Paper DS14

Solving the Fragmentation Challenge in RA Trials: Deriving deeper insights

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease impacting inflammation, physical ability, quality of life, and joint integrity. RA trials rely on endpoints such as DAS28, ACR20/50/70, CDAI, HAQ-DI, and the Sharp/van der Heijde Score. While each metric provides valuable insights, analysing them in isolation often leads to fragmented interpretation and limited clinical context.

This fragmentation can result in:

- Delayed signal detection and decisions
- Inefficient data processing
- Regulatory ambiguity and timeline risks
- Lack of patient-level insight

Addressing this requires aligning endpoints into a unified framework that enables clear, actionable interpretation. By integrating these data into longitudinal, clinically relevant views, sponsors can accelerate informed decisions across trial design, monitoring, and submissions.

This shift from disjointed data to strategic insight that supports more adaptive, efficient, and personalized RA trials. Our paper will feature this approach with a case study.

CURRENT RA TRIAL LANDSCAPE

Rheumatoid Arthritis (RA) is a chronic autoimmune condition characterized by persistent inflammation, progressive joint damage, and impaired physical function. Affecting approximately 0.5–1% of the global population, RA imposes a substantial burden on patients' quality of life and healthcare systems [Smolen et al., 2016; Aletaha & Smolen, 2018].

Clinical trials in RA are inherently complex due to the multidimensional nature of the disease. To capture its diverse manifestations, sponsors collect a broad spectrum of endpoints, including:

Composite Scores: DAS28, CDAI, SDAI

Response Criteria: ACR20/50/70

Patient-Reported Outcomes (PROs): HAQ-DI, pain VAS, fatigue scales

Radiographic Measures: Sharp/van der Heijde Score

Biomarkers: CRP, ESR

While each endpoint is individually validated and clinically meaningful, analyzing them in isolation often leads to fragmented interpretation, delayed signal detection, and limited clinical context. The proliferation of these measures creates an "endpoint soup," making data interpretation resource-intensive and introducing inefficiencies in trial design, monitoring, and regulatory submissions.

SYSTEMIC CHALLENGES

RA trial data interpretation faces several systemic issues that hinder efficiency and clinical relevance.

FRAGMENTED INTERPRETATION AND LIMITED CLINICAL CONTEXT: Endpoints are often analyzed in isolation, obscuring the relationships between inflammation, physical function, and structural progression. For instance, a patient may demonstrate DAS28 improvement while continuing to experience HAQ-DI impairment, raising questions about overall benefit.

DELAYED SIGNAL DETECTION AND DECISION-MAKING: Siloed analyses slow the identification of early efficacy or safety signals, delaying adaptive trial decisions and increasing development costs.
Regulatory Ambiguity and Timeline Risks: Regulators require a clear, integrated benefit–risk narrative. Disparate endpoint reporting can lead to prolonged review cycles and additional queries.
Lack of Patient-Level Insight: Aggregated summaries mask individual variability, limiting understanding of response heterogeneity—critical for personalized medicine and enrichment strategies.

IMPACT OF FRAGMENTATION

Operational inefficiency arises from manual integration of multiple datasets, increasing analytical burden. Strategic blind spots emerge when sponsors lack a holistic view, making confident go/no-go decisions difficult. Clinically, physicians and regulators face uncertainty regarding the real-world impact of treatment across domains, undermining clarity and confidence in therapeutic outcomes.

THE UNIFIED FRAMEWORK SOLUTION

To overcome the inefficiencies and ambiguity caused by fragmented endpoint analysis, we propose a Unified Framework Dashboard—a patient-centric, longitudinal visualization platform that integrates multiple RA trial endpoints into a single, coherent narrative. This approach moves beyond simple co-location of data to true integration, enabling stakeholders to understand interdependencies between disease activity, physical function, and structural progression.

The framework is built on five core principles as per table 1.

Hierarchical Drill-Down	Start with a high-level study overview, then allow dynamic drill-down to subgroup analysis and individual patient profiles.
Modular and Customizable	Widget-based design lets users prioritize views relevant to their role (e.g., regulatory vs. clinical teams).
Storytelling with Data	Visualizations reveal not just what happened but how treatment effects evolved over time.
Contextual and Comparative	Benchmark patient and cohort data against study averages, placebo arms, and clinical thresholds.
Patient-Centricity	Enable granular exploration of individual patient journeys to uncover heterogeneity of response.

Table 1: Core principles of unified framework

VISUALIZATION COMPONENTS

The dashboard integrates multiple visualization types to address fragmentation as per Table 2.

Visualization Type	Description	Benefit
Multi-Metric Spaghetti Plots	Display DAS28, HAQ-DI, pain VAS, and Sharp score trajectories on normalized scales over time for individual patients.	Reveals simultaneous changes across domains.
Event-Driven Timelines	Annotate treatment initiation, dose changes, and adverse events alongside metric trends.	Links clinical events to outcome shifts.
ACR Response Waterfall Charts	Show cumulative achievement of ACR20/50/70 across time points and treatment arms.	Simplifies responder analysis.
Heatmaps for Cohort Trends	Color-coded patient rows across time points for DAS28 or HAQ-DI.	Identifies clusters of responders/non-responders.
Animated Scatter Plots	Plot DAS28 vs. HAQ-DI with time-based animation to visualize correlation dynamics.	Highlights relationships between inflammation and function.
Radar Charts	Compare multi-dimensional profiles (disease activity, pain, fatigue, QoL) at a single time point.	Provides a quick “fingerprint” of patient or subgroup status.

Patient level visualization	Patient-level visualization focuses on individual trajectories and heterogeneity of response, moving beyond population averages.	Uncovers heterogeneity in RA responses for precision medicine and biomarker discovery, while strengthening regulatory narratives through clinically meaningful patterns beyond aggregate averages.

