeks (q12w). Patients with disease activity (DA) will be interval adjusted to q8w.
References	Dugel et al, "HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration", 2020

Interventions in the HAWK and HARRIER



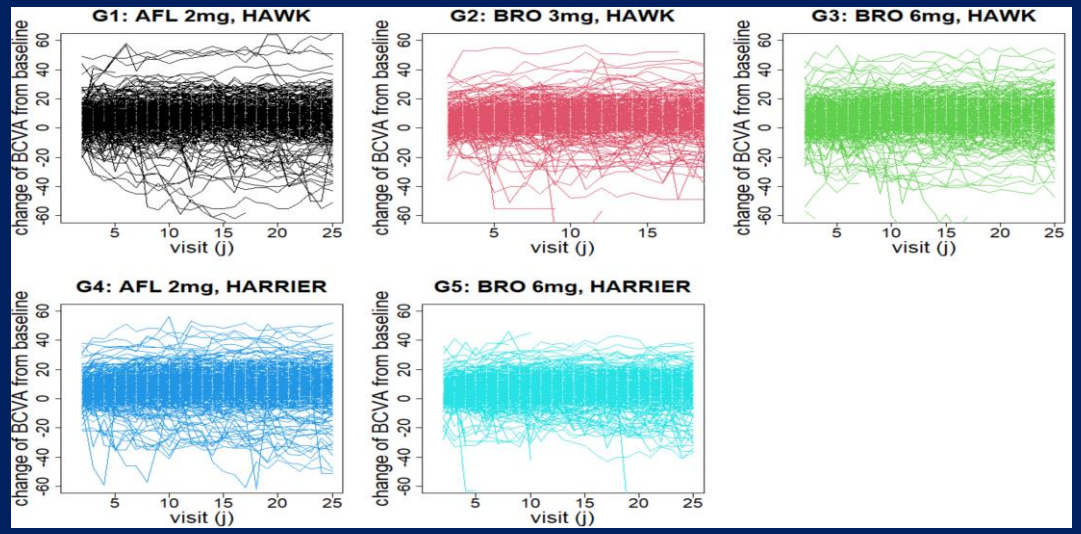
Disease activity assessment

Disease activity assessments were conducted at pre-specified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on functional and anatomical characteristics. Additional assessments and potential dosing interval adjustments occurred at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only. Sham injections were administered to maintain masking. Visual and anatomic assessments were made prior to injections at Weeks 16 and 48. DA, disease activity; q8w, 8-week dosing interval; q12w, 12-week dosing interval

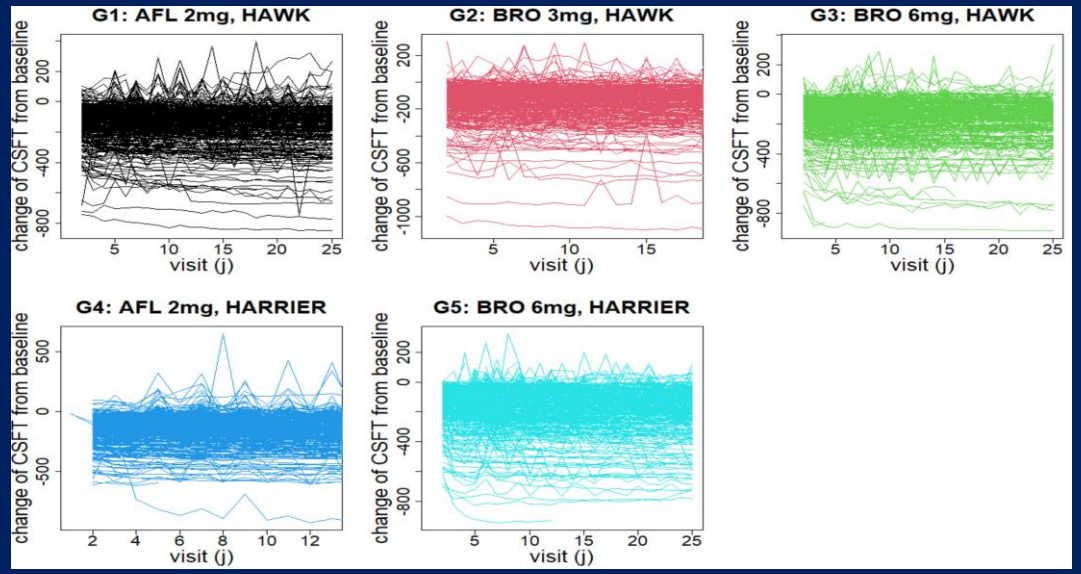
Two efficacy end points in wetAMD data: BCVA and CSFT trajectories

