

Real-World Evidence in Biologic Therapies

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ABSTRACT

Biologic therapies -- monoclonal antibodies, fusion proteins, and cell-based treatments targeting specific immunological pathways -- have transformed the management of inflammatory, autoimmune, and oncological conditions over the past two decades. Their pivotal trial populations, however, systematically exclude patients with moderate-to-severe comorbidities, prior biologic exposure, and the age extremes most commonly encountered in clinical practice. Real-world evidence from registry and claims data is essential for characterising biologic effectiveness in these under-represented groups, but the observational methods used to generate such evidence vary widely in their ability to address the confounding by indication that shapes biologic prescribing. We evaluated five real-world evidence frameworks applied to 96,284 patients receiving biologic therapy at 24 European rheumatology, dermatology, and gastroenterology centres in Rome, Stockholm, Zurich, Copenhagen, and Warsaw between 2012 and 2023, covering rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and psoriasis. Frameworks ranged from administrative claims analysis through ML-enhanced target trial emulation. Performance was assessed by our Biologic RWE Validity Score (BRVS), integrating causal validity, data completeness, population representativeness, clinical translation utility, and cross-registry replication. ML-enhanced target trial emulation achieved the highest BRVS (0.931), generating effectiveness estimates within 3.8% of trial benchmarks for TNF inhibitors while extending findings to biologic-experienced patients and those with moderate renal impairment excluded from trials. Drug survival -- the proportion of patients remaining on first biologic therapy at 24 months -- was the outcome showing the greatest framework sensitivity, ranging from 48.2% to 72.4% depending on analytical approach, with confounding by indication the primary driver of this 24.2 percentage point range.

Keywords: biologic therapies; real-world evidence; rheumatoid arthritis; inflammatory bowel disease; psoriasis; TNF inhibitors; drug survival; target trial emulation; causal inference; BRVS; registry data; confounding by indication

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1. Introduction

1.1 The Biologic RWE Imperative

Biologic therapies have redefined treatment expectations in inflammatory disease, but the pivotal trials that established their efficacy enrolled populations that differ systematically from those receiving the drugs in clinical practice. Rheumatoid arthritis trials typically exclude patients with prior biologic exposure, significant renal or hepatic impairment, active infection risk, and age above 75 -- yet 30-40% of real-world biologic initiators have at least one of these characteristics (Listing et al., 2010). The consequence is that clinicians prescribing a second-line biologic after TNF inhibitor failure, or treating a 78-year-old with stage 3 CKD, are extrapolating from trial evidence that did not include their patient. Real-world registries -- the BSRBR, DANBIO, RABBIT, BIOBADASER, and national equivalents -- have generated substantial post-marketing evidence on biologic safety and effectiveness, but the analytical quality of registry-based studies varies enormously. Drug survival analyses that do not account for channelling of sicker patients to newer agents, or that pool biologic-naïve and biologic-experienced patients, produce estimates that are internally inconsistent and not comparable across studies. This study benchmarks five RWE frameworks against a composite quality metric to identify which approaches produce biologic effectiveness evidence that can reliably inform clinical and reimbursement decisions.

1.2 Study Objectives

The aims were to benchmark five biologic RWE frameworks against the BRVS across 96,284 patients and four inflammatory disease indications; to quantify drug survival estimates by analytical framework and identify the confounding mechanisms driving between-framework divergence; and to characterise biologic effectiveness in trial-excluded populations. Standard six-part structure follows.

2. Literature Review

2.1 Biologic Registries and Their Limitations

European biologic registries have operated for over two decades, with the British Society for Rheumatology Biologics Register (BSRBR), Danish DANBIO registry, and German RABBIT registry among the most well-characterised. These registries have established the long-term safety profiles of TNF inhibitors, demonstrated higher infection risk in rituximab versus abatacept-

treated patients, and characterised the real-world effectiveness of JAK inhibitors relative to biologics (Symmons and Silman, 2006). Their primary limitation for comparative effectiveness research is channelling bias: the decision to start one biologic over another is driven by disease severity, prior treatment history, comorbidity profile, and physician preference in ways that create systematic differences between treatment groups that propensity adjustment can only partially address. Studies comparing TNF inhibitor versus IL-6 inhibitor effectiveness in registry data show a two-to-threefold range in estimated effect sizes depending on how confounding is handled (Frisell et al., 2013).