Table 2: Visualization components and benefits

INTERACTIVE FEATURES

- Global filters for treatment arms, demographics.
- Time slider for phase-specific analysis.
- Drill-down functionality from cohort to patient level.
- Export options for regulatory reporting.
- Point on the data point inside the dashboard to identify the details behind the visuals

OPERATIONAL REQUIREMENTS

- Harmonizing diverse data types (continuous, categorical, imaging) across endpoints: DAS28, HAQ-DI, Pain VAS, CRP, ACR20/50/70, Sharp Score are required.
- Implementing ETL pipelines for longitudinal data capture at multiple time points (Baseline, Week 4, Week 12, Week 24).

TRADITIONAL ANALYSIS VS. UNIFIED FRAMEWORK

Traditional Approach:
Separate tables and charts for each endpoint, requiring manual synthesis to interpret overall treatment effect.

Unified Framework Approach:
Integrated dashboards provide longitudinal, patient-centric views and cohort-level trends.

CASE STUDY – APPLYING THE UNIFIED FRAMEWORK

To demonstrate the practical application of the Unified Framework Dashboard, we present a case study using a simulated Phase III RA trial dataset. The trial compares Treatment A versus Treatment B in patients with moderate-to-severe RA, assessing multiple endpoints over 36 weeks.

This dashboard was developed using R Shiny to provide an interactive, multi-perspective visualization of trial data. This dashboard enables both cohort-level summaries and individual patient drilldowns, facilitating deeper insights into treatment efficacy, variability, and safety.

DATA OVERVIEW

Population: 100 patients (P1 to P100) randomized (Treatment A: 51; Treatment B: 49)
Endpoints Collected: DAS28, HAQ-DI, ACR20/50/70, Sharp Score
Time Points: Baseline, Week 4, Week 12, Week 24, Week 36
Variables: DAS28 (disease activity), CDAI (clinical disease activity index), HAQ-DI (functional disability), SvH Score (radiographic damage), Treatment assignment (A vs B).
ACR Responses: Simulated binary outcomes for ACR20/50/70 with increasing probability over time.
Events: Randomized clinical events (routine visits, adverse events, medication changes, hospitalizations).

DASHBOARD ARCHITECTURE:

Framework: R Shiny for interactivity, plotly for dynamic visualization, ggplot2 for plotting, fmsb for radar charts.
Layout: Custom header, tabbed navigation, responsive panels.

DASHBOARD SECTIONS, PLOTS DERIVED IN EACH AND INTERPRETATION:

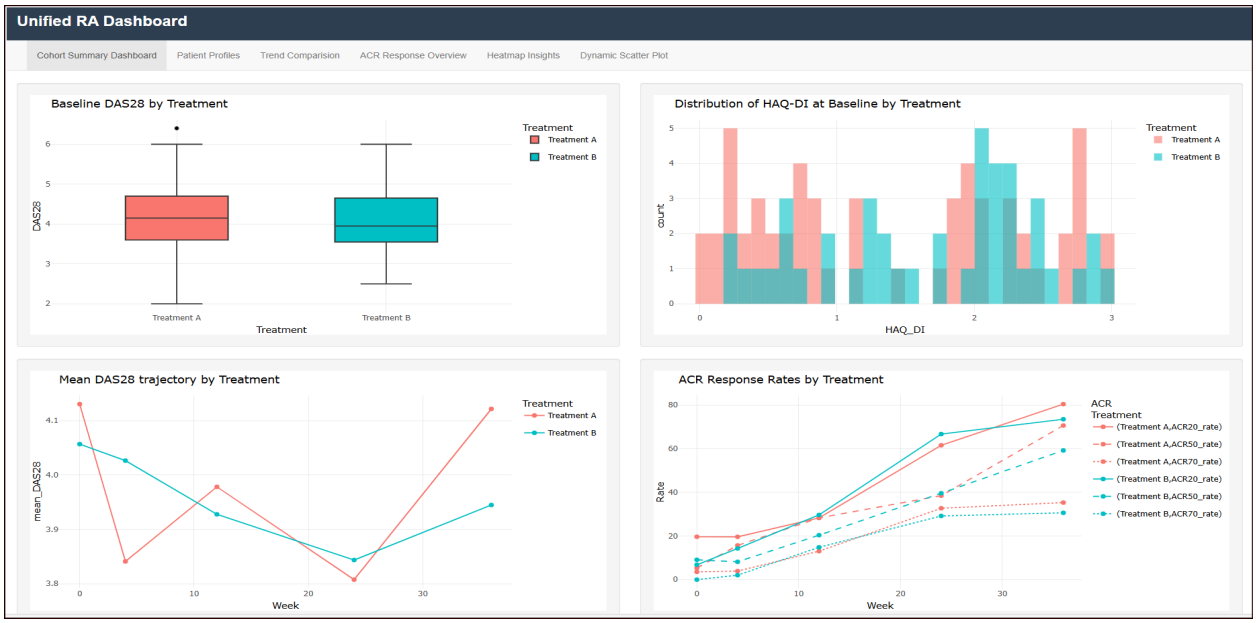

Figure 1: Unified RA Dashboard

Cohort Summary Dashboard:

This part establishes baseline comparability and highlights treatment differences in disease activity and response rates. Below are the plots derived under this section.

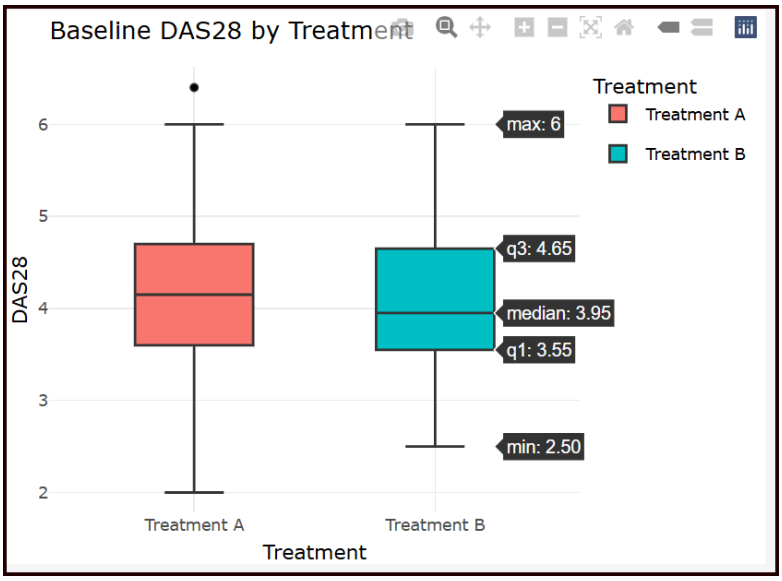

Figure 2: Box Plot of Baseline DAS28 by Treatment

Figure 2 compares baseline disease activity between treatment arms. Both treatment groups show **moderate baseline RA disease activity**, with close medians and nearly identical spreads. Treatment A has slightly **higher median** and **more extreme values**, suggesting mild imbalance. Treatment B appears **more homogeneous**, with no outliers. Overall, the boxplot indicates **baseline comparability** between Treatment A and Treatment B, with only minor distributional differences.