BCVA and CSFT trajectories at *individual-patient level*

BCVA

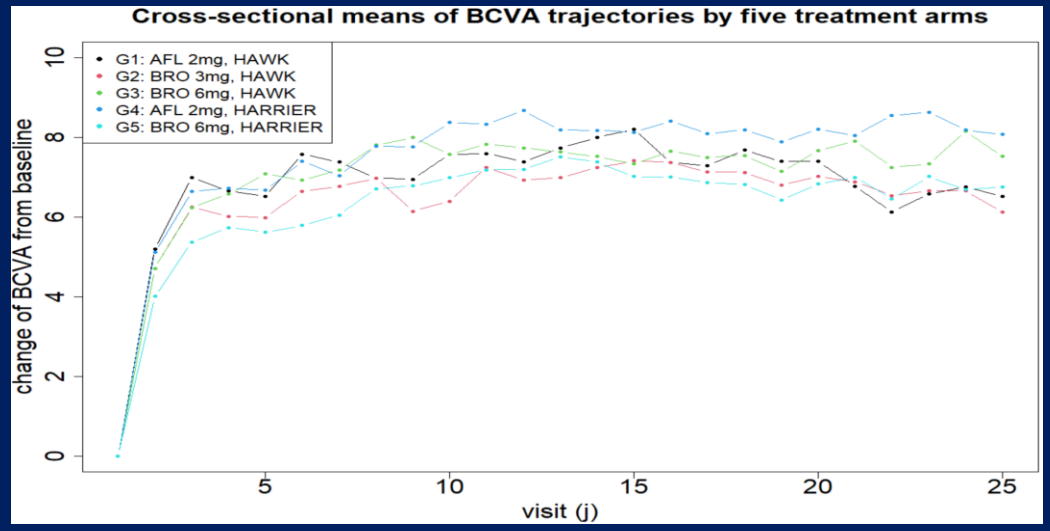


CSFT

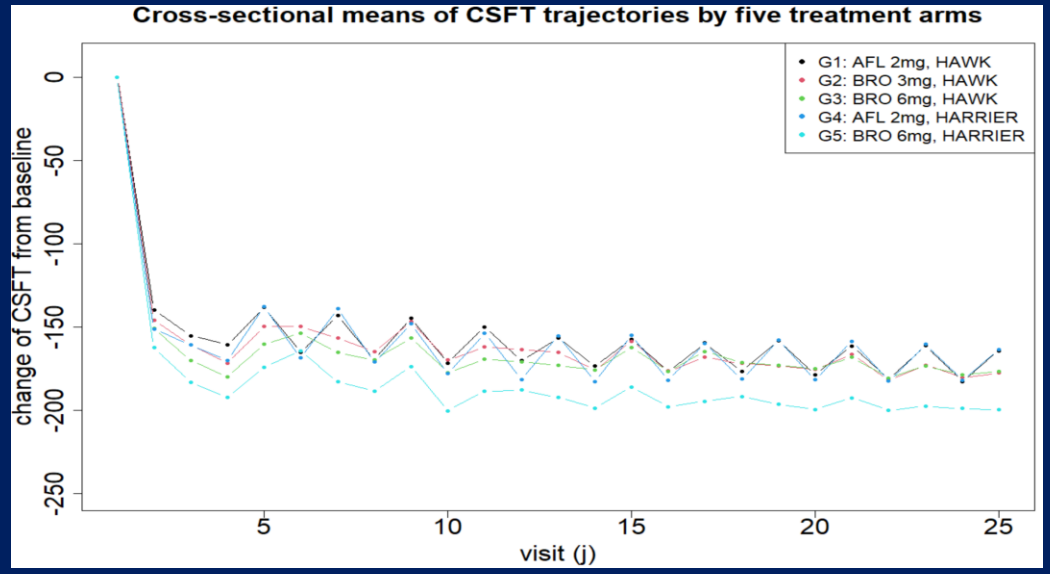


BCVA and CSFT trajectories at *sub-population level*

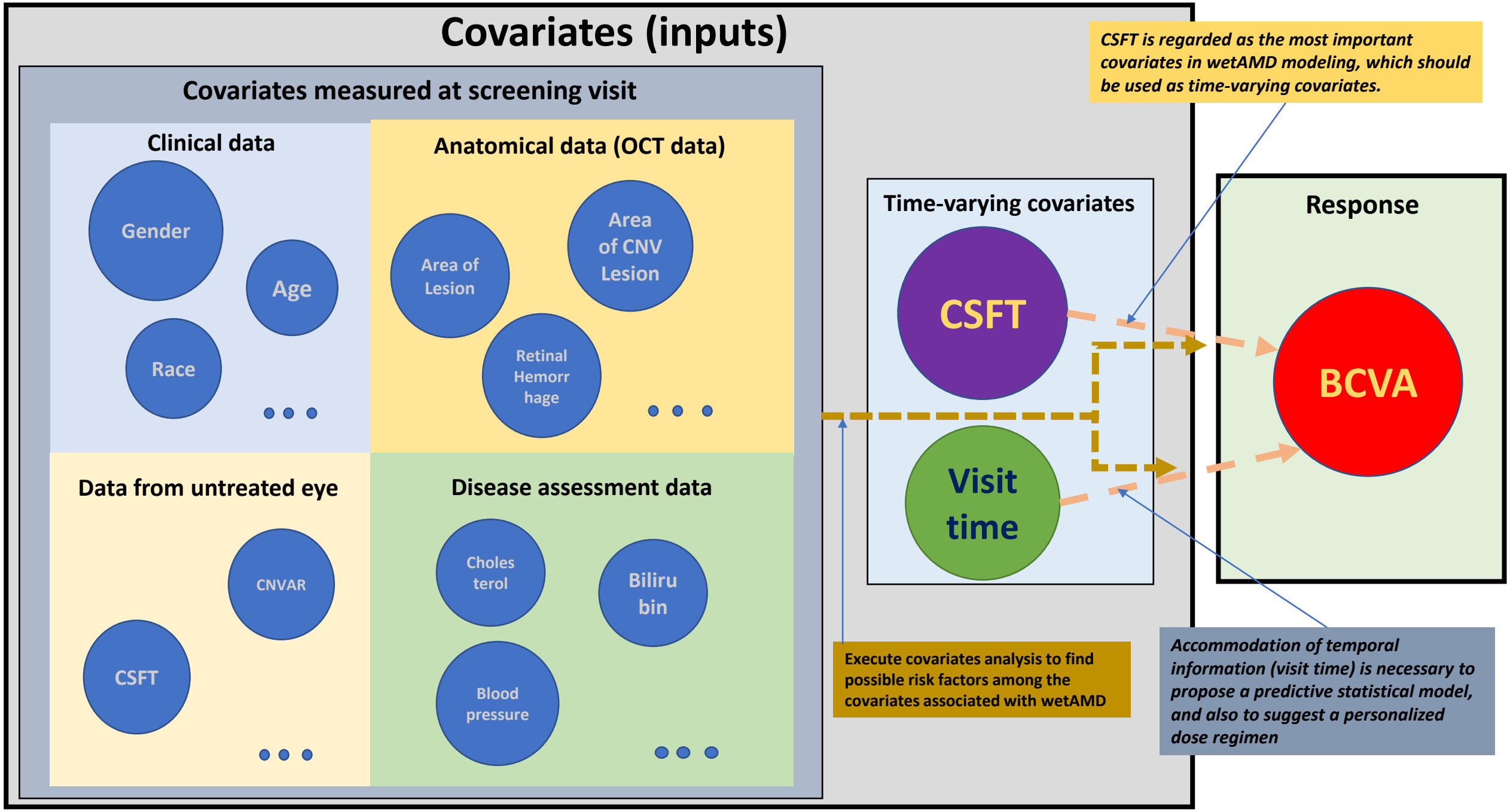
BCVA



CSFT



wetAMD dataset from the perspective of a model builder



Summaries of patients' data with wetAMD in HAWK and HARRIER

- **Data type**

1. **Unbalanced longitudinal data** (i.e., patients can have different number of visits.).
2. **Big data** (N ≈1,800 patients, the maximum number of visit M = 25, and number of predictors p=22)
3. **Known five sub-populations** (G_1, G_2, G_3, G_4, and G_5) that represent five treatment arms.

- **Data characteristics/challenges → Modeling Idea**

1. **Non-linear feature** of BCVA trajectory over time → Use a transformed time;
2. **A delayed outcome** of BCVA improvement → Use a lagged CSFT;
3. Presences of **heterogeneity** in BCVA/CSFT trajectories at individual-patient level & **clear patterns** in BCVA/CSFT trajectories at sub-population level

   → Use a hierarchical model (also called a population model or multi-level model)

Research outline

❖ **Primary goal:** Predict BCVA trajectory over the maintenance phase.

❖ **Secondary goal:** Identify possible risk factors for the wetAMD.

