



PROACTIVE VERSUS REACTIVE THERAPEUTIC DRUG MONITORING OF BIOLOGIC THERAPIES IN INFLAMMATORY BOWEL DISEASE AND RHEUMATOLOGY: EVIDENCE, THRESHOLDS AND PHARMACIST-LED IMPLEMENTATION

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ABSTRACT

Monoclonal antibodies against tumour necrosis factor (TNF) and other cytokine targets fail in a predictable fraction of patients with inflammatory bowel disease (IBD) and inflammatory arthritis, and a large share of that failure is pharmacokinetic. Therapeutic drug monitoring (TDM) measures trough drug concentration and anti-drug antibodies (ADA) so that dosing can be corrected. Reactive TDM, performed when response is lost, is supported by randomised and observational evidence and by every major guideline. Proactive TDM, in which levels are checked in stable patients and doses adjusted to a target, is contested. This review appraises the randomised trials in both specialties and their observational precursors. In infliximab maintenance, the NOR-DRUM B trial (n=458)

reported sustained disease control in 73.6% of patients under proactive TDM against 55.9% under standard care, and a 2024 meta-analysis estimated a relative risk of 1.26 (95% CI 1.14 to 1.40) for this setting, rated low certainty. Proactive dosing during induction (TAILORIX, NOR-DRUM A) and adult adalimumab maintenance (SERENE CD) showed no benefit, whereas paediatric adalimumab (PAILOT) and Bayesian infliximab dosing (PRECISION) favoured concentration-guided care. Rheumatology evidence centres on avoiding overexposure: adalimumab response plateaus at 5 to 8 mg/L, and interval extension above 8 µg/mL proved non-inferior. Proposed thresholds, their derivations and their limits are tabulated. Pharmacist-run programmes in Australia and Spain have tripled the proportion of patients in the target range and reduced surgery and hospitalisation against historical controls. A pharmacist-led pathway is proposed for Indian hospitals, where cost and turnaround currently restrict TDM to a minority of centres. Proactive monitoring is justified for maintenance infliximab; elsewhere, reactive TDM with structured interpretation remains the defensible standard.

Keywords: Drug Monitoring; Infliximab; Adalimumab; Inflammatory Bowel Diseases; Arthritis, Rheumatoid; Pharmacists; Antibodies, Monoclonal; Precision Medicine



1. Introduction

Roughly one patient in four with Crohn's disease does not respond to the first anti-TNF agent. In the prospective PANTS cohort of 1610 anti-TNF-naïve patients, primary non-response at week 14 reached 23.8%, and by week 54 almost two-thirds were not in remission.¹ The single independent predictor of non-response was a low drug concentration at week 14. That finding reframes treatment failure. A patient labelled refractory may simply be underexposed.

Monoclonal antibodies behave unlike small molecules. Clearance rises with inflammatory burden, faecal protein loss, low serum albumin, high body weight and male sex, and it rises sharply once ADA form.² Interindividual variation in trough concentration at a fixed weight-based dose is therefore wide. In rheumatoid arthritis (RA), 28% of 272 adalimumab-treated patients developed antibodies over three years, most within 28 weeks, and those with antibodies were three times more likely to stop treatment for failure.³ The association between detectable trough infliximab and remission had already been shown in 2006, when 82% of Crohn's patients with a detectable level were in remission against 6% of those without.⁴

Two strategies follow. Reactive TDM measures drug and ADA after loss of response and uses the result to choose between dose intensification, a within-class switch and a change of mechanism. Proactive TDM measures levels in patients who are doing well and adjusts dosing toward a

predefined target, aiming to prevent the loss of response rather than explain it. Guidelines diverge on the second strategy. The American Gastroenterological Association (AGA) supports reactive testing but made no recommendation on proactive testing,⁵ EULAR advises against routine proactive TDM in rheumatic disease,⁶ an expert panel endorsed proactive anti-TNF monitoring after induction and once in maintenance,⁷ and a 2024 BMJ guideline, built on a fresh meta-analysis, gave a weak recommendation for proactive TDM only during intravenous infliximab maintenance.^{8,9}

The disagreement is not about pharmacology, which is settled, but about whether adjusting doses in stable patients changes outcomes that matter. This review weighs the trial evidence for each setting, sets out the concentration thresholds with the provenance of each, and argues that the clinical pharmacist is the professional best placed to run a monitoring service, with specific attention to Indian practice.

