TEMPORALBIO™
4D RESEARCH FRAMEWORK

The Temporal Biology Operating System

A Framework for Time-Aware Research Design

WHITE PAPER

Scientari LLC | January 2026

Important Notice Regarding Framework Validation

The TRS scoring examples and validation analyses presented in this white paper are currently hypothetical, designed to illustrate the framework's methodology and potential applications.

Scientari LLC is actively developing a comprehensive TRS Agent product that will enable systematic, reproducible scoring of research protocols and published studies.

The final version of this white paper will include analyses of 500 peer-reviewed papers using our validated TRS Agent, along with complete methodological documentation, inter-rater reliability metrics, and a full list of scored papers with transparent scoring rationales. See Appendix B for our paper selection methodology designed to minimize selection bias.

Executive Summary

Biology doesn’t happen in snapshots—it unfolds through time. Yet most research and clinical studies measure biological processes at arbitrary timepoints, missing critical windows of therapeutic opportunity and generating data that fails to capture the dynamic nature of disease and treatment response.

The Temporal Biology Operating System introduces a systematic framework for aligning experimental design with the temporal architecture of biological processes. Through the T0-T6 Ontology and Temporal Readiness Score (TRS) methodology, researchers can design studies that capture causality, predict therapeutic windows, and prevent costly failures caused by temporal misalignment.

Key Benefits by Stakeholder

- **Pharma/Biotech R&D:** De-risk $10M+ Phase 2 trials by identifying temporal design flaws before patient enrollment
- **Academic Researchers:** Increase grant competitiveness with TRS-validated temporal study designs (TRS ≥25 typically indicates competitive temporal design)
- **Diagnostic Companies:** Identify the "Goldilocks Zone"—the optimal measurement window for maximum clinical utility and commercial value
- **Clinical Scientists:** Translate complex longitudinal data into actionable treatment decisions through temporal trajectory mapping

This white paper presents the core framework and demonstrates practical applications across oncology, immunotherapy, metabolic disease, and precision medicine.

1. The Problem: Biology's Missing Dimension

1.1 The Static Snapshot Paradigm

Current research approaches biological questions by taking measurements at convenient or traditional timepoints:

- **Drug development trials:** Measure tumor response at 8 weeks "because that's what we've always done"
- **Diagnostic assays:** Sample at 6-month intervals based on patient visit schedules
- **Academic studies:** Sacrifice animals at predetermined timepoints based on historical precedent
- **Clinical monitoring:** Order labs on monthly cycles driven by healthcare system logistics

Result: Significant resources are spent annually on clinical trials that miss early response signals, diagnostic tests administered after therapeutic windows close, and published studies with conclusions potentially undermined by temporal gaps.

1.2 The Causality Problem

Without proper temporal resolution, researchers face challenges in:

- **Distinguishing cause from correlation:** Does protein X activate before or after disease progression?
- **Identifying mechanism of action:** When does the drug actually engage its target?
- **Predicting clinical outcomes:** Which early signals forecast long-term response?
- **Optimizing intervention timing:** When does the reversible to irreversible transition occur?

Illustrative Case: Checkpoint Inhibitor Development

Consider a pharmaceutical company measuring tumor size at Week 8 to assess checkpoint inhibitor response. The trial shows limited efficacy, but the actual problem lies in measurement timing: the mechanism operates at Week 2 (T-cell activation and infiltration), while measurement occurred at Week 8 (tumor size change). Non-responders could potentially have been identified 6 weeks earlier with proper temporal design.[1]

2. The Temporal Biology Operating System

2.1 The T0-T6 Ontology: Biology's Natural Timescales

The temporal framework organizes biological processes across seven fundamental timescales, from molecular interactions to population-level changes.[2]

T0: Molecular Kinetics (Milliseconds to Seconds)

Biological Processes: Protein-protein binding and unbinding, ion channel gating, enzyme catalysis, drug-target engagement

Representative Technologies: Surface plasmon resonance (SPR), patch-clamp electrophysiology, single-molecule fluorescence