❖ **A proposed model: Bayesian Hierarchical Linear Model (BHLM)** **(Software is written in R; contact: seyoonlee@stat.tamu.edu)**

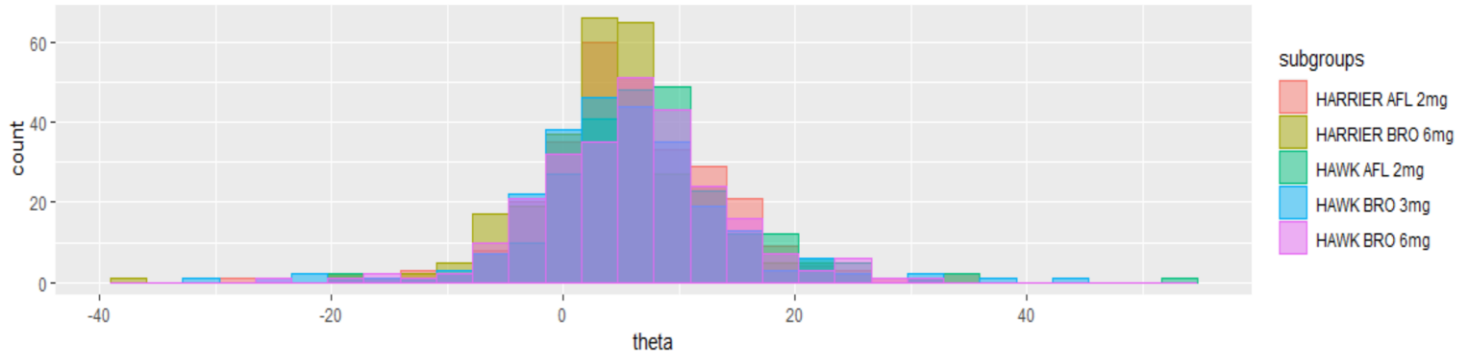
BHLM is a fully Bayesian version of two-stage linear mixed effect model with the Lindley-Smith form where

(i) on the first stage, the model describes the BCVA trajectory adjusted by the CSFT trajectory at the individual patient level;

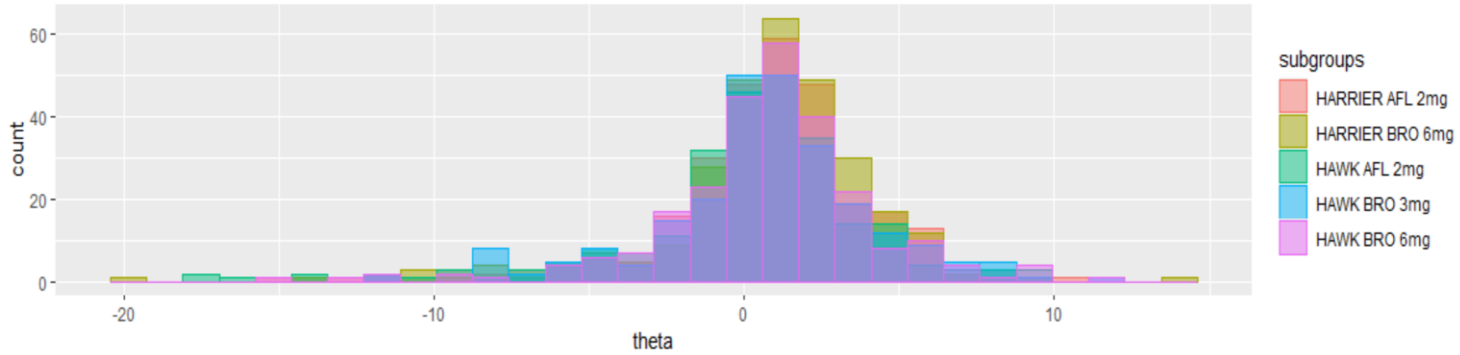
(ii) on the second stage, the model identifies possible risk factors for the wetAMD.

Result: Histograms of posterior means of individual-patient level parameters of BHLM

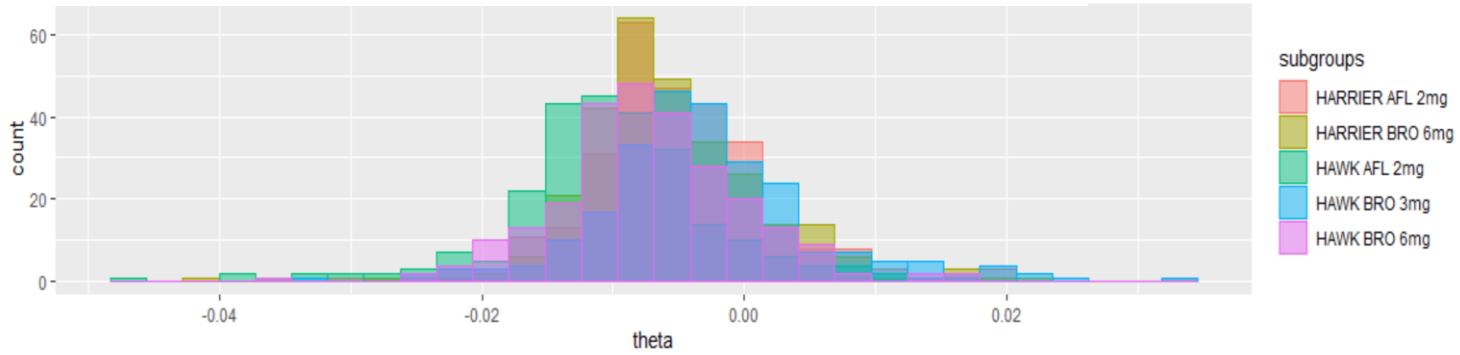
❖ Initial injection effect ($\theta_{1i},\ i = 1, \cdots, N$)



❖ VISIT effect ($\theta_{2i}\ ,\ i = 1, \cdots, N$)

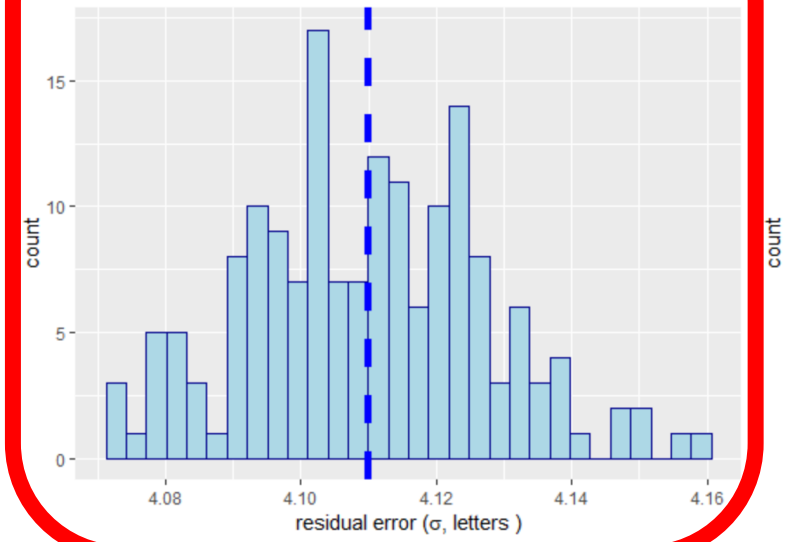


❖ CSFT effect ($\theta_{3i}\ ,\ i = 1, \cdots, N$)