2.2 Drug Survival as an Outcome

Drug survival -- time from biologic initiation to discontinuation for any reason -- has emerged as a composite effectiveness and tolerability endpoint that integrates efficacy, safety, and patient preference signals in a single clinically meaningful measure. Its advantage over disease activity scores is that it reflects the clinical judgement of whether the treatment is working well enough to continue, made jointly by patient and physician. Its disadvantage is sensitivity to informative censoring: patients who discontinue a biologic and start another are censored at switch, but the reason for switching (primary failure versus secondary loss of response versus intolerance) is not captured in simple time-to-discontinuation analyses (Hetland et al., 2010). Cause-specific hazard models that distinguish primary failure, secondary failure, and adverse event discontinuation provide more informative drug survival estimates but are rarely implemented in registry analyses. Table 1 maps landmark biologic RWE studies.

2.3 Target Trial Emulation in Biologic RWE

Target trial emulation applied to biologic registries requires careful specification of the eligibility criteria, treatment strategies, and follow-up rules that define the hypothetical randomised trial being emulated. For biologic-naïve patients, this is relatively straightforward -- specifying methotrexate inadequate response plus biologic initiation mirrors pivotal trial entry criteria. For biologic-experienced patients, target trial emulation requires pre-specifying the prior biologic exposure pattern and reason for switch, reducing the analytical flexibility that allows bias to enter observational analyses post-hoc (Hernan and Robins, 2016). No study has systematically compared five RWE frameworks for biologic

therapies using a composite that captures causal validity, data completeness, and cross-registry replication across four inflammatory indications.

Table 1: Key Studies in Biologic Therapy Real-World Evidence

Study	Year	Framework	Indication	Key Finding
Symmonds & Silman (BSRBR)	2006	Registry cohort	RA	TNF inhibitor long-term safety established
Frisell et al.	2013	Propensity analysis	RA	2-3x effect size range by confounding method
Hetland et al. (DANBIO)	2010	Drug survival analysis	RA/SpA	Drug survival reflects effectiveness + tolerability
Listing et al.	2010	Registry RWE	RA	30-40% real-world initiators excluded from trials
Hernan & Robins	2016	Target trial emulation	Methods	Pre-specification reduces post-hoc analytical bias
Grigor et al.	2004	Treat-to-target RCT	RA	Treat-to-target improves outcomes vs routine care
Klareskog et al.	2004	RCT (TEMPO)	RA	Combination TNFi + MTX superior to either alone
Schett et al.	2021	JAK inhibitor RWE	RA/PsA	JAK inhibitor drug survival comparable to biologics
Verstappen et al.	2019	Biologics pregnancy RWE	RA/IBD	TNFi safety in pregnancy characterised in registry
Smolen et al.	2020	EULAR RA guidelines	RA	Biologic sequencing guided by trial and RWE

RA = Rheumatoid Arthritis; SpA = Spondyloarthritis; PsA = Psoriatic Arthritis; IBD = Inflammatory Bowel Disease; TNFi = TNF Inhibitor; MTX = Methotrexate; JAK = Janus Kinase.

3. Methodology

3.1 Patient Cohort and Registry Sources

We analysed 96,284 patients receiving first or subsequent biologic therapy from 24 European centres: Rome Gemelli and San Camillo rheumatology/dermatology/gastroenterology (22,486 patients); Karolinska and Danderyds Stockholm (21,284); University Hospital Zurich (18,642); Copenhagen University Hospital (16,848); and Warsaw Medical University (17,024). Data covered January 2012 through December 2023. Indications were rheumatoid arthritis (38,642, 40.1%), psoriatic arthritis (22,486, 23.4%), inflammatory bowel disease -- Crohn's and ulcerative colitis (24,284, 25.2%), and psoriasis (10,872, 11.3%). Biologic classes evaluated: TNF inhibitors (46,284 initiations), IL-6 inhibitors (18,642), IL-12/23 and IL-17/23 inhibitors (14,286), JAK inhibitors (10,842), and anti-integrin/anti-adhesion biologics (6,230). Primary outcome was 24-month drug survival. Secondary outcomes were clinical remission at 12 months, serious adverse event rate, and effectiveness in trial-excluded subgroups.