Critical Application: Target engagement assays must measure within seconds to minutes post-dosing to capture peak target occupancy.[3]

T1: Cellular Signaling (Minutes to Hours)

Biological Processes: Phosphorylation cascades (MAPK, PI3K/AKT), calcium waves, immediate-early gene transcription

Representative Technologies: Flow cytometry (phospho-flow), live-cell imaging, Western blotting

Critical Application: Pathway inhibitor studies typically require 15-60 minute post-treatment sampling.[4]

T2: Gene Expression (Hours to Days)

Biological Processes: Transcriptional response to stimuli, interferon response cascades, cell cycle checkpoint activation

Representative Technologies: Bulk RNA-seq, single-cell RNA-seq, spatial transcriptomics, qPCR panels

Critical Application: Measuring T-cell activation transcriptional signatures at 24-72 hours can provide early predictive information.[5]

T3: Tissue Remodeling (Days to Weeks)

Biological Processes: Immune cell infiltration, angiogenesis, ECM remodeling, tumor microenvironment evolution

Representative Technologies: Spatial transcriptomics, multiplexed immunofluorescence, mass cytometry imaging

State-Shift Concept: The transition from reversible to irreversible tissue states represents a critical measurement window.[6]

T4: Organ-Level Adaptation (Weeks to Months)

Biological Processes: Tumor growth/regression dynamics, cardiac remodeling, liver regeneration

Representative Technologies: MRI/CT imaging with volumetric analysis, ultrasound, PET imaging

Critical Application: RECIST tumor measurements operate at T4 scale but typically lag mechanistic changes by weeks.[8]

T5: Chronic Disease & Resistance (Months to Years)

Biological Processes: Metabolic syndrome progression, cancer resistance evolution, neurodegenerative protein aggregation

Representative Technologies: ctDNA longitudinal tracking, epigenetic aging clocks, longitudinal proteomics

Critical Application: ctDNA monitoring can detect molecular changes months before radiographic progression.[9]

T6: Population Dynamics (Years to Decades)

Biological Processes: Longitudinal cohort aging trajectories, pharmacogenomic response stratification

Representative Technologies: Biobank longitudinal studies (UK Biobank, All of Us), polygenic risk scores

Critical Application: Mendelian randomization at T6 scale provides supporting evidence for drug effects.[10]

2.2 Why Seven Timescales Matter

Each transition represents a potential causal link. Measuring only at higher timescales (T4-T6) can obscure mechanistic causality:

Transition	Mechanism	Example
T0 → T1	Molecular binding triggers signaling	Drug-receptor binding activates MAPK
T1 → T2	Signaling activates transcription	NFκB drives cytokine genes
T2 → T3	Gene expression recruits cells	Chemokines recruit immune infiltration

T3 → T4	Cellular changes alter tissue	Immune attack affects tumor architecture
T4 → T5	Repeated insults create chronic states	Repeated injury leads to fibrosis
T5 → T6	Chronic states stratify populations	Genetic variants influence progression

3. The Temporal Readiness Score (TRS)

3.1 What is TRS?

The Temporal Readiness Score (TRS) is a quantitative framework (0-40 scale) for evaluating whether a study design captures the temporal architecture of the biological question being investigated.

TRS addresses four fundamental questions:

- **Temporal Alignment (0-10 points):** Do measurement timepoints match biological phases?
- **Temporal Coverage (0-10 points):** Are measurements spanning relevant T-scales?
- **Temporal Extensibility (0-10 points):** Can individual trajectories be modeled?
- **Diagnostic Velocity (0-10 points):** Does the design capture rate-of-change?

3.2 Component 1: Temporal Alignment

Question: Do timepoints match the biological phases of the process?

Scoring Anchors

Points	Criterion	Example
0	No alignment with biological phases	Single arbitrary endpoint
3	Captures baseline only	Baseline + single late measurement
6	Captures baseline + peak OR resolution	Day 0 + Day 7 peak measurement
9	Captures baseline + peak + resolution	Day 0, Day 3 peak, Day 14 resolution
10	Full alignment including transitions	Day 0, 1, 3, 7, 14 with rationale

3.3 Component 2: Temporal Coverage

Question: Are measurements spanning multiple T-scales to capture mechanism?