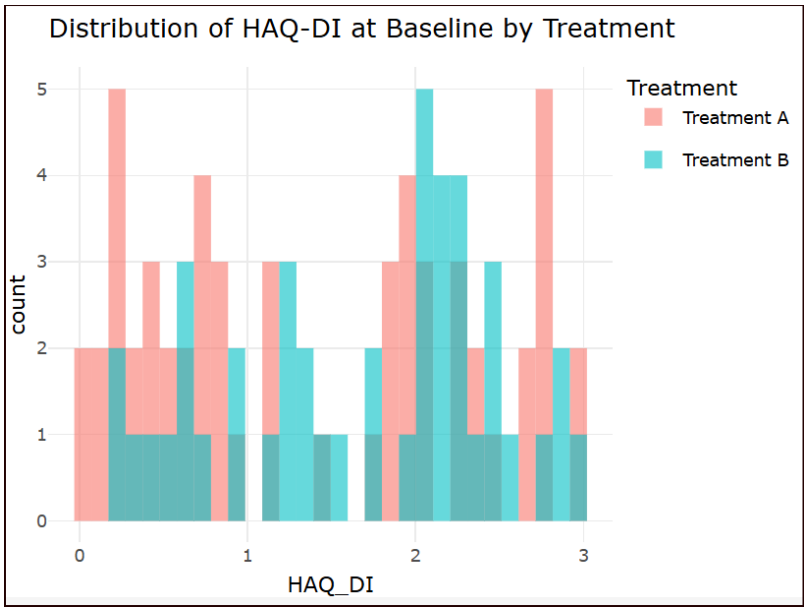

Figure 3: Histogram of Distribution of HAQ-DI at baseline by Treatment

Figure 3 histogram shows that both treatment arms have **broad and overlapping distributions** of baseline HAQ-DI. **Treatment A** is a highly variable, with clusters at low, moderate, and high disability, while **Treatment B** is more centralized around moderate disability, fewer extremes. Baseline comparability is **reasonable but not perfect**, differences in distribution shape should be acknowledged in any statistical or clinical interpretation.

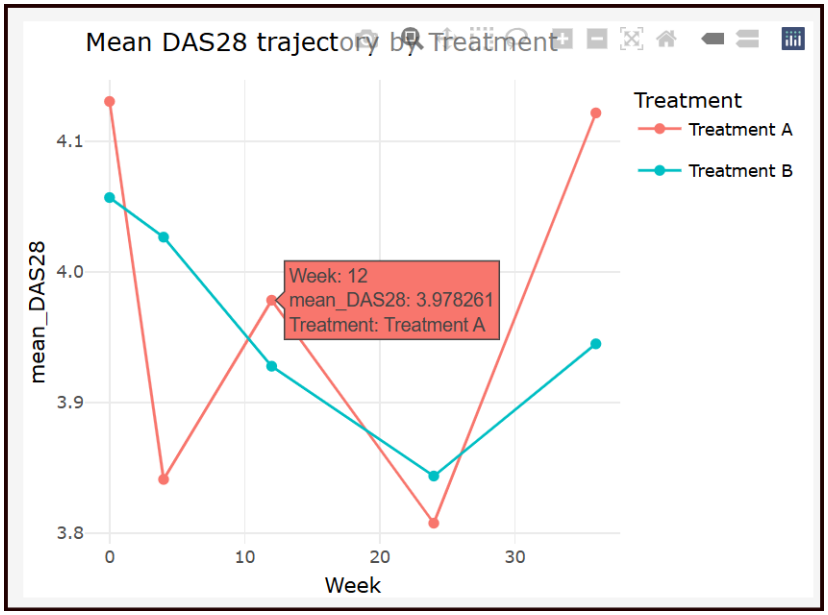

Figure 4: Line Plot of Mean DAS28 trajectory by Treatment over time

From Figure 4, we can see both treatments improve DAS28, but with different patterns. Treatment A shows strong early response, marked fluctuations, ends near baseline → **unstable durability.** Treatment B shows smaller but steady improvements and ends below baseline → **stable and sustained efficacy.** So, Treatment B may be the preferable therapy if long-term control is prioritized.

