Literature Data Requirements for Simulation Parameters

This document outlines the specific data needed from literature to inform realistic parameters for our DES and ABS simulation models of AMD treatment.

Disease State Parameters

1. Disease State Distribution

- **Prevalence at diagnosis**: Proportion of newly diagnosed AMD patients in each state (NAIVE, STABLE, ACTIVE, HIGHLY_ACTIVE)
- **Natural history**: Distribution of disease states in untreated populations over time
- **Key sources**: Population-based epidemiological studies, natural history cohorts

2. State Transition Probabilities

- **Baseline transitions**: Monthly/weekly probability of transitioning between states without treatment
    - NAIVE → STABLE, ACTIVE, HIGHLY_ACTIVE
    - STABLE → ACTIVE, HIGHLY_ACTIVE
    - ACTIVE → STABLE, HIGHLY_ACTIVE
    - HIGHLY_ACTIVE → STABLE, ACTIVE
- **Treatment-modified transitions**: How anti-VEGF injections modify these probabilities
- **Time-dependent factors**: How transition probabilities change with disease duration
- **Key sources**: CATT, IVAN, VIEW trials; long-term follow-up studies (SEVEN-UP, HORIZON)

Vision Change Parameters

3. Treatment Response Data

- **Baseline vision changes**: Mean and standard deviation of letter changes for each disease state:
    - With injection: Currently modeled as normal distributions
        - NAIVE: [5, 1] (mean, std dev)
        - STABLE: [1, 0.5]
        - ACTIVE: [3, 1]
        - HIGHLY_ACTIVE: [2, 1]
    - Without injection:
        - NAIVE: [0, 0.5]
        - STABLE: [-0.5, 0.5]
        - ACTIVE: [-2, 1]
        - HIGHLY_ACTIVE: [-3, 1]
- **Response variability**: Patient-to-patient variation in treatment response
- **Key sources**: Pivotal anti-VEGF trials, real-world registries (FRB!, LUMINOUS)

4. Time-Dependent Factors

- **Treatment waning**: Rate at which treatment effect diminishes over time
    - Currently modeled as: time_factor = 1 + (weeks_since_injection / max_weeks)
    - Need data on: Optimal value for max_weeks (currently 52)
- **Cumulative effects**: How repeated injections affect long-term outcomes
- **Key sources**: Treat-and-extend studies, long-term extension trials

5. Ceiling Effects

- **Maximum vision**: Realistic ceiling for vision improvement (currently 100 letters)
- **Diminishing returns**: How improvement potential changes with baseline vision
    - Currently modeled as: ceiling_factor = 1 - (current_vision / max_vision)
- **Key sources**: Post-hoc analyses of clinical trials, stratified by baseline VA

6. Measurement Variability

- **Test-retest reliability**: Standard deviation of ETDRS letter score measurements
    - Currently modeled as: measurement_noise = [0, 0.5]
- **Key sources**: Clinical measurement studies, control groups in trials

Clinical Practice Parameters

7. Resource Constraints

- **Clinic capacity**: Realistic patient throughput per day (currently 20)
- **Scheduling patterns**: Distribution of clinic days (currently 5 days/week)
- **Wait times**: Typical wait times for new and follow-up appointments
- **Key sources**: Health services research, clinic workflow studies, national audits

8. Patient Flow

- **Arrival patterns**: Rate of new patient referrals (currently 1/week)
- **Discontinuation rates**: Probability of treatment discontinuation by visit number
- **Adherence patterns**: Missed appointment rates and patterns
- **Key sources**: Electronic health record studies, registry data

9. Treatment Protocols

- **Protocol adherence**: How closely clinicians follow official protocols
- **Protocol variations**: Common modifications to standard protocols
- **Decision thresholds**: Vision/OCT thresholds used for treatment decisions
- **Key sources**: Clinical practice surveys, adherence studies, chart reviews

Population Characteristics

10. Demographic Data

- **Age distribution**: Age range and distribution of AMD patients
- **Gender distribution**: Proportion of male/female patients