Scoring Anchors

Points	Criterion	Example
0	Single T-scale only	Tumor size measurements only (T4)
3	Two T-scales, no transition captured	Gene expression + tumor size, unlinked
6	Multiple T-scales with some transitions	T1 signaling + T3 tissue changes

9	Comprehensive multi-scale with transitions	T1 → T2 → T3 cascade with timing
10	Full mechanistic cascade to outcome	Target engagement through endpoint

3.4 Component 3: Temporal Extensibility

Question: Can the study design support individual trajectory modeling?

Scoring Anchors

Points	Criterion	Example
0	Pooled group data only	Group means at each timepoint
3	Individual data but insufficient (<4 pts)	Per-patient data at 3 timepoints
6	Individual trajectories with 4-6 timepoints	Per-patient sampling at 5 timepoints
9	Rich individual data (≥7 pts) enabling modeling	Dense longitudinal sampling
10	Full trajectory modeling with change-point	Individual curves with slope analysis

3.5 Component 4: Diagnostic Velocity

Question: Does the design capture rate-of-change and state-shift detection?

Scoring Anchors

Points	Criterion	Example
0	No rate metrics, static thresholds only	Single ctDNA level measurement
3	Some rate capability but limited density	Two measurements enabling basic slope
6	Rate metrics with moderate density	Quarterly sampling with doubling time
9	Strong velocity + Goldilocks Zone ID	Dense sampling around transition window
10	Full velocity + multi-scale correlation	Rate predicts outcome months ahead

The Goldilocks Zone: The optimal measurement window where biological signals are detectable AND intervention is still feasible.

3.6 TRS Interpretation Scale

TRS Range	Interpretation	Typical Characteristics
35-40	Paradigm-shifting	Exceptional temporal design, high-impact
30-34	Excellent	Strong coverage, competitive for grants
25-29	Good	Solid design, adequate for most conclusions
20-24	Adequate	Acceptable but with opportunities
15-19	Marginal	Significant gaps may limit insights
<15	High Risk	Major temporal design limitations

Important Note: A TRS of 25 represents competitive temporal design. Scores above 30 often represent temporal innovations.

4. Framework Validation: Analysis of Published Research

Note: The following validation analyses are illustrative examples demonstrating how TRS methodology will be applied. The final version will include comprehensive analyses of 500 papers with full methodological documentation. See Appendix B for our unbiased paper selection methodology.

4.1 Methodology

To validate that temporal design correlates with research quality and impact, we are conducting a systematic analysis of published longitudinal studies from major scientific journals.

Analysis Scope (Planned): 500 papers selected using stratified random sampling from Nature, Cell, Science, and related journals (2020-2024), scored by multiple independent raters.

Inclusion Criteria: Longitudinal studies with ≥3 timepoints, multi-omics or systems biology approaches

4.2 Anticipated Findings

Anticipated Finding 1: Temporal Design Varies Significantly

We expect substantial variation in temporal design quality, with the majority of papers scoring below the TRS ≥25 competitive threshold.

Anticipated Finding 2: Common Temporal Design Limitations

Design Limitation	Expected Frequency	TRS Impact
Missing early timepoints (<24h)	60-80%	-5 to -8 points
No intermediate sampling (>2 weeks gap)	50-70%	-4 to -6 points
Single-scale measurements (T4 only)	40-60%	-8 to -12 points
Pooled data without individual trajectories	50-65%	-6 to -8 points
No velocity/rate metrics	75-90%	-3 to -6 points

Significance: These limitations are often addressable by adding 2-3 strategic timepoints, improving TRS by 10-15 points.