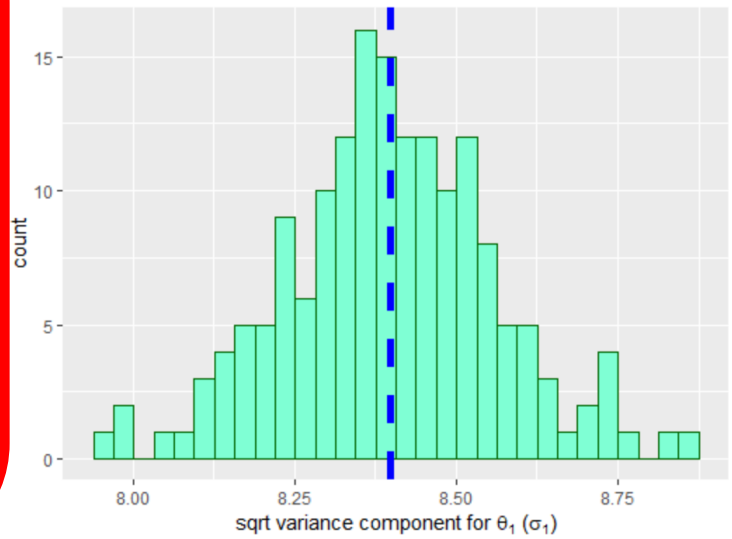


Result: Histograms of posterior samples for error terms used in the BHLM

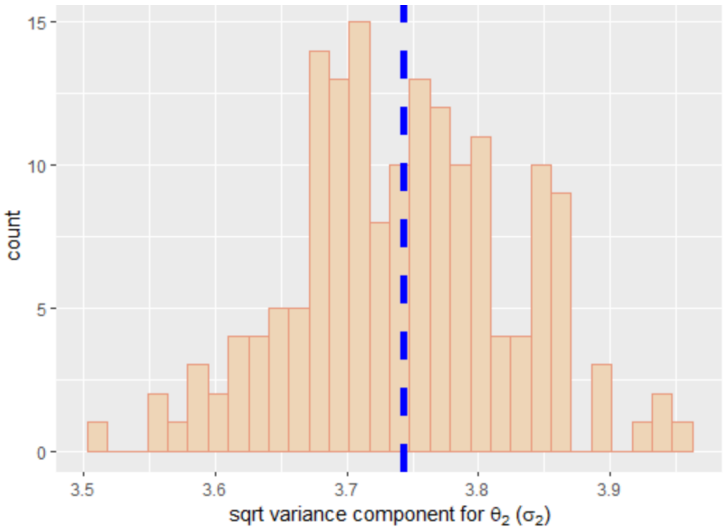
Residual error (σ)



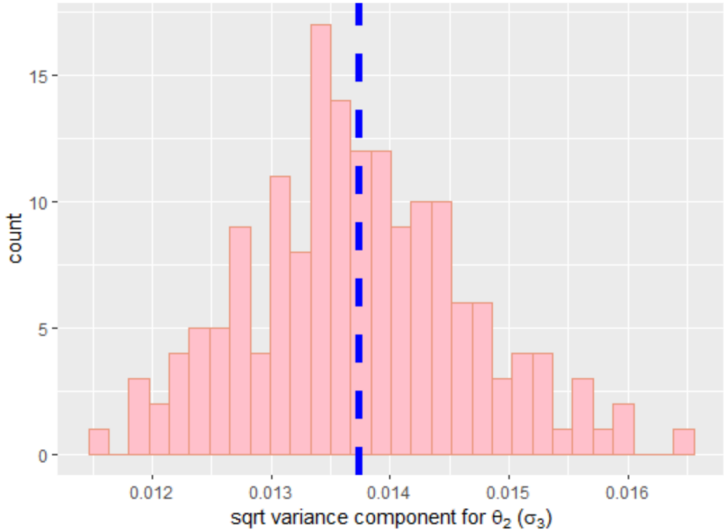
Sqrt Variance component for θ_1 (σ_1)



Sqrt Variance component for θ_2 (σ_2)



Sqrt Variance component for θ_3 (σ_3)



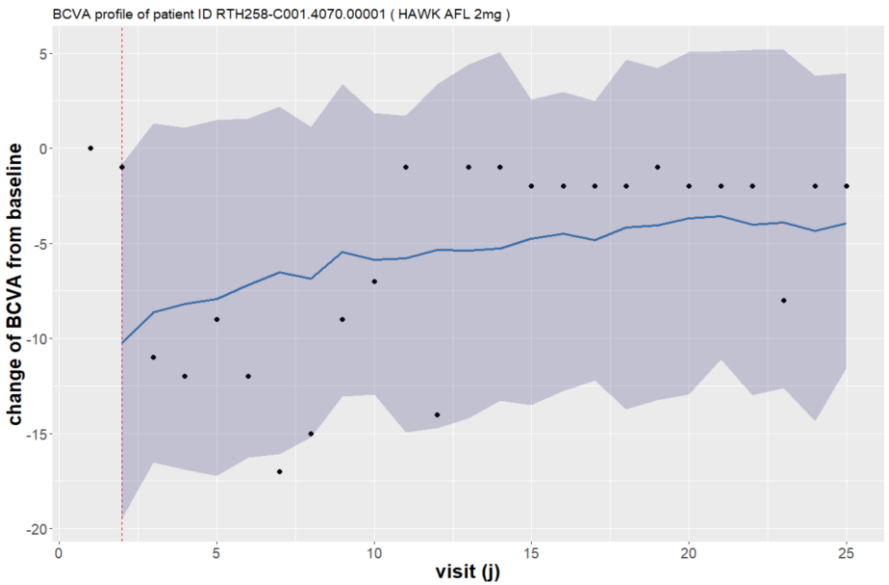
As a practical convention, in modeling involving BCVA trajectories from wetAMD patients' data, it is known that an estimate for the residual error $(\hat{\sigma})$ of a desirable model takes