2. Literature identification

Literature published between January 2006 and September 2026 was identified through PubMed-indexed records, Crossref and OpenAlex metadata, and publisher websites, using combinations of *therapeutic drug monitoring*, *proactive*, *reactive*, *trough*, *anti-drug antibodies*, *infliximab*, *adalimumab*, *vedolizumab*, *ustekinumab*, *inflammatory bowel disease*, *rheumatoid arthritis*, *spondyloarthritis* and *pharmacist*. Randomised trials, prospective cohorts, meta-analyses, cost-effectiveness



models and society guidelines were prioritised; reference lists of retrieved papers were hand-searched. Each bibliographic record was checked against its source. The review is narrative and does not claim systematic completeness.

3. Reactive TDM: the settled ground

Reactive TDM earns its place on cost and on decision quality, not on remission rates. In a Danish trial of 69 Crohn's patients with secondary infliximab failure, an algorithm based on drug and antibody levels produced response rates similar to empirical intensification to 5 mg/kg every four weeks (58% versus 53%) at 34% lower cost (€6038 versus €9178 per patient over 12 weeks).¹⁰ The saving came from not escalating patients whose failure was immunogenic or inflammatory.

The interpretation matrix that underlies this decision was quantified by Yanai and colleagues across 330 loss-of-response events.¹¹ Infliximab above 3.8 µg/mL or adalimumab above 4.5 µg/mL identified, with 90% specificity, patients in whom intensification or a within-class switch would fail; a change of mechanism was the better choice. High antibody titres (infliximab above 9 µg/mL-equivalent, adalimumab above 4 µg/mL-equivalent) predicted that dose escalation would not overcome immunogenicity. Four phenotypes emerge (Figure 2): pharmacokinetic failure with low drug and no antibody, immunogenic failure, mechanistic failure despite adequate drug, and the less discussed state of overexposure in a patient already in remission.

The 2021 consensus panel extended this logic: reactive testing is appropriate for all biologics at primary non-response or secondary loss of response, and infliximab or adalimumab should not be abandoned for want of efficacy until levels reach at least 10 to 15 µg/mL.⁷ Earlier appropriateness ratings reached similar conclusions.¹² No major guideline disputes reactive TDM. The open question lies elsewhere.

4. Proactive TDM in inflammatory bowel disease

4.1 Observational signal

The case for proactive monitoring began in retrospective cohorts from a small number of North American centres. In 2014, 48 patients whose infliximab was titrated proactively were less likely to discontinue than 78 conventionally managed controls (10% versus 31%).¹³ A multicentre comparison of 264 patients followed for a median of 2.4 years then reported hazard ratios favouring proactive monitoring of 0.16 for treatment failure, 0.30 for surgery and 0.16 for hospitalisation.¹⁴ A further cohort showed that adding proactive checks after an initial reactive test outperformed reactive testing alone (treatment failure HR 0.15).¹⁵

These effect sizes are too large to be plausible as unbiased estimates. Patients selected for proactive testing were seen at specialist centres by clinicians committed to the strategy, and the comparison groups were assembled retrospectively. The weak point is confounding by attentiveness: a patient whose levels are



checked every few months is also a patient whose symptoms, adherence and calprotectin are checked every few months.

4.2 Randomised trials

Randomised evidence is summarised in Table 1, and the primary endpoints are compared in Figure 1. The pattern is uneven, and the unevenness is informative.