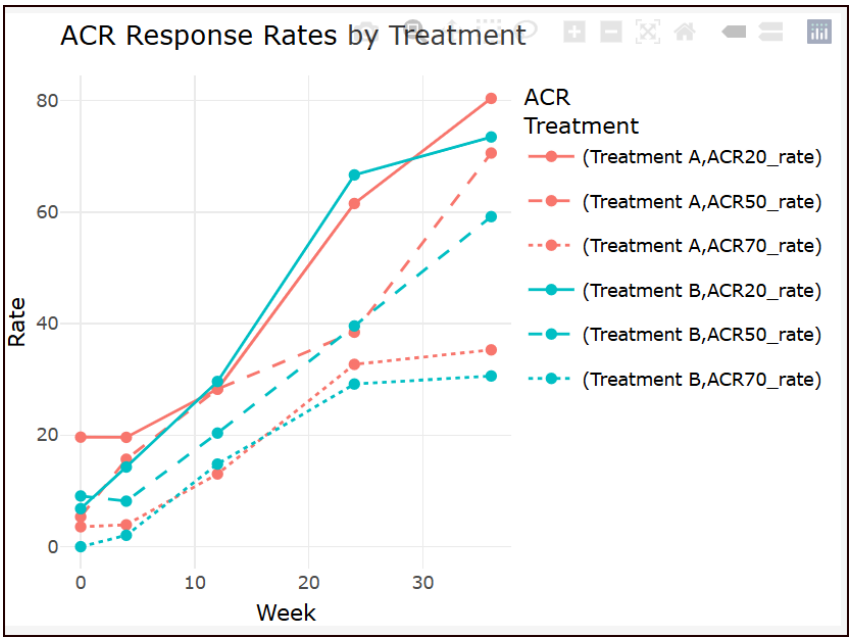

Figure 5: Line plot of ACR Response Rates by Treatment

As per Figure 5 both treatments are effective in improving rheumatoid arthritis symptoms. Treatment A shows stronger late-stage performance across all ACR levels, particularly notable jumps in ACR50 and ACR70 after Week 24. The pattern suggests a delayed but robust onset of deeper response. On the other hand, Treatment B has better early to mid-response, smoother progression without large fluctuations and reaches strong ACR20 and ACR50 rates but does not accelerate late like Treatment A. So, to conclude, if the goal is rapid initial improvement, Treatment B appears more favourable and if the goal is achieving higher and deeper responses by end of study, Treatment A performs better.

Patient-level Longitudinal analysis: This section of the Dashboard enables personalized monitoring and contextualizing individual responses against cohort averages. This section has individual trajectory plots for each patient over time, individual events timeline plot displaying clinical events across weeks, and Radar chart displaying baseline multidimensional disease profile for each subject.

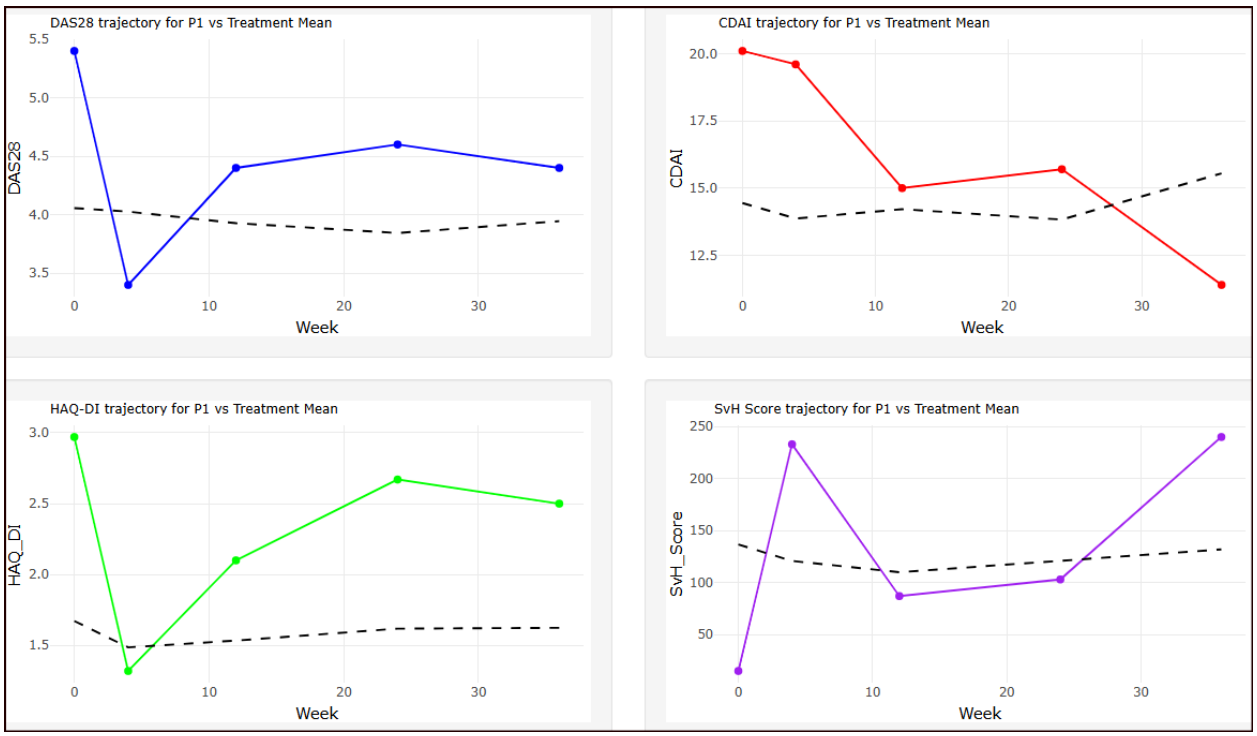

Figure 6: Individual patient trajectory line plots for each metric over time

Figure 6 compares Patient P1's individual trajectory (colored solid line) against the treatment arm mean trajectory (black dashed line) for key rheumatoid arthritis (RA) clinical outcomes: DAS28, CDAI, HAQ-DI, and SvH score. Together, these plots illustrate how P1 is responding relative to the average patient in their treatment group. Here, we can see early improvements are visible in DAS28, HAQDI, and CDAI. CDAI shows the most durable improvement, with P1 ending better than the mean. DAS28 and HAQDI both show that P1 remains worse than average across most of the study. SvH progression is dramatically worse than the treatment mean → P1's disease is structurally aggressive. So, likely interpretation is that P1 appears to be a clinical partial responder but a structural nonresponder, with aggressive underlying disease, high baseline severity, and transient improvements but poor long-term control. This is a typical pattern for patients who need treatment escalation or combination therapy due to ongoing radiographic damage despite some symptomatic relief.