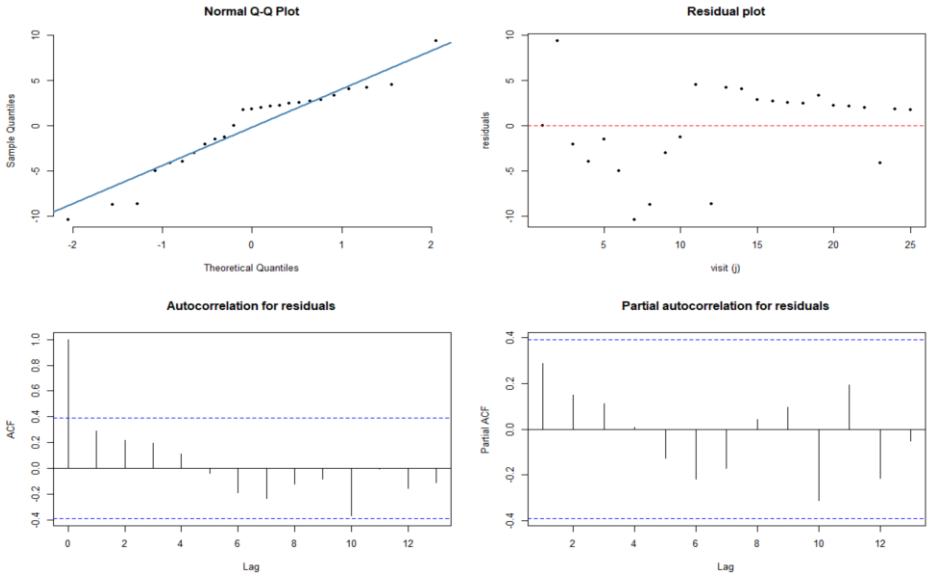
(a) a value between 4 and 5 letters $(4 \leq \hat{\sigma} \leq 5)$*;*
(b) and if it is closer to the 4, then it is regarded even better.

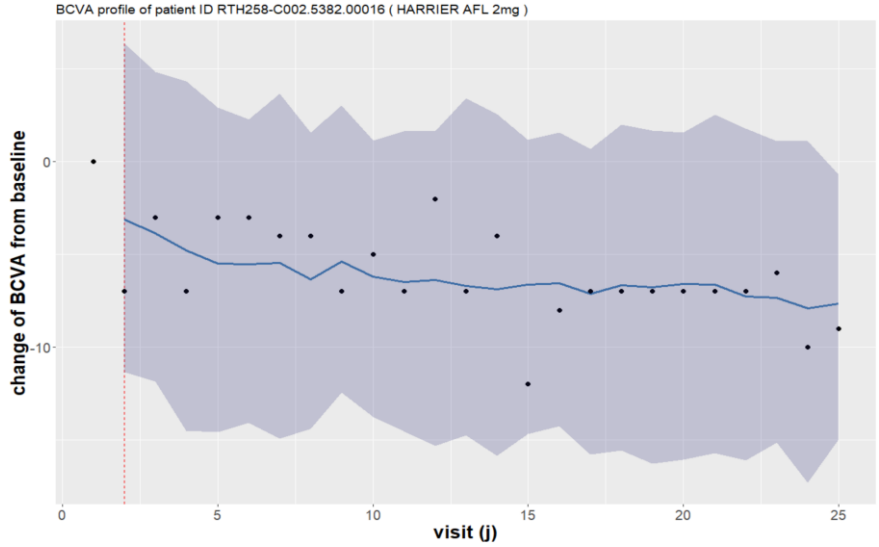
- **Result:** *the proposed model induces the posterior mean of the σ to be 4.11 letters* which means that the model retains a nice operating characteristics to explain the heterogeneity of BCVA trajectories across patients.

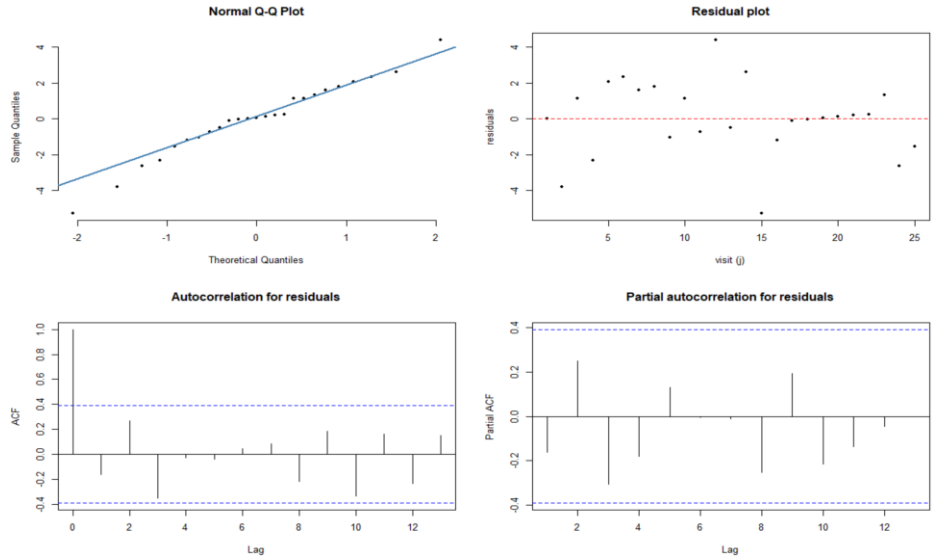
Result: diagnosis of model assumption (e.g., two patients)

- : observed BCVA trajectory — : Posterior mean of BCVA trajectory : 95% posterior credible interval