4.3 Illustrative Case Studies

Case Study 1: High-TRS Immunotherapy Study (Hypothetical TRS 38/40)

Study Design Elements:

- T1 (1-6h): Phospho-STAT1 in CD8+ T-cells
- T2 (24-72h): Cytokine gene expression profiling

- T3 (Weeks 1, 2, 4): Spatial transcriptomics of tumor biopsies
- T4 (Weeks 4, 8, 12): Tumor volume by CT

TRS Breakdown: Alignment: 10/10 | Coverage: 10/10 | Extensibility: 9/10 | Velocity: 9/10

Case Study 2: Moderate-TRS Metabolic Study (Hypothetical TRS 19/40)

Study Design: Annual blood draws for 5 years with metabolomic profiling

TRS Breakdown: Alignment: 6/10 | Coverage: 7/10 | Extensibility: 6/10 | Velocity: 0/10

Design Limitation: The pre-diabetes to diabetes transition often occurs over 3-6 months, but annual sampling misses this critical window.

5. Practical Applications: Before and After Temporal Redesign

These hypothetical scenarios illustrate how TRS-guided temporal redesign could transform study outcomes.

5.1 Pharma Vignette: Phase 2 IO Trial Rescue

Scenario: Anti-PD-1 Combination Trial

Original Design (TRS 14/40):

- Primary endpoint: RECIST response at Week 12
- Biomarker: PD-L1 at baseline only
- Problem: 70% of patients complete 12 weeks before being classified as non-responders

TRS Analysis Identified:

- Temporal Alignment: 4/10 — Missing mechanistic window (Weeks 1-3)
- Temporal Coverage: 3/10 — T4 only, no T1-T3 mechanistic data
- Diagnostic Velocity: 3/10 — No early response dynamics captured

Redesigned Protocol (TRS 32/40):

- Added: Peripheral T-cell activation (phospho-flow) at Days 1, 3, 7
- Added: Circulating cytokine panel at Days 3, 7, 14, 28
- Added: Optional Week 2 tumor biopsy for TIL assessment
- Modified: Adaptive design with Week 4 interim for early switching

Potential Impact: Early non-responder identification could reduce per-patient costs by $50K-100K while enabling earlier access to alternative therapies.

5.2 Diagnostics Vignette: ctDNA Monitoring Optimization

Scenario: Post-Surgical Recurrence Monitoring

Original Concept (TRS 12/40):

- Single ctDNA measurement at 6-month follow-up visits
- Binary threshold: Detectable vs. Undetectable
- Problem: By the time ctDNA is detectable, imaging often shows established recurrence

Redesigned Strategy (TRS 28/40):

- Monthly ctDNA sampling for first 6 months, then quarterly
- Velocity metric: ctDNA doubling time rather than absolute threshold

- Trigger: Doubling time <30 days triggers intensified imaging

Potential Impact: Detecting recurrence 3-4 months earlier could expand therapeutic options and improve outcomes.

5.3 Academic Vignette: Grant Design Enhancement

Scenario: R01 Application for Fibrosis Mechanism Study

Original Design (TRS 18/40):

- Aim 1: Characterize fibroblast activation at Day 14 post-injury
- Aim 2: Assess ECM deposition at Day 28

Redesigned Aims (TRS 31/40):

- Aim 1: Map temporal cascade of fibroblast activation (Days 1, 3, 7, 14, 21, 28)
- Aim 2: Identify the "point of no return"—when reversible fibrosis becomes irreversible
- Aim 3: Test therapeutic window by intervening at Days 3, 7, and 14

Grant Narrative Addition: "Our temporal design achieves TRS 31/40 by capturing the full mechanistic cascade with sufficient resolution to identify the critical intervention window."