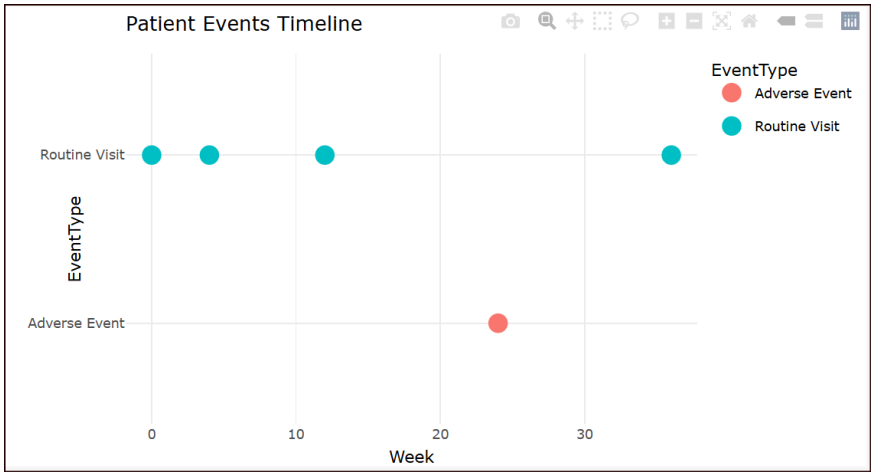

Figure 7: Scatter plot of patient events timeline

Figure 7 plot displays all recorded events for a single patient across the study duration. Each point represents occurrence of a specific event at a particular study week. The above plot shows that patient P1's adherence is good and had adverse event, but it did not impact subsequent study participation.

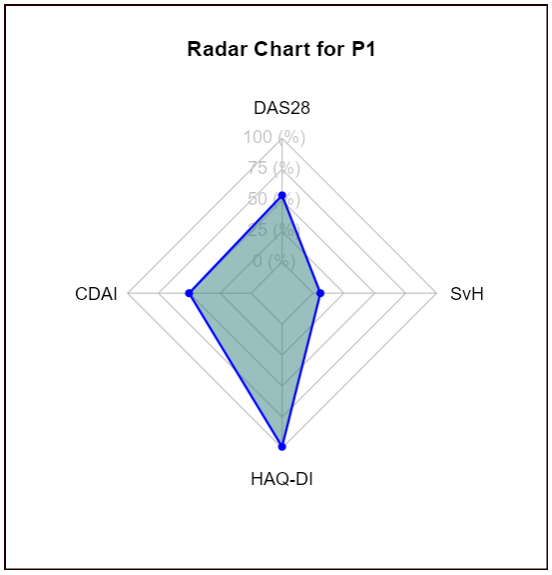

Figure 8: Spider plot of baseline DAS28, CDAI, HAQ-DI, and SvH

This radar chart from figure 8 summarizes P1's disease status across four key rheumatoid arthritis outcome domains. All values appear to have been normalized to a percentage scale, where larger values represent worse status relative to the measurement range. The filled blue polygon represents P1's overall profile across these domains. Larger the

area, more severe is the disease at baseline. In the above plot, P1's radar profile suggests high functional impairment, moderate to persistent disease activity, moderate clinical symptoms (CDAI), and moderate radiographic burden at baseline.

Trend Comparison: This section displays multi-metric spaghetti plots showing individual trajectories for each metric, coloured by treatment. It reveals heterogenicity of response, identifies outliers and visualizes consistency of treatment effect.

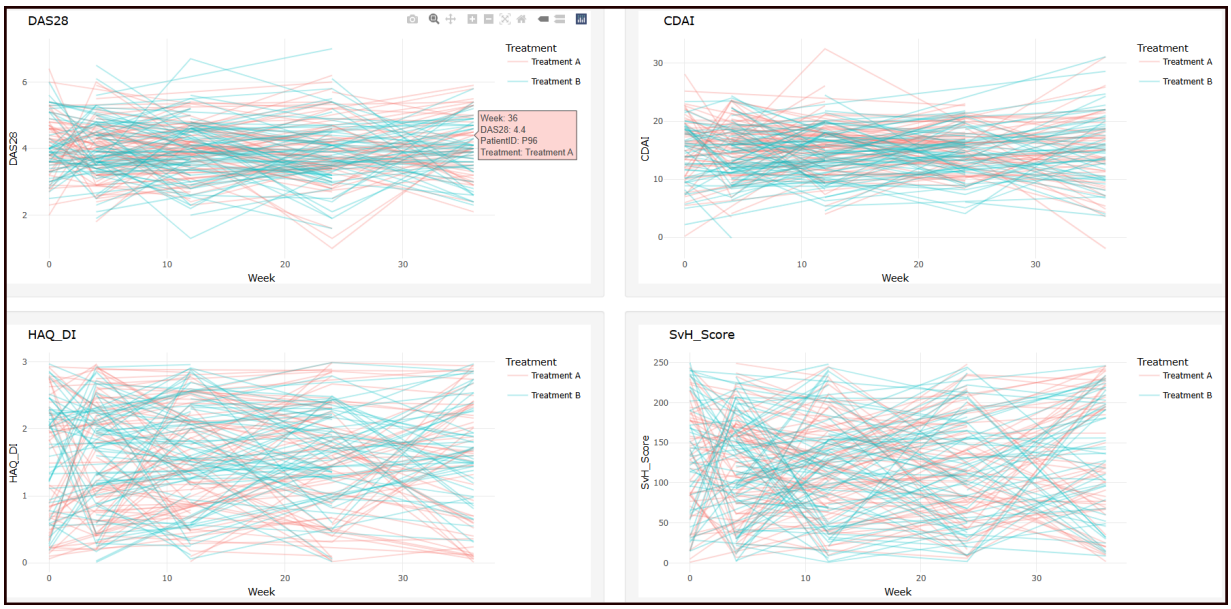

Figure 9: Multi-metric Spaghetti plots for each patient trajectories over time by treatment

By looking at Figure 9, we can see that across all four scales, the dominant themes are high patient-to-patient variability, each outcome shows wide distribution of trajectories and individual patterns vary widely irrespective of treatment arm. There is substantial overlap between Treatment A and Treatment B, no visual indication that one treatment performs better, which suggests comparable clinical efficacy or that differences, if present, require statistical modelling (MMRM, mixed effects) to detect. There is early improvement followed by stabilization, particularly visible in DAS28 and CDAI (symptom-based outcomes). Functional (HAQ-DI) and structural scores (SvH) change more slowly. Also, we can see outliers exist in every outcome, a few patients show dramatic increases or decreases. This may represent non-responders, flares, requiring individual review (e.g., patient-level profiles).