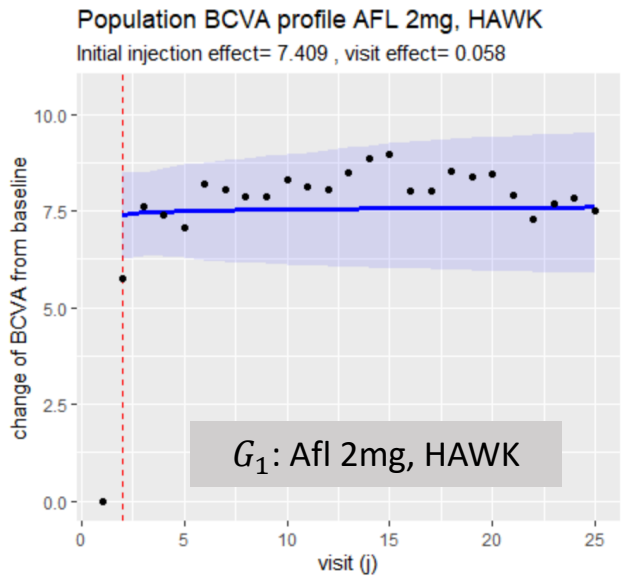


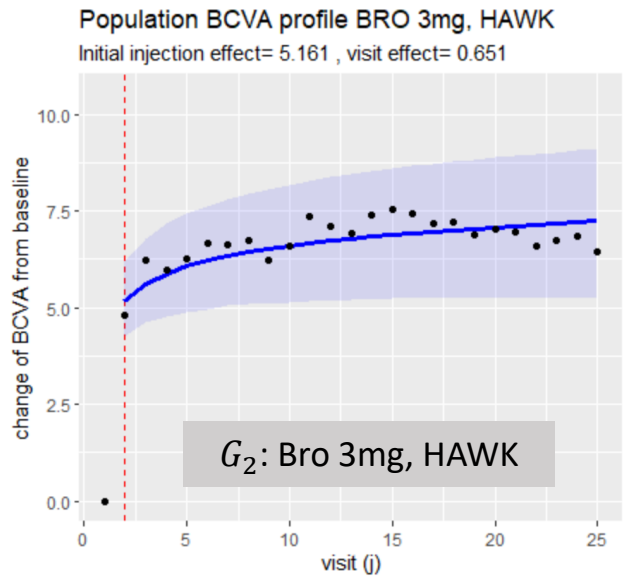


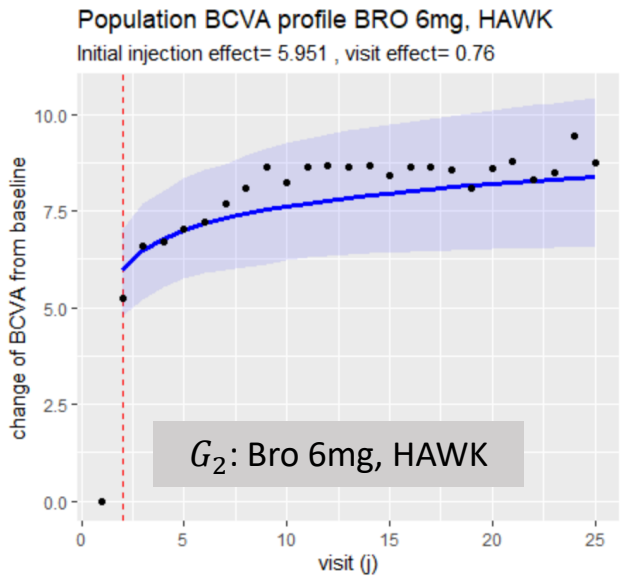


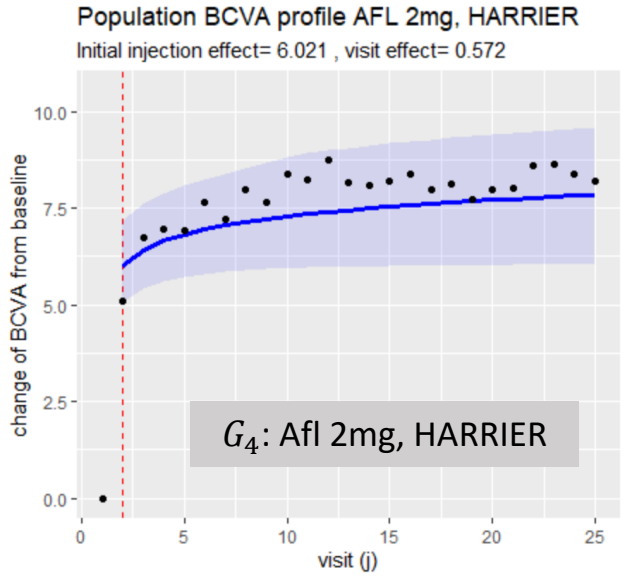
Result: Sub-population BCVA trajectories for the five treatment arms

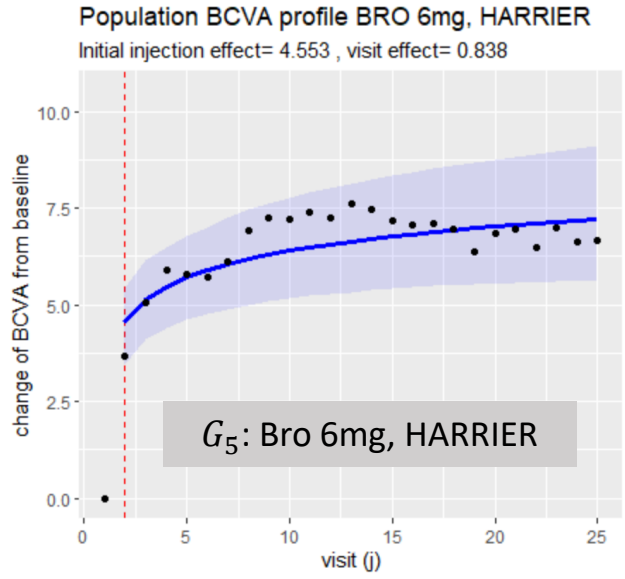
● : Cross-sectional mean of BCVA trajectory — : Posterior mean of BCVA trajectory (mean part) ▭ : 95% posterior credible interval