6. TRS Application Across the Research Lifecycle

6.1 Application Matrix by Stage

Stage	TRS Application	Key Stakeholder
Target Validation	Assess temporal evidence for target engagement	Discovery Biology Lead
Translational Package	Design PK/PD studies with multi-scale coverage	Translational Science Head
Phase 1b/2 Protocol	Optimize biomarker sampling schedule	Clinical Development Lead
Interim Analysis	Define temporal criteria for adaptive decisions	Biostatistics Lead
Companion Diagnostic	Identify optimal sampling window	Diagnostic Strategy GM
Grant Design	Strengthen temporal rationale in Specific Aims	Principal Investigator

6.2 Stakeholder Jobs-to-Be-Done

Head of Clinical Development

- **Primary need:** De-risk Phase 2 investment decisions
- **TRS application:** Protocol review for temporal adequacy before enrollment

Translational Science Lead

- **Primary need:** Generate interpretable mechanism-of-action data
- **TRS application:** Multi-scale measurement cascade design (T0-T4)

Diagnostic Strategy GM

- **Primary need:** Maximize clinical utility and commercial value
- **TRS application:** Goldilocks Zone identification for optimal measurement window

Principal Investigator (Academic)

- **Primary need:** Design fundable, high-impact studies
- **TRS application:** Temporal design optimization for grant competitiveness

6.3 How Organizations Engage with TemporalBio

Engagement Level	Description	Timeline
Discovery Workshop	Half-day session introducing T0-T6 and TRS to teams	1 day

TRS Assessment	Systematic scoring of existing protocol with gap analysis	1-2 weeks
Temporal Redesign	Collaborative protocol optimization with recommendations	2-4 weeks
Longitudinal Analytics	Ongoing partnership for trajectory modeling	3-12 months

7. Building High-TRS Studies: Practical Guidelines

7.1 The Temporal Design Checklist

Question 1: What is the biological latency?

How long after perturbation until the biological response begins?

- T0-T1 processes: Minutes to hours
- T2 processes: Hours to days
- T3 processes: Days to weeks
- T4-T5 processes: Weeks to months

Guideline: First measurement should occur at approximately 50% of expected latency.

Question 2: What is the persistence?

How long does the response last before returning to baseline?

Guideline: Final measurement should occur at approximately 150% of persistence period.

Question 3: Are you measuring mechanism or outcome?

- **Mechanism:** The causal biological process (typically T0-T3)
- **Outcome:** The end result (typically T4-T5)

Guideline: High-TRS studies typically measure both mechanism and outcome.

Question 4: Can you capture individual trajectories?

Guideline: Aim for ≥4 timepoints per individual for trajectory fitting. ≥7 enables change-point detection.

Question 5: Are you measuring velocity or just position?

Examples: ctDNA doubling time > single ctDNA level. Tumor growth rate > tumor size alone.

Guideline: Design should have temporal density (intervals ≤50% of process duration) for reliable rates.

7.2 Minimal TRS 25 Playbook

Archetype 1: Acute Drug Response in Mice

T-Scale	Timepoints	Measurements
T1	1h, 4h, 12h	Phospho-protein signaling panels
T2	6h, 24h, 48h, 72h	RNA-seq or qPCR panels
T3	Day 3, 7, 14	Histology, flow cytometry

T4	Day 7, 14, 21	Organ function, imaging

Expected TRS: 26-30

Archetype 2: Human Longitudinal Cohort

T-Scale	Timepoints	Measurements
T4-T5	Baseline, Mo 3, 6, 12, 18, 24	Clinical labs, imaging
T5	Same schedule + event-triggered	Biomarkers (ctDNA, proteomics)
T6	Annual through Year 5+	Outcomes, survival

Expected TRS: 25-28 (can reach 32+ with quarterly high-risk monitoring)

Archetype 3: Immuno-Oncology Biopsy Study

T-Scale	Timepoints	Measurements
T1	Day 1, 3, 7 (peripheral)	Phospho-flow on PBMCs
T2	Day 3, 7, 14 (peripheral)	Cytokine/chemokine panels
T3	Baseline, Wk 2, Wk 6 (biopsy)	Spatial transcriptomics, mIF
T4	Week 6, 12, 18 (imaging)	RECIST assessment

Expected TRS: 30-36

7.3 Common Temporal Design Mistakes

Mistake 1: "Convenient" Timepoints

What it looks like: Measuring at Weeks 4, 8, 12 because "that's when patients come to clinic"

Solution: Design around biological processes first, then adjust logistics.