ACR Response Overview: This section displays two waterfall plots. The first one lets us understand patient-level change in DAS28 from baseline to selected week, faceted by treatment, colored by highest ACR response. This provides granular view of treatment efficacy distribution, highlighting responders vs non-responders.

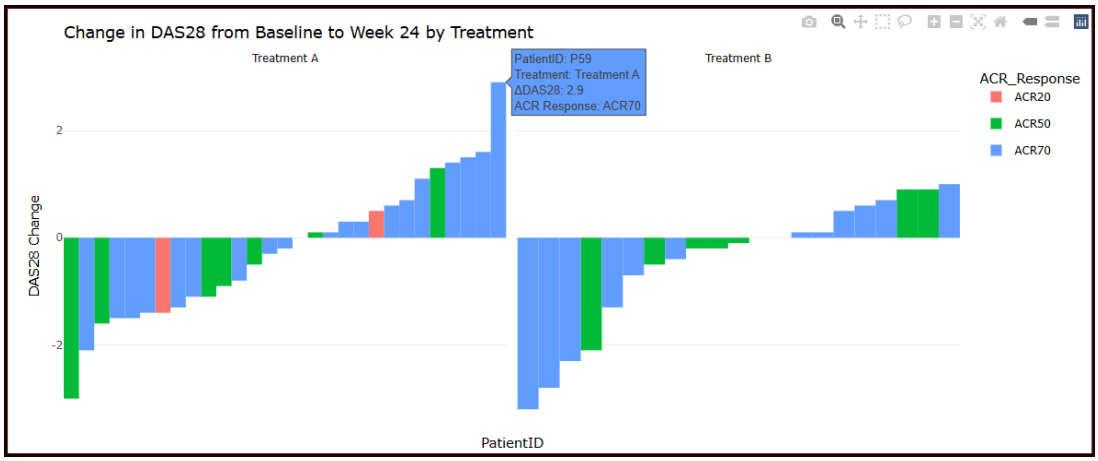

Figure 10: Waterfall Plot of Change in DAS28 from Baseline to Week 24 by Treatment

Figure 10 tells us that Treatment A shows higher maximum efficacy (best individual responses), while Treatment B shows more stable efficacy (more patients improving moderately). Also, Treatment A has more large positive changes suggesting potential non-responsive or worsening subgroup, while Treatment B shows fewer worsening trajectories.
The second waterfall plot plots change in HAQ-DI from Baseline to Week 24 by treatment.

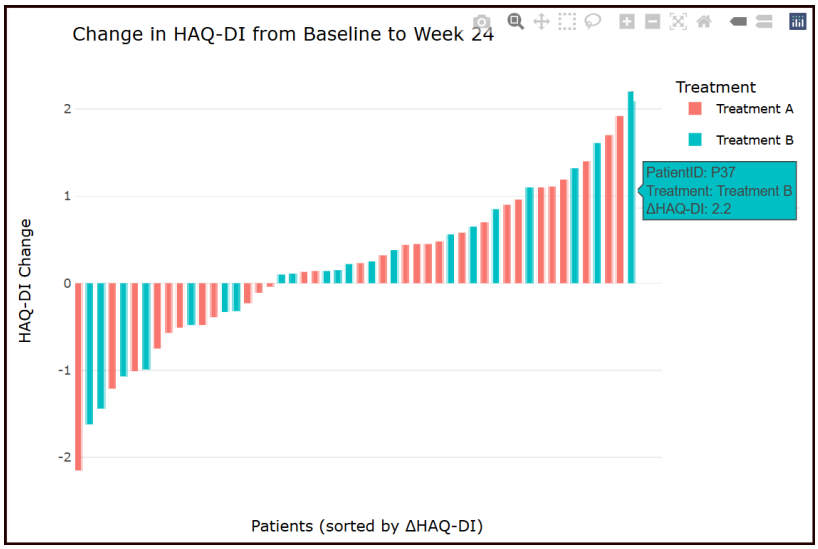

Figure 11: Waterfall plot of Change in HAQ-DI from Baseline to Week 24 by Treatment

Figure 11 displays both treatments show mixed responses, neither arm uniformly improves or worsens. Treatment A appears to produce more large improvements, based on the left tail. Both arms have patients who worsen substantially, with some values reaching +2 or more. Treatment B has fewer extreme improvements, but variability remains. This type of visualization is useful to detect heterogeneous treatment effects, identify responders vs. non-responders, and explore outliers or unusual worsening.

Heatmap displays heatmaps for each metric for each patient. This helps us identify clusters of patients with similar trajectories.