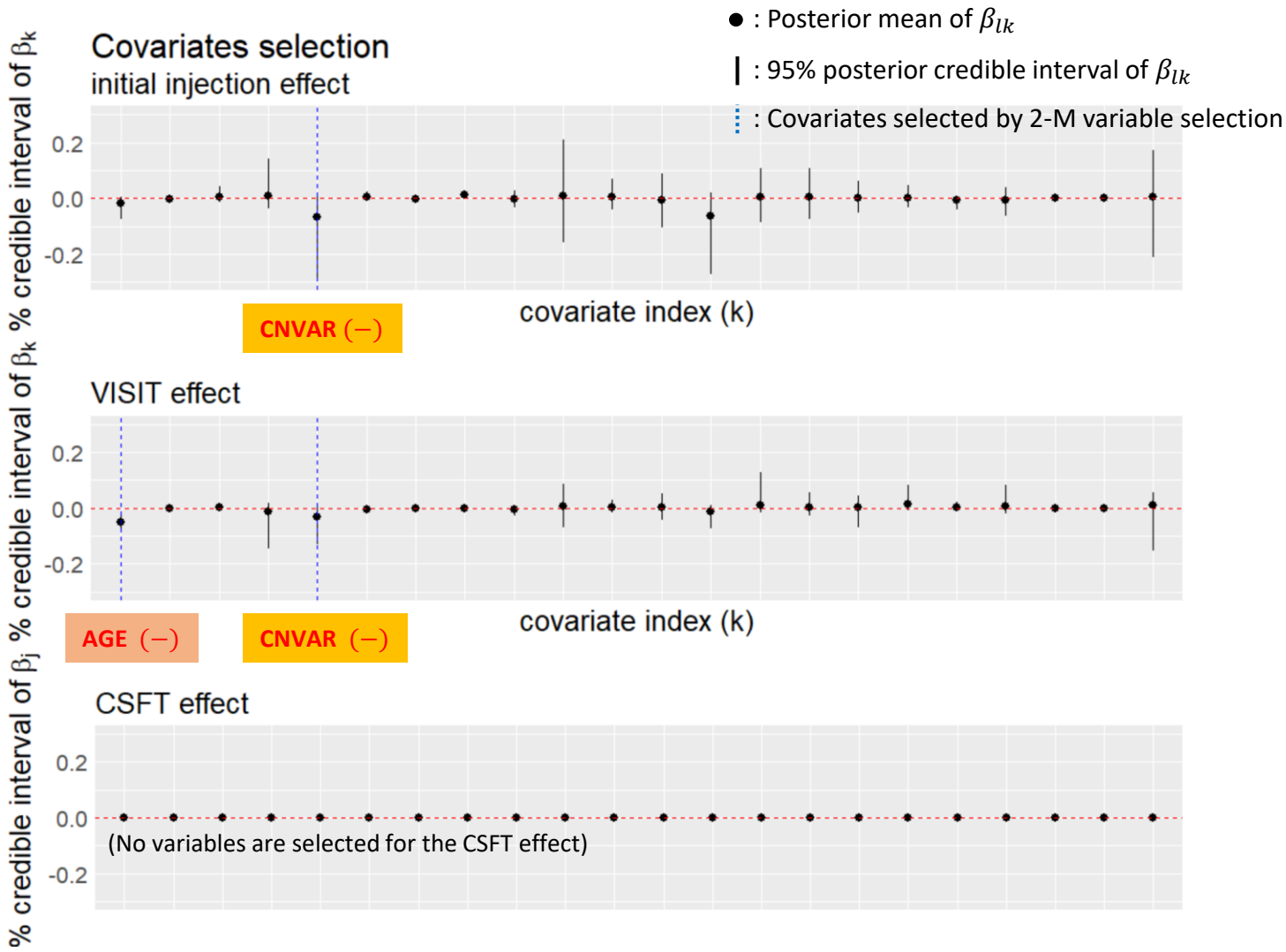






Result: Covariates analysis by the sparse horseshoe prior + 2-M variable selection (*Carvalho et al., 2010* / Li et al., 2017)

Index k	Covariates obtained at screening visit	Abbreviations
1	**Age**	**AGE**
2	Alkaline Phosphatase	ALP
3	Alkaline Aminotransferase	ALT
4	Cholesterol	CHOL
5	**Area of Choroidal Neovascularization Lesion**	**CNVAR**
6	Creatinine	CREAT
7	Central Subfield Thickness	CSFT
8	Central Subfield Thickness Neurosensory-Retina	CSFTNS
9	Diastolic Blood Pressure	DIABP
10	Evaluation of Vitreal Cells	EVALCELL
11	Glucose	GLUCC
12	Potassium	K
13	Area of Lesion	LESAR
14	Retinal Hemorrhage	RET_HEM
15	Retinal Hemorrhage Size	RETHEMSZ
16	Retinal Tear/Detachment	RETTRDT
17	Sodium	SODIUM
18	Systolic Blood Pressure	SYSBP
19	Area of CNV Lesion from untreated eye	untreated_eye CNVAR
20	Central Subfield Thickness from untreated eye	untreated_eye CSFT
21	Central Subfield Thickness Neurosensory-Retina from untreated eye	untreated_eye CSFTNS
22	Area of Lesion from untreated eye	untreated_eye LESAR



Summary:

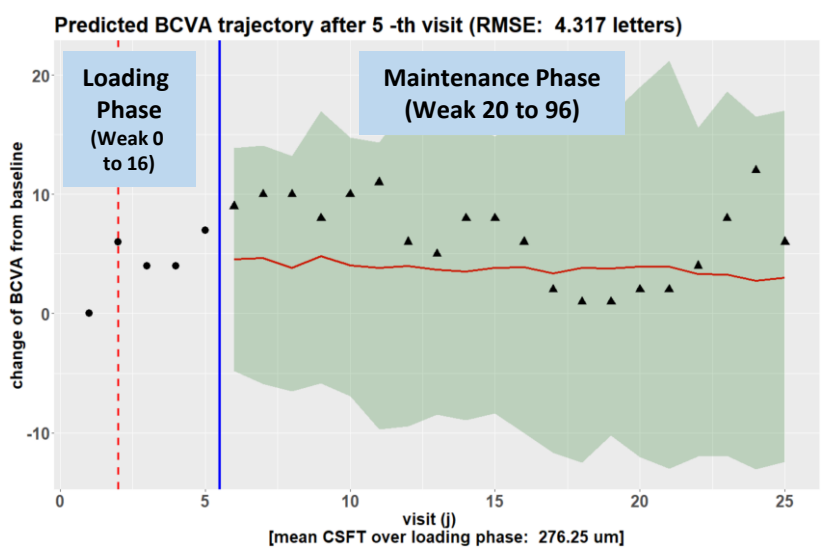
1. **An increase in Area of CNV Lesion deteriorates BCVA improvement during the entire course of study.**
2. **The older the wet-AMD patients, the lesser the patients get benefit from the anti-VEGF treatments.**

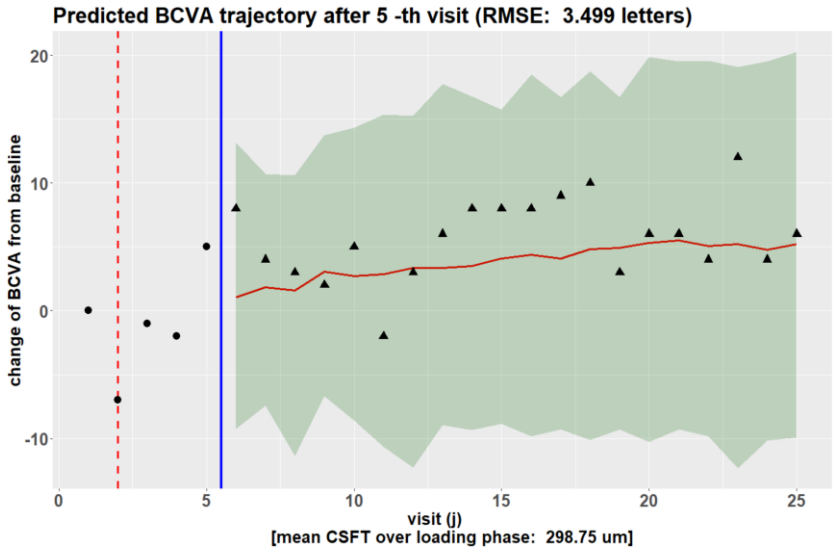
(●The obtained results are aligned with some published medical papers: see Domalpally et al (2008) and Ehrlich at al (2008))