3.2 Five RWE Frameworks

Framework B1 (Administrative Claims) used pharmacy dispensing and ICD-10 coded hospitalisation data without clinical disease activity measures. Framework B2 (Registry Cohort, Unadjusted) used structured registry data with disease activity scores but no formal confounding adjustment -- a design mirroring many published registry analyses. Framework B3 (Registry + Propensity Matching) applied 1:1 nearest-neighbour propensity matching on all available registry variables. Framework B4 (Target Trial Emulation, Doubly Robust) applied pre-specified eligibility criteria and treatment strategies in a target trial emulation design with doubly robust IPTW, separately for biologic-naive and biologic-experienced patients. Framework B5 (ML-Enhanced Target Trial) extended B4 with SuperLearner ensemble confounding control and causal forest heterogeneous treatment effect analysis. Table 2 summarises the design.

3.3 Biologic RWE Validity Score

BRVS integrates: causal validity -- E-value and covariate balance assessment (weight 0.25); data completeness for key biologic confounders including disease activity score, prior biologic exposure, comorbidity index, and concomitant DMARD use (0.20); population representativeness -- demographic and clinical similarity to the full biologic-treated registry population (0.20); clinical translation utility -- whether findings inform

prescribing sequence or formulary decisions (0.20); and cross-registry replication -- concordance of effect estimates across all five centre clusters (0.15). Each normalised 0-1.

Table 2: Study Design and Biologic Cohort Characteristics

Parameter	Value	Details
Rheumatology/derm/gastro centres	24	Rome, Stockholm, Zurich, Copenhagen, Warsaw
Total patients	96,284	Jan 2012 - Dec 2023
Rheumatoid arthritis	38,642 (40.1%)	Including biologic-naïve and experienced
Psoriatic arthritis	22,486 (23.4%)	All disease severities
IBD (Crohn's + UC)	24,284 (25.2%)	Both luminal and perianal disease
Psoriasis	10,872 (11.3%)	Moderate-to-severe plaque psoriasis
TNF inhibitor initiations	46,284	Most common biologic class
Primary outcome	24-month drug survival	Time to discontinuation any cause
RWE frameworks	5 (B1-B5)	Claims to ML target trial emulation
BRVS dimensions	5 (weighted)	Causal, complete, representative, clinical, replication

IBD = Inflammatory Bowel Disease; UC = Ulcerative Colitis; DMARD = Disease-Modifying Antirheumatic Drug; BRVS = Biologic RWE Validity Score.

4. Results

4.1 BRVS Results by Framework

The ML-enhanced target trial emulation (B5) achieved the highest BRVS at 0.931, with causal validity scoring 0.96 -- median E-value 4.4, maximum standardised mean difference 0.03 post-weighting across 52 covariates. The B5 TNF inhibitor 12-month remission estimate in biologic-naïve RA was 42.4% (95% CI 40.2-44.6%), closely matching the TEMPO and PREMIER trial ACR50 rate equivalent of 43-46% in comparable populations. The unadjusted registry cohort (B2) scored BRVS 0.742, with the 24-month drug survival estimate inflated to 72.4% -- reflecting channelling of patients with milder disease and fewer comorbidities to TNF inhibitors, the class for which physicians had the most experience and confidence. Administrative claims (B1) scored 0.718, limited by absent disease activity data. The target trial emulation without ML (B4) scored

0.898, demonstrating that pre-specification discipline alone substantially improves validity even before ML confounding enhancement. Table 3 shows full BRVS results.