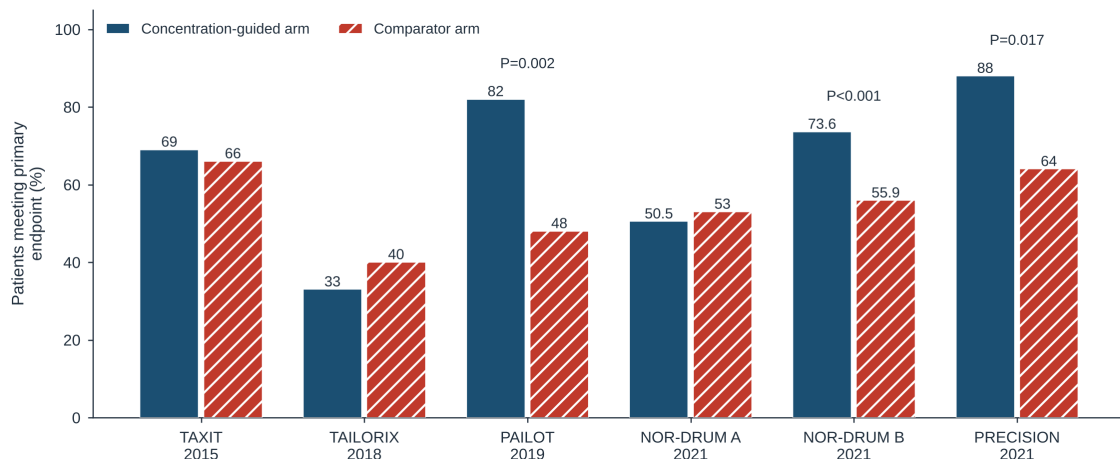


Figure 1. Primary endpoint results in six randomised trials of concentration-guided versus conventional biologic dosing. Bars give the percentage of patients meeting each trial's own primary endpoint: remission at 1 year (TAXIT, PRECISION), sustained steroid-free remission with mucosal healing (TAILORIX, DIS1 arm against symptom-driven control), sustained steroid-free remission (PAILLOT, paediatric adalimumab), remission at week 30 (NOR-DRUM A, induction) and sustained disease control (NOR-DRUM B, maintenance). P values are shown where the trial reported a significant difference. Endpoints differ between trials, so bar heights are not comparable across trials. Values extracted from the trial reports [16-18,20-22].

Table 1. Randomised trials comparing concentration-guided with conventional dosing of biologics in IBD and immune-mediated inflammatory disease.

Trial (year)	Population, n	Strategy and target	Primary outcome: concentration-guided vs comparator
TAXIT (2015) [16]	Adults on IFX maintenance, CD and UC; 263 optimised, 251 randomised	All optimised to trough 3-7 µg/mL, then proactive vs clinically based dosing	Remission at 1 year 69% vs 66% (P=0.686); relapse 7% vs 17% (P=0.018)
TAILORIX (2018) [17]	Biologic-naïve active CD, n=122	Escalation on symptoms, biomarkers or trough <3 µg/mL vs symptoms alone	Sustained steroid-free remission with mucosal healing 33% (DIS1) vs 40% (P=0.50)
PAILLOT (2019) [18]	Paediatric CD responding to ADA induction, n=78	Proactive trough ≥5 µg/mL vs reactive	Sustained steroid-free remission 82% vs 48% (P=0.002)
SERENE CD (2022) [19]	Adult CD on ADA maintenance, 92 per arm	TDM-based vs clinically adjusted dosing	Week 56 efficacy similar between arms
NOR-DRUM A	IFX induction across six	Proactive TDM during	Remission at week 30 50.5% vs 53.0% (difference 1.5%,



Trial (year)	Population, n	Strategy and target	Primary outcome: concentration-guided vs comparator
(2021) [20]	IMIDs, n=398	induction vs standard	95% CI -8.2 to 11.1)
NOR-DRUM B (2021) [21]	IFX maintenance across six IMIDs, n=454	Proactive TDM, trough 3-8 µg/mL, vs standard	Sustained disease control 73.6% vs 55.9% (difference 17.6%, 95% CI 9.0 to 26.2)
PRECISION (2021) [22]	IFX maintenance in remission, CD and UC, n=80	Bayesian dashboard dosing, trough 3 µg/mL, vs standard	Sustained remission at 1 year 88% vs 64% (P=0.017)

ADA, adalimumab; CD, Crohn's disease; IFX, infliximab; IMID, immune-mediated inflammatory disease (Crohn's disease, ulcerative colitis, RA, spondyloarthritis, psoriatic arthritis, psoriasis); UC, ulcerative colitis.