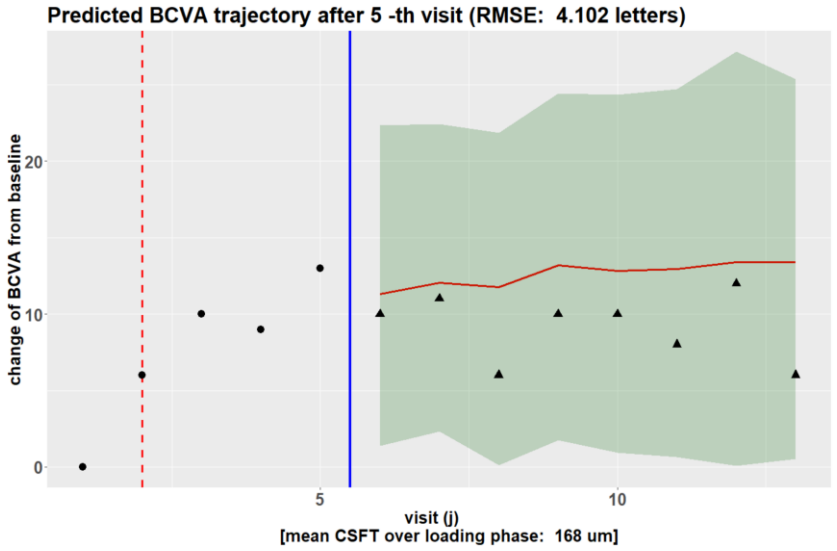
Result: Prediction of BCVA over maintenance phase, Week 20 to 96 (e.g., six patients)

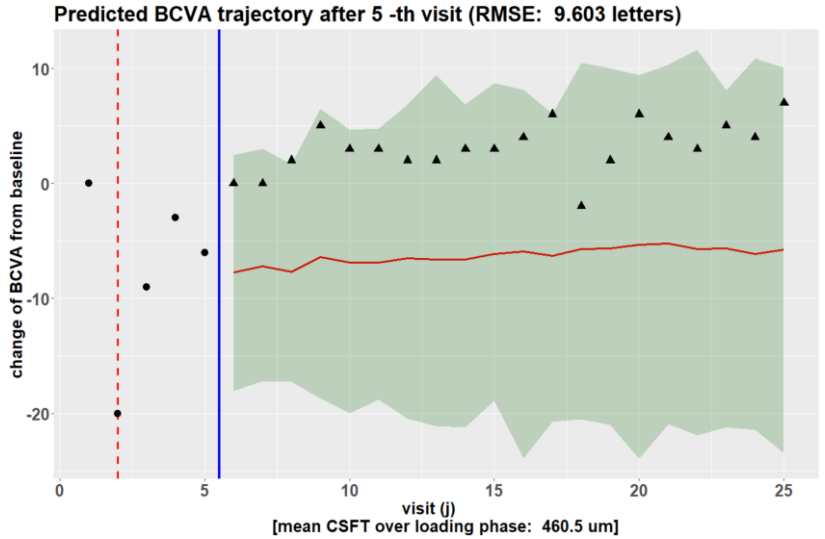
❖ Results obtained by dividing the full data with *Testing : Training data ratio = 3 : 7*

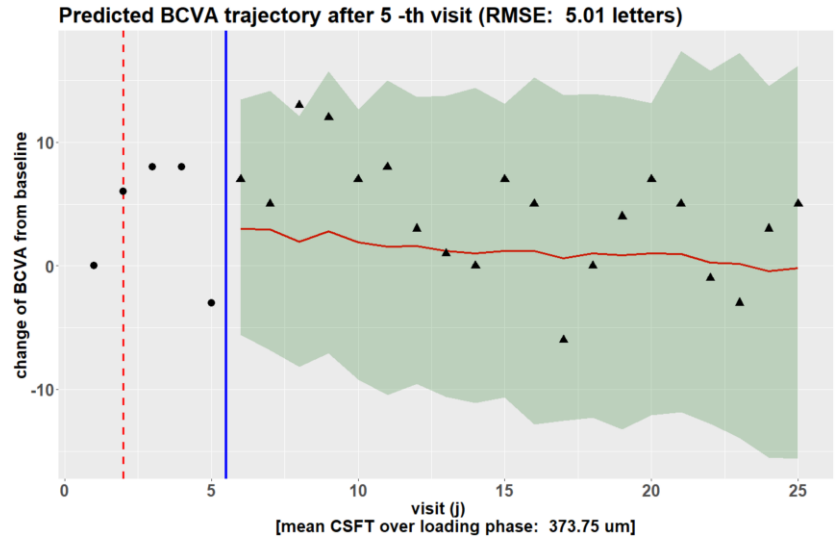
● : Training data for BCVA ▲ : Testing data for BCVA — : Posterior predictive mean of BCVA trajectory : 95% posterior predictive credible interval

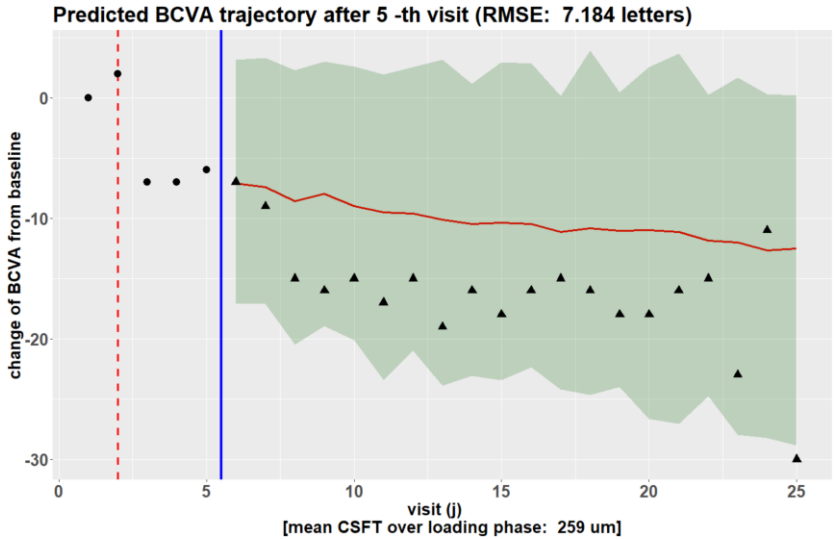












α: proportion testing patients among the all the data, K : number of visits for the testing patients (for e.g., K = 3,4,5 can be used), $\alpha = 0.3$, K = 5

References

Dugel, Pravin U., et al. "HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration." *Ophthalmology* 127.1 (2020): 72-84.

Lindley, Dennis V., and Adrian FM Smith. "Bayes estimates for the linear model." *Journal of the Royal Statistical Society: Series B (Methodological)* 34.1 (1972): 1-18.

Carvalho, Carlos M., Nicholas G. Polson, and James G. Scott. "The horseshoe estimator for sparse signals." *Biometrika* 97.2 (2010): 465-480.

Lee, Se Yoon, Bowen Lei, and Bani K. Mallick. "Estimation of COVID-19 spread curves integrating global data and borrowing information." *PLOS ONE* (2020).

Zhang, D., Lin, X., Raz, J. and Sowers, M., 1998. Semiparametric stochastic mixed models for longitudinal data. *Journal of the American Statistical Association*, *93*(442), pp.710-719.