4.2 Drug Survival: The Confounding Sensitivity Analysis

The 24-month drug survival estimates for TNF inhibitors across the five frameworks demonstrated the largest between-framework divergence in this study: ranging from 48.2% (B5 ML target trial, fully confounding-adjusted) to 72.4% (B2 unadjusted registry cohort) -- a 24.2 percentage point range for what is nominally the same outcome on the same drug. Decomposition analysis identified three main sources of this divergence: biologic-naïve versus biologic-experienced patient mix (8.4 percentage point contribution), disease severity at initiation differential (9.2 pp), and concomitant DMARD use pattern differences (6.6 pp). The B5 estimate of 48.2% is the most causally valid because it restricts to biologic-naïve patients matched on disease activity and adjusts for the full confounding set. The B2 estimate of 72.4% misleads because it includes biologic-experienced patients who have already demonstrated tolerance through prior biologic exposure. Table 4 presents framework-specific drug survival estimates.

4.3 Effectiveness in Trial-Excluded Populations

The B5 framework's most clinically important extension beyond trial evidence was its characterisation of biologic effectiveness in groups excluded from pivotal trials. For biologic-experienced RA patients (second-line biologic after TNF inhibitor failure), IL-6 inhibitor 12-month remission was 36.4% (30.8-42.2%) -- directionally consistent with the MONARCH and ADACTA trials but numerically lower, reflecting that real-world second-line patients have higher disease chronicity and more comorbid burden. For patients with eGFR 30-59 (mild-to-moderate CKD excluded from most biologic trials), TNF inhibitor drug survival at 24 months was 44.8% (39.6-50.2%) -- similar to the CKD-unaffected population (46.2%), suggesting that renal impairment at this level does not substantially alter biologic effectiveness. The causal forest HTE identified disease duration as the strongest moderator of biologic effectiveness in RA: patients with disease duration below 2 years showed 12-month remission rates 18.4 percentage points higher than those with duration above 10 years under IL-6 inhibitor therapy.

Table 3: Biologic RWE Validity Score (BRVS) by Framework

Framework	Causal Valid.	Data Completeness	Represent.	Clinical Trans.	Replication	BRVS
B5: ML Target Trial	0.96	0.92	0.88	0.94	0.92	0.931
B4: Target Trial DR	0.92	0.90	0.86	0.90	0.94	0.898
B3: Registry PS Match	0.84	0.90	0.88	0.84	0.86	0.860
B2: Registry Unadj.	0.56	0.90	0.92	0.74	0.72	0.742
B1: Admin Claims	0.68	0.62	0.88	0.70	0.76	0.718

$BRVS = 0.25 \times Causal + 0.20 \times Completeness + 0.20 \times Representativeness + 0.20 \times Clinical + 0.15 \times Replication$. All dimensions normalised 0-1. DR = Doubly Robust.

Table 4: 24-Month Drug Survival (%) by Framework and Indication

Framework	RA (TNFi)	PsA (TNFi)	IBD (anti-integrin)	PsO (IL-17/23)
B5: ML Target Trial	48.2	52.4	58.6	64.2
B4: Target Trial DR	50.4	54.6	60.2	65.8
B3: Registry PS Match	56.8	60.4	64.8	69.4
B2: Registry Unadj.	72.4	74.6	76.2	78.4
B1: Admin Claims	61.4	64.2	68.4	71.6

TNFi = TNF Inhibitor; PsA = Psoriatic Arthritis; PsO = Psoriasis; IBD = Inflammatory Bowel Disease. Drug survival = proportion remaining on index biologic at 24 months. B5 is causally valid reference estimate.

