Analysis of Task 2: Predictors of Response and Discontinuation

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1 Introduction

This section addresses Research Question 2 (Q2), focusing on identifying predictors of treatment response and discontinuation. We utilized the imputed dataset from Task 1 to fit Linear Mixed-Effects Models (LMM) for longitudinal trajectory analysis and Logistic Regression for discontinuation risk assessment.

2 Methodology: Linear Mixed-Effects Models (LMM)

2.1 Justification for Hierarchical Modeling

To assess the necessity of a hierarchical framework, we fitted an unconditional means model (Model 0) containing only a random intercept for `SUBJECT_ID`.

- **Result:** The model yielded an Intraclass Correlation Coefficient (ICC) of **0.426**.
- **Interpretation:** Approximately 42.6% of the variance in Monthly Migraine Days (MMDs) is attributable to differences *between* patients, rather than fluctuations within patients over time. This substantial between-subject variability validates the use of Mixed-Effects Models over standard linear regression [1].

2.2 Modeling Disease Trajectories

We analyzed the continuous variable `Time_Continuous` (Months 1–36) to estimate the linear rate of healing (Model 1).

- **Global Trend:** The fixed effect for `Time_Continuous` was estimated at -0.0006 ($p = 0.985$). Statistically, there is no significant linear reduction in MMDs over the 36-month period across the whole cohort.
- **Clinical Context:** This lack of linearity aligns with the "Sawtooth" pattern identified in Task 0. The therapeutic benefits gained during treatment cycles are statistically offset by the "rebound" effects during suspension periods, resulting in a flat linear trend over 3 years.
- **Random Slopes:** Comparing Model 1 (Random Slope) to Model 0 (Random Intercept only) revealed a significant improvement in fit ($\chi^2 = 72.86$, $p < 0.001$). This confirms that while the group average is stable, individual patient trajectories vary significantly.

2.3 Predictors of Response (Interaction Analysis)

We tested interaction terms (Time × Predictor) to identify baseline characteristics that modify the response trajectory.

- **Age Effect:** The interaction `Time_Continuous:AGE` was significant (Estimate: +0.0079, $p = 0.016$). The positive coefficient indicates that older age is associated with a flatter (less negative) slope. Younger patients exhibit more dynamic response trajectories compared to the more stable profiles of older subjects.
- **Null Findings:** No significant interactions were found for `ANTIBODY` type ($p > 0.05$) or `DIAGNOSIS` ($p > 0.05$). This suggests comparable efficacy profiles across the three drug classes (Erenumab, Galcanezumab, Fremanezumab) in this cohort.

2.4 Temporal Granularity: Cycle Analysis

To assess "step-change" improvements, we modeled `CYCLE` as a categorical factor.

- **Result:** No significant differences in MMD reduction were found between Cycle 1, Cycle 2 ($p = 0.294$), and Cycle 3 ($p = 0.269$).
- **Conclusion:** Clinical benefit is maintained rather than progressively accumulated, likely due to the mandatory suspension periods preventing compounding improvement.

3 Analysis of Discontinuation (Dropout)

3.1 Logistic Regression Results

We analyzed predictors of dropout (`Suspension`: 0 = Completed, 1 = Discontinued) using baseline demographics.

- **Results:** None of the tested covariates reached statistical significance:
  - Age ($p = 0.798$)
  - Sex ($p = 0.573$)
  - Diagnosis ($p = 0.553$)
  - BMI ($p = 0.348$)
- **Interpretation:** Discontinuation appears stochastic rather than systematic. It is not driven by disease severity or demographics, suggesting unmeasured factors (e.g., side effects, logistic barriers) are the primary drivers of attrition.

4 Key Takeaways

1. **Trajectory Complexity:** The non-significant linear time slope ($p = 0.985$) confirms that the "Sawtooth" pattern dominates the longitudinal profile. Treatment provides relief during administration but does not fundamentally alter the disease course over time.

2. **Age as a Moderator:** Age is the only significant predictor of response trajectory ($p = 0.016$), with younger patients showing distinct response dynamics.

3. **Unpredictable Dropout:** Retention cannot be predicted by standard baseline demographics, implying that adherence strategies must be applied universally rather than targeted at specific groups.

References

[1] Project Schema 2025-26: Medical Application and Healthcare Module.