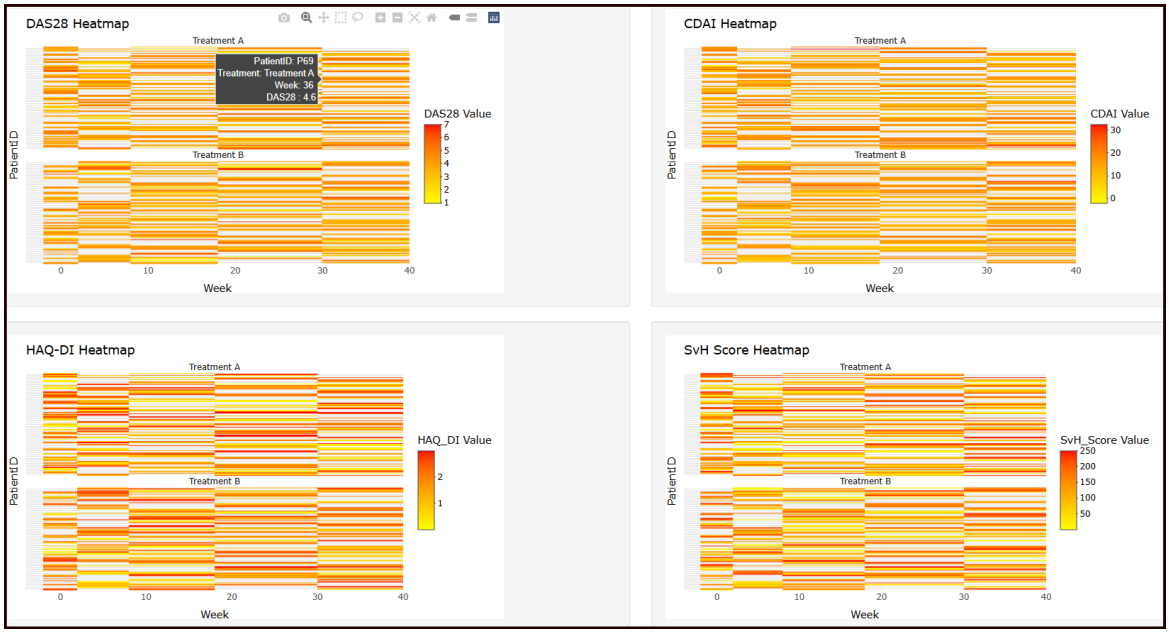

Figure 12: Heatmaps of DAS28, CDAI, HAQ-DI, and SvH scores across all patients and all study weeks by treatment

These heatmaps from figure 12 help identify patterns, clusters, stability, and variability in disease outcomes across the entire study population. As per above heatmaps, across both DAS28 and CDAI, patients in both treatment arms show a general shift from higher disease activity at baseline (more orange/red) to lower disease activity by later weeks (lighter yellow), indicating an overall improvement over time. Both treatments demonstrate clinically meaningful reductions in disease activity over 40 weeks. Responses are heterogeneous, with some patients showing continuous improvement, while others experience flare-like fluctuations or persistently elevated disease activity. No substantial visual differences in disease activity trajectories between Treatment A and Treatment B are evident, suggesting comparable control of inflammatory disease activity. A subset of patients in each arm maintains higher DAS28 or CDAI values, consistent with partial responders or non-responders commonly observed in RA studies.

Dynamic Scatter Plot displays animated scatter plot, where patients are plotted over time, colored by treatment and animated by week. It demonstrates correlation between DAS28 and CDAI, tracks movement of patients toward remission zones, and compares treatment arms dynamically.

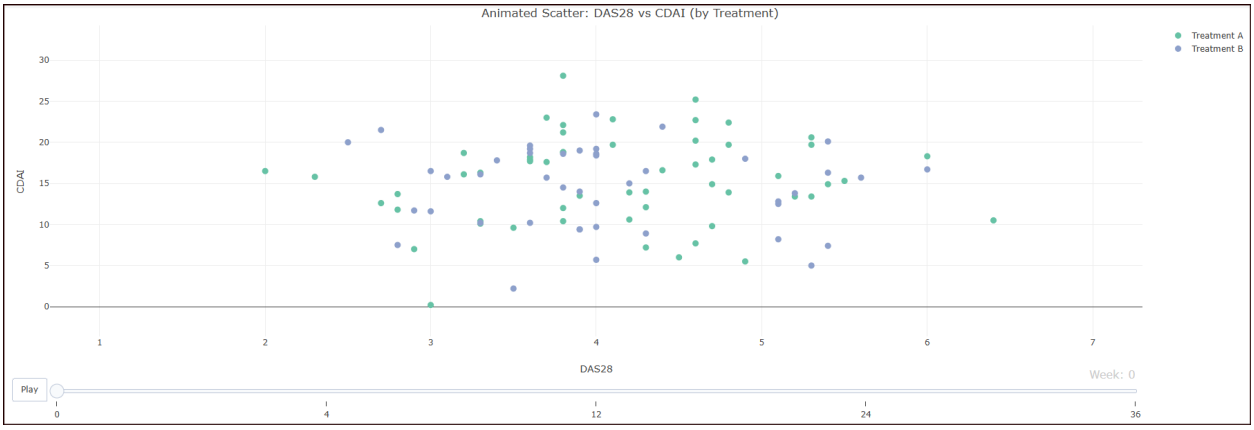

Figure 13: Animated scatter plot of DAS28 vs CDAI by Treatment

From Figure 13, animated scatter plot demonstrates a strong positive correlation between DAS28 and CDAI across all time points, moderate improvements early, followed by stabilization, high between patient variability but relatively stable within-patient trajectories, and no visible differences between Treatment A and Treatment B in reducing disease activity. Overall, the disease burden across the population shows consistent, modest improvement without dramatic shifts, and both treatments perform similarly when assessed through combined DAS28–CDAI dynamics.

Results of Unified Framework Application

Applying the Unified Framework Dashboard to the simulated Phase III RA trial revealed several key improvements compared to traditional siloed analysis:

Dimension	Details
Early Signal Detection	DAS28 improvement in Drug X arm visible by Week 4, enabling earlier go/no-go decisions. Traditional analysis would require multiple tables and delay interpretation.
Integrated Clinical Context	Event-driven timelines linked adverse events to functional outcomes (HAQ-DI), clarifying benefit-risk trade-offs.
Patient-Level Insights	Spaghetti plots and heatmaps highlighted heterogeneity of response, identifying non-responders and exceptional responders for biomarker analysis.
Regulatory Narrative Simplification	Cohesive visualization of multi-endpoint trends supported a clear, clinically meaningful benefit-risk profile, reducing ambiguity and potential review delays.

Table 2: Key Insights and Strategic Impact of Unified Framework

Area	Impact

a) Accelerated Decision-Making	Trial Design: Integrated insights enable adaptive strategies (e.g., enrichment for responder subgroups). Monitoring: Real-time visualization supports proactive adjustments to dosing or trial parameters. Monitoring: Real-time visualization supports proactive adjustments to dosing or trial parameters.
b) Regulatory Efficiency	Unified, patient-centric narratives strengthen submissions and reduce back-and-forth with agencies. Demonstrates clinical meaningfulness beyond statistical significance.
c) Operational Efficiency	Centralized integration eliminates manual data synthesis, reducing analytical burden and timelines.
d) Patient-Centric Development	Enables identification of responder profiles, paving the way for personalized medicine in RA.