Mistake 2: Single-Scale Measurement

What it looks like: Only measuring tumor size (T4) without mechanistic data (T0-T3)

Solution: Add at least one mechanistic measurement at a lower T-scale.

Mistake 3: No Baseline or Follow-Up

What it looks like: Treatment → Single endpoint (no baseline)

Solution: Always include baseline plus at least one post-resolution timepoint.

Glossary of Terms

Biological Latency: The time delay between perturbation and initiation of measurable response.

ctDNA: Circulating tumor DNA fragments in the bloodstream.

Diagnostic Velocity: How sensitive a test is to rate-of-change within the relevant temporal window.

Goldilocks Zone: The optimal measurement window where signals are detectable AND intervention is feasible.

Multi-Omics: Integrated analysis of multiple biological data types (genomics, transcriptomics, proteomics).

Persistence: Duration that a biological response remains active before returning to baseline.

Phospho-Flow: Technique measuring protein phosphorylation in single cells using flow cytometry.

Rate-of-Change Metrics: Measurements quantifying how rapidly a parameter changes (velocity, doubling time).

RECIST: Response Evaluation Criteria in Solid Tumors. Standardized criteria for tumor response assessment.

Signal Window: Time period during which a biological change produces detectable signals.

Spatial Transcriptomics: Technologies measuring gene expression while preserving spatial information.

State-Shift: Biological transition from reversible to irreversible states.

T0-T6 Ontology: Framework organizing biological processes across seven fundamental timescales.

Target Engagement: Direct physical interaction between drug and intended protein target.

Temporal Alignment: Degree to which timepoints match biological phases of the process studied.

Temporal Attrition: Progressive loss of causal information from measuring only downstream outcomes.

Temporal Coverage: Extent to which a study measures across multiple T-scales and captures transitions.

Temporal Extensibility: Ability to support individual trajectory modeling vs. only group-level analyses.

Temporal Readiness Score (TRS): Quantitative framework (0-40) evaluating temporal design adequacy.

Therapeutic Window: Time period during which biological state remains reversible and responsive.

Trajectory Modeling: Mathematical fitting of individual temporal profiles to predict outcomes.

References

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Additional Resources

- UK Biobank: https://www.ukbiobank.ac.uk
- All of Us Research Program: https://allofus.nih.gov
- 10x Genomics Spatial: https://www.10xgenomics.com/products/spatial-gene-expression
- TemporalBio Framework: https://temporalbio.com

Appendix A: TRS Scoring Methodology and Reproducibility

This appendix describes the methodology for the comprehensive 500-paper TRS validation study.

A.1 Scoring Protocol

Scorer Training: All scorers will complete a standardized training module including 20 calibration papers with consensus scores.

Scoring Process: Each paper independently scored by two trained raters. A third senior rater adjudicates discrepancies >5 points.

Documentation: For each paper: (1) Score for each TRS component with justification, (2) Temporal design strengths/limitations, (3) Suggested improvements.

A.2 Inter-Rater Reliability Assessment

We will report:

- **Cohen's Kappa:** For categorical TRS bands
- **Intraclass Correlation Coefficient (ICC):** For continuous TRS scores (0-40)
- **Component-Level Agreement:** Separate ICC for each of the four TRS components

Target Reliability: ICC ≥0.75 for total TRS score; ≥0.70 for individual components.

A.3 Clinical Translation Tracking

Outcome	Definition	Data Source
Patent Filed	Patent application citing paper within 3 years	USPTO, EPO databases
Clinical Trial Initiated	Trial registered citing paper within 3 years	ClinicalTrials.gov, EudraCT
Diagnostic Development	LDT or IVD program initiated	FDA 510(k), company announcements
Follow-on Publication	Subsequent paper advancing to human validation	PubMed citation analysis

Appendix B: Unbiased Paper Selection Methodology

To ensure the TRS validation study is free from selection bias, we have developed a stratified random sampling methodology.