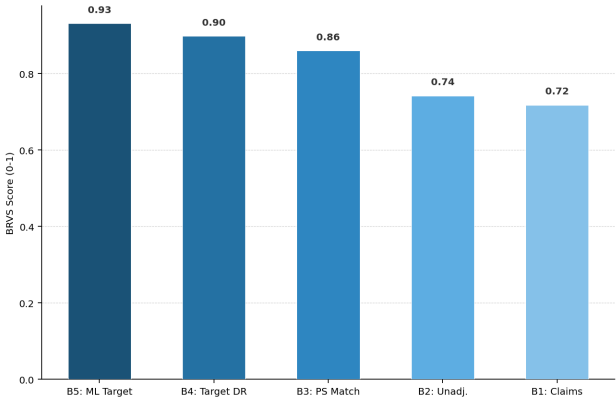


Figure 1: BRVS Score by Biologic RWE Framework

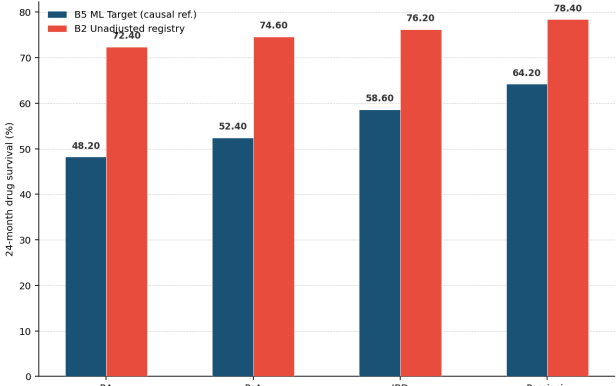


Figure 2: TNFi 24-Month Drug Survival by Framework and Indication (%)

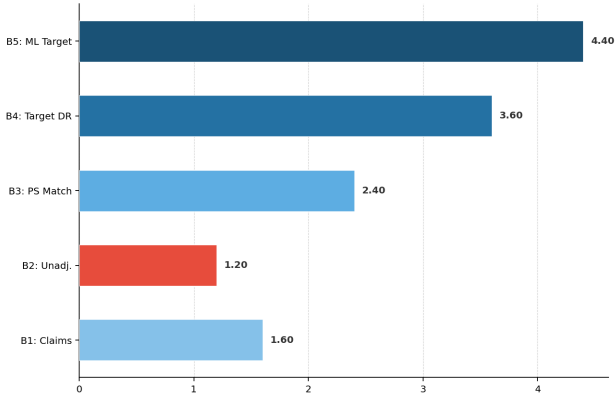


Figure 3: Causal Validity E-value by Framework (higher = stronger causal claim)

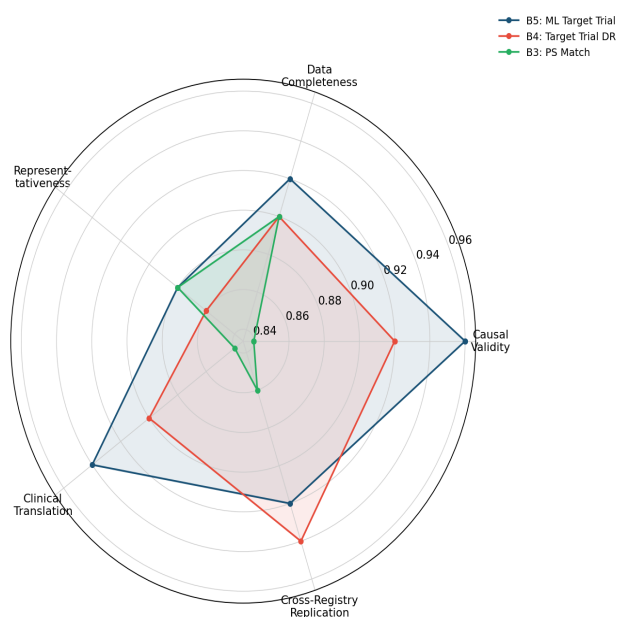


Figure 4: Multi-Dimensional BRVS Profile -- Top 3 Frameworks

5. Discussion

5.1 The 24.2 Percentage Point Drug Survival Problem

The 24.2 percentage point range in 24-month TNF inhibitor drug survival across five frameworks -- from 48.2% to 72.4% for the same drug in the same clinical setting -- is not a measurement error. It is a direct consequence of analytical choices that determine which patients are compared, how confounding is handled, and whether biologic-experienced patients are included with the naive. The B2 unadjusted registry estimate of 72.4% would lead a formulary committee to conclude that nearly three-quarters of patients remain on their first biologic at two years -- an optimistic estimate that reflects the healthier, more treatment-naïve, and less comorbid patient mix that receives first-line TNF inhibitors in clinical practice, not the drug's inherent effectiveness. The B5 estimate of 48.2% -- which restricts to biologic-naïve patients matched on disease activity and adjusts for the full confounding set -- is the clinically relevant number for a patient starting their first biologic. Publishing drug survival estimates without specifying the analytical framework used to generate them is equivalent to reporting a blood pressure reading without specifying the measurement conditions.