Table 3: Strategic Impact

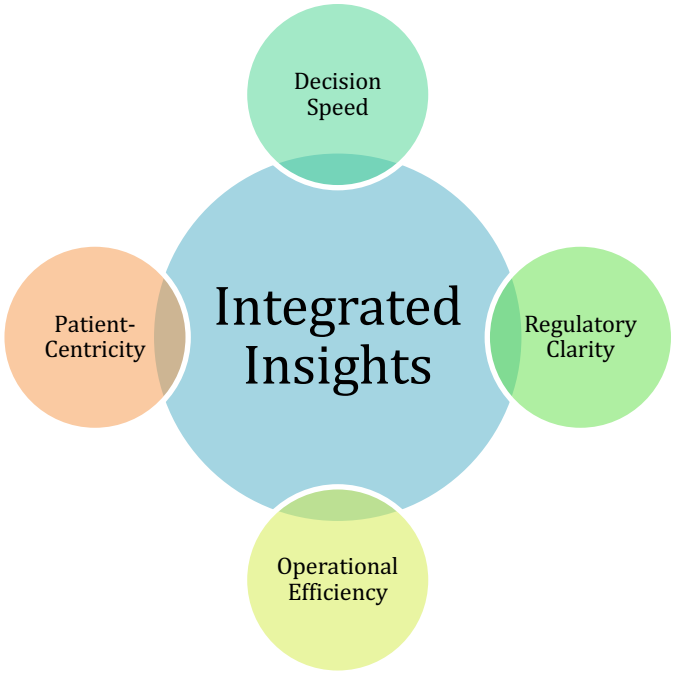

Figure 14: Strategic Impact of Unified Framework

DISCUSSION

ADDRESSING FRAGMENTATION

The Unified Framework fundamentally resolves the systemic issues identified in RA trial data interpretation. By integrating multiple endpoints into a longitudinal, patient-centric view, it eliminates the need for manual synthesis of siloed reports. This approach transforms raw data into actionable insights, enabling stakeholders to understand the interplay between inflammation, function, and structural progression in real time.

COMPARATIVE ADVANTAGE OVER TRADITIONAL METHODS

Traditional RA trial analysis relies on separate tables and charts for DAS28, HAQ-DI, ACR responses, and radiographic scores. This siloed approach creates delays, increases analytical burden, and obscures clinical context.

In contrast, the Unified Framework:

Aspect	Traditional Approach	Unified Framework

Data Integration	Manual, fragmented	Automated, holistic
Signal Detection	Delayed (weeks/months)	Early (real-time visualization)
Regulatory Narrative	Disparate endpoint reports	Cohesive, patient-centric story
Patient-Level Insight	Limited	Granular, longitudinal profiles
Operational Efficiency	High resource burden	Streamlined, dashboard-drive

CLINICAL AND STRATEGIC IMPLICATIONS

The Unified Framework reinforces clinical meaningfulness by correlating DAS28 improvements with HAQ-DI scores and radiographic stability, demonstrating patient benefit that goes beyond statistical significance. At the regulatory level, integrated visualizations present a clear and comprehensive benefit–risk profile, reducing ambiguity and accelerating review timelines. Furthermore, real-time insights enable adaptive trial designs, allowing dynamic adjustments such as dose optimization and enrichment strategies for responder subgroups, ultimately driving more efficient and patient-focused development.

LIMITATIONS AND CONSIDERATIONS

Although the Unified Framework delivers substantial benefits, successful implementation depends on several critical factors. First, a robust data infrastructure is essential to harmonize diverse data types, including continuous, categorical, and imaging variables. Second, comprehensive stakeholder training is required to ensure clinical, regulatory, and analytical teams can accurately interpret and apply integrated visualizations. Finally, rigorous validation through pilot studies is necessary to demonstrate reproducibility and secure regulatory acceptance.

FUTURE DIRECTIONS

The Unified Framework represents a transformative step in RA trial data interpretation, and its evolution can redefine how clinical insights are generated and applied. Building on its current capabilities, the next stage involves integrating advanced analytics, including machine learning, to identify early predictors of treatment response and optimize therapeutic strategies. Standardization of reporting formats in collaboration with regulatory bodies will further strengthen its acceptance and utility. Expanding the framework to encompass other complex chronic conditions and incorporating real-world evidence from electronic health records and registries will enhance its relevance and ensure long-term safety monitoring. Ultimately, the vision is to create a dynamic, predictive ecosystem that supports adaptive trial designs, enabling real-time adjustments to dosing, sample size, and randomization. Complementing these innovations, intuitive clinician dashboards and patient-facing tools will foster shared decision-making and empower patients through self-monitoring, transforming the platform into a truly patient-engaged and data-driven solution.

CONCLUSION

Rheumatoid Arthritis trials have long struggled with fragmented data and siloed analyses that obscure the full clinical picture. The Unified Framework Dashboard offers a transformative solution by integrating diverse endpoints into a single, patient-centric view that accelerates decision-making, strengthens regulatory submissions, and supports adaptive trial design. This is not merely a technological enhancement—it is a paradigm shift toward strategic insight and patient-focused development. By embracing integrated analytics, piloting this framework in ongoing trials, and collaborating with industry consortia for standardization, we can move beyond traditional limitations and deliver therapies faster and more effectively. Uniting endpoints into a cohesive narrative will empower clinicians, regulators, and patients alike, ultimately transforming RA trials into adaptive, insight-driven engines of innovation.

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Getting started with Shiny Dashboard

Comparison of Disease Activity Score in 28 joints with ESR (DAS28), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire Disability Index (HAQ-DI) & Routine Assessment of Patient Index Data with 3 measures (RAPID3) for assessing disease activity in patients with rheumatoid arthritis at initial presentation - Indian Journal of Medical Research

Visualizing Clinical Data with Radar Polar Charts | Bold BI

Development of a scoring model for the Sharp/van der Heijde score using convolutional neural networks and its clinical application | Rheumatology | Oxford Academic

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