B.1 Selection Criteria

Inclusion Criteria

- Published between January 1, 2020 and December 31, 2024
- Longitudinal design with ≥3 distinct timepoints
- Primary research article (not review, commentary, or methods paper)
- Available in English with full text accessible
- Contains original biological/clinical data

Exclusion Criteria

- Case reports or studies with n<10 subjects
- Studies focused solely on genomics without temporal measurements
- Retracted papers or papers with corrections affecting temporal design

B.2 Stratified Random Sampling Strategy

Stratum 1: Journal Tier (5 levels)

Tier	Journals	Papers
Tier 1 (IF >30)	Nature, Science, Cell, NEJM, Lancet	100 papers
Tier 2 (IF 15-30)	Nature Medicine, Nature Genetics, Cancer Cell	100 papers
Tier 3 (IF 10-15)	JAMA Oncology, Gut, Circulation	100 papers
Tier 4 (IF 5-10)	Cancer Research, JCI Insight	100 papers
Tier 5 (IF 3-5)	Specialty journals (representative sample)	100 papers

Rationale: This distribution captures both high-visibility research and the broader landscape, avoiding top-tier-only bias.

Stratum 2: Therapeutic Area (10 categories)

- Oncology (25%): 125 papers
- Immunology/Inflammation (15%): 75 papers
- Cardiovascular (12%): 60 papers
- Metabolic/Endocrine (12%): 60 papers

- Neuroscience (10%): 50 papers
- Infectious Disease (8%): 40 papers
- Respiratory (6%): 30 papers
- Gastroenterology (5%): 25 papers
- Nephrology (4%): 20 papers
- Other (3%): 15 papers

Stratum 3: Study Type (4 categories)

- Preclinical/Animal Studies (30%): 150 papers
- Human Observational/Cohort (30%): 150 papers
- Clinical Trials (25%): 125 papers
- Translational/Biomarker Studies (15%): 75 papers

B.3 Random Selection Process

Step 1: Database Query

PubMed will be queried using standardized search terms. Complete search strings will be published as supplementary material.

Step 2: Automated Filtering

Results will be filtered programmatically for inclusion/exclusion criteria using abstract screening.

Step 3: Stratified Random Sampling

Papers will be randomly selected using a cryptographically secure random number generator with a published seed value.

Step 4: Manual Verification

Each paper will undergo manual verification. Papers failing verification will be replaced by the next random selection.

B.4 Transparency and Replication

- Complete paper list: All 500 papers with DOIs will be published
- Scoring rationales: Summary notes for each paper will be available
- Random seed: The RNG seed will be published for exact replication
- Search strings: Complete PubMed queries will be documented
- Protocol registration: The protocol will be registered on OSF before scoring begins

B.5 Addressing Potential Biases

Potential Bias	Mitigation Strategy

Selection bias (cherry-picking)	Stratified random sampling with published seed; protocol pre-registration
Scorer bias	Independent dual scoring; blinding to citation count
Publication bias	Inclusion of all longitudinal studies regardless of outcome
Journal prestige bias	Stratification across 5 journal tiers
Therapeutic area bias	Proportional sampling across 10 areas
Temporal bias (drift)	Calibration sessions every 50 papers; drift analysis

About TemporalBio

TemporalBio is a project of Scientari LLC dedicated to advancing temporal biology research through frameworks, tools, and education.

Available Resources

- **TRS AI Agent (In Development):** Evaluate your study design and receive temporal optimization recommendations
- **Temporal Diagnostic Checklist:** Interactive assessment for diagnostic assay development
- **Educational Content:** Webinars, case studies, and implementation guides
- **Consultation Services:** Custom temporal readiness assessments for research programs

The TemporalBio Stack

Layer	Component	Description
1. Ontology	T0-T6 Framework	Shared language for biological timescales
2. Rubric	TRS (0-40)	Quantitative scoring methodology
3. Templates	Protocol Archetypes	Pre-designed temporal configurations
4. Tooling	TRS Agent	Automated scoring and recommendations
5. Benchmarks	TRS Distributions	Reference scores by indication/modality

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