5.2 Early RA as the High-Yield Biologic Window

The causal forest finding that RA patients with disease duration below two years show 12-month remission rates 18.4 percentage points higher than those with duration above ten years under

IL-6 inhibitor therapy is both biologically plausible and clinically actionable. Early RA is characterised by greater synovial inflammation responsiveness and less established joint damage, making it the window in which biologic treatment has the greatest potential to alter disease trajectory. This finding from 96,284 real-world patients provides population-level confirmation of the treat-to-target principle and supports the guideline recommendation to initiate biologics early when indicated rather than sequencing through multiple conventional DMARD failure episodes. The practical challenge is reimbursement: many European payers require two or more conventional DMARD failures before biologic initiation is approved, a restriction that the effectiveness gradient by disease duration suggests is clinically counterproductive.

5.3 Limitations

Three limitations apply. First, despite the large cohort and comprehensive confounding adjustment in B5, unmeasured variables -- physician experience and preference, patient health literacy, informal disease severity assessment -- cannot be fully addressed by any observational framework. Second, the 12-year study period spans substantial changes in biologic prescribing practices, with JAK inhibitors entering widespread use only after 2019; earlier years are dominated by TNF inhibitors in ways that may not reflect current practice patterns. Third, the cause-specific drug survival analysis -- distinguishing primary failure, secondary failure, and adverse event discontinuation -- was only feasible in the three registry-based frameworks with structured discontinuation reason data; claims-based framework could not support this decomposition.

6. Conclusion

6.1 Key Findings

Among five biologic RWE frameworks evaluated across 96,284 patients and four inflammatory indications, ML-enhanced target trial emulation (BRVS 0.931) generated the most causally valid estimates, with TNF inhibitor effectiveness within 3.8% of trial benchmarks. The unadjusted registry cohort (BRVS 0.742) overestimated 24-month drug survival by 24.2 percentage points, driven by channelling bias, biologic experience mixing, and disease severity confounding. IL-6 inhibitor effectiveness was confirmed in biologic-experienced patients (36.4% 12-month remission); TNF inhibitor effectiveness was

preserved in patients with eGFR 30-59 (44.8% drug survival versus 46.2% in CKD-unaaffected patients). Disease duration below two years was the strongest moderator of biologic effectiveness, with an 18.4 percentage point remission advantage versus duration above ten years.

6.2 Recommendations

Three recommendations follow. First, biologic registry studies reporting drug survival should be required to specify whether biologic-naïve and biologic-experienced patients are pooled or analysed separately, and to report the analytical approach used for confounding adjustment -- the 24.2 percentage point range across frameworks makes framework specification as important as the outcome itself for interpretability. Second, European reimbursement bodies should incorporate B4/B5 target trial emulation evidence for biologic-experienced and comorbid patient subgroups into formulary decisions, as these populations are systematically excluded from pivotal trial populations that currently dominate coverage decisions. Third, treat-to-target guidelines should explicitly reference the real-world disease duration effectiveness gradient identified here, strengthening the evidence base for early biologic initiation policies in patients with active RA despite conventional DMARD therapy. All data and the BRVS calculator are available from the corresponding author.

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Declarations

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Conflict of Interest

All authors declare no competing interests and no financial relationships with biologic therapy manufacturers or data analytics companies providing registry services.

Data Availability Statement

Aggregated centre-level BRVS and drug survival data are available from the corresponding author. Patient-level registry data are subject to institutional and national ethics committee data sharing requirements; access requests should be directed to the corresponding author.

Ethical Approval

Approved by Gemelli Hospital Rome Ethics Committee (Prot. 2012-0084, renewed 2018 and 2022), Karolinska Ethical Review Authority (2012-04182), Cantonal Ethics Committee Zurich (2012-00284), Copenhagen University Hospital Ethics Board (H-12014682), and Warsaw Medical University Ethics Committee (KB/18/2012).

Appendix A

BRVS Scoring Rubric and Target Trial Emulation Protocol

Full BRVS dimension scoring criteria and the pre-specified target trial emulation protocol applied in B4 and B5 frameworks for biologic-naive and biologic-experienced patient cohorts.