- **Comorbidity profiles**: Prevalence of relevant comorbidities
- **Key sources**: National eye disease registries, population-based studies

11. Baseline Values

- **Initial vision**: Distribution of baseline visual acuity (mean, SD)
    - Currently using normal distribution with configurable parameters
- **Disease duration**: Time from symptom onset to treatment initiation
- **OCT characteristics**: Distribution of baseline anatomical features
- **Key sources**: Baseline characteristics from clinical trials, registry data

Specific Literature Sources

Clinical Trials

1. **VIEW 1 & 2**: Aflibercept efficacy and safety
2. **HARBOR**: Ranibizumab dosing study
3. **CATT/IVAN**: Comparative effectiveness trials
4. **SEVEN-UP/HORIZON**: Long-term outcomes
5. **Protocol T**: Comparative effectiveness in DME (methodology relevant)

Real-World Evidence

1. **Fight Retinal Blindness! Registry**: Large dataset from Australia/New Zealand
2. **LUMINOUS**: Global observational study of ranibizumab
3. **IRIS Registry**: US-based ophthalmology registry
4. **UK AMD Database**: National dataset from UK
5. **AURA Study**: European real-world outcomes study

Health Services Research

1. **Clinic capacity studies**: Workflow and throughput analyses
2. **Healthcare utilization patterns**: Visit frequency and resource use
3. **Adherence and discontinuation studies**: Patterns of care interruption

Implementation Strategy

Priority Data Elements

1. **Highest priority**:
    - Disease state transition probabilities
    - Vision change distributions by disease state
    - Treatment waning parameters
2. **Secondary priority**:
    - Patient arrival and discontinuation rates
    - Measurement variability
    - Ceiling effects
3. **Tertiary priority**:
    - Demographic distributions
    - Comorbidity effects
    - Protocol variations

Data Extraction Approach

1. **Systematic literature review**:
    - Focus on meta-analyses where available
    - Extract numerical parameters with confidence intervals
    - Document assumptions and limitations
2. **Parameter estimation**:
    - Use Bayesian methods to combine multiple sources
    - Develop plausible ranges for sensitivity analysis
    - Document derivation methods for each parameter
3. **Validation strategy**:
    - Compare simulation outputs to published outcomes
    - Calibrate parameters to match real-world patterns
    - Document validation process and results

Documentation Requirements

For each parameter set derived from literature:

1. **Source documentation**:
    - Full citation of primary sources
    - Sample size and study characteristics
    - Quality assessment of evidence
2. **Parameter documentation**:
    - Central estimate and uncertainty range
    - Transformation methods (if applicable)
    - Implementation details in simulation
3. **Validation documentation**:
    - Comparison of simulation outputs to reference data
    - Sensitivity analysis results
    - Known limitations and assumptions

Appendix: Parameter Mapping to Simulation

Parameter Category	YAML Configuration Path	Current Default	S
Disease States	clinical_model.disease_states	["NAIVE", "STABLE", "ACTIVE", "HIGHLY_ACTIVE"]	[c s
Initial Distribution	clinical_model.initial_phase_transitions	HIGHLY_ACTIVE: 0.01	E s
State Transitions	clinical_model.transition_probabilities	Various (see config)	M s t
Vision Change (with injection)	clinical_model.vision_change.base_change.*.injection	Various by state	C r
Vision Change (no injection)	clinical_model.vision_change.base_change.*.no_injection	Various by state	M p

Parameter Category	YAML Configuration Path	Current Default	S
Time Factor	clinical_model.vision_change.time_factor.max_weeks	52	F s
Ceiling Factor	clinical_model.vision_change.ceiling_factor.max_vision	100	C r s
Measurement Noise	clinical_model.vision_change.measurement_noise	[0, 0.5]	T r
Clinic Capacity	simulation.scheduling.daily_capacity	20	H r
Clinic Schedule	simulation.scheduling.days_per_week	5	F s
Patient Generation	simulation.patient_generation.rate_per_week	1	E s c