TAXIT is often cited as a negative trial, which misreads it. Before randomisation, every patient was brought into the 3 to 7 µg/mL range; the 76 patients below range improved Crohn's remission from 65% to 88%, and dose reduction in those above range cut drug cost by 28%.¹⁶ The randomised comparison therefore tested continued proactive adjustment against clinical dosing in patients who were already optimised. The primary endpoint did not separate, but relapse fell from 17% to 7%.

Induction is different. Neither TAILORIX nor NOR-DRUM A showed that concentration-guided escalation during the first 14 weeks improves remission.^{17,20} Two explanations compete. Early inflammation consumes drug faster than a trough measured at a single visit can capture, so the targets used may have been too low; alternatively, the outcome at week 30 or 54 is dominated by whether the mechanism suits the disease, which no amount of dose adjustment can alter. The second explanation is more consistent with PANTS, in which low week-14 levels predicted failure but a substantial minority failed despite adequate exposure.¹

Against this, maintenance infliximab has the strongest randomised support of any setting. NOR-DRUM B enrolled 458 patients with six diagnoses at 20 Norwegian hospitals and reported an absolute gain of 17.6 percentage points in sustained disease control without any rise in adverse events (60% versus 63%).²¹ PRECISION, which used a pharmacokinetic model to forecast the next dose rather than react to the last level, achieved 88% sustained remission against 64%.²² A Bayesian approach applied during induction in 180 patients similarly linked adherence to model-forecast dosing with fewer antibodies and better persistence, though without a randomised comparator.²³

Adalimumab results split by age. The paediatric PAILOT trial showed a 34-point difference in sustained steroid-free remission,¹⁸ while the adult SERENE CD maintenance comparison found none [19]. Children clear antibodies faster per kilogram and were dosed proactively at a higher target; whether that explains the gap or whether PAILOT's open-label design inflated the effect is not known.



The 2024 meta-analysis by Zeraatkar and colleagues pooled ten trials and 2383 patients.⁸ For infliximab maintenance (four trials, 901 patients) proactive TDM increased sustained disease control or remission with a relative risk of 1.26 (95% CI 1.14 to 1.40), about 146 more patients per 1000, at low certainty. Effects during infliximab induction and in adalimumab maintenance were uncertain. An earlier meta-analysis of nine studies, all on infliximab maintenance, found no remission benefit for either strategy but better drug durability with proactive monitoring and cost savings with reactive testing.²⁴ The two syntheses agree more than their headlines suggest: neither supports proactive TDM outside infliximab maintenance.

For vedolizumab and ustekinumab, exposure-response relationships exist, but no completed randomised trial of proactive dosing has been published. The 2025 British Society of Gastroenterology guideline describes the benefit of anti-TNF TDM as uncertain and sees no current role for TDM with non-anti-TNF advanced therapies.²⁵

5. Rheumatology: the problem of too much drug

Rheumatology asks a different question. Methotrexate co-therapy is near universal in RA, antibody rates are lower than in Crohn's disease, and the clinical concern is as often unnecessary exposure as inadequate exposure.

The concentration-effect curve for adalimumab in 221 RA patients rose to a plateau at 5 to 8 mg/L, with no additional DAS28 improvement

above 8 mg/L.²⁶ Median trough was 4.1 µg/mL on monotherapy and 7.4 µg/mL with methotrexate. A substantial fraction of patients on standard fortnightly dosing therefore sit above the range where extra drug buys extra effect. The randomised test of that idea came in 2018: among 55 RA patients with adalimumab levels above 8 µg/mL, extending the interval to three weeks was non-inferior to continued fortnightly dosing over 28 weeks, and mean levels fell from 10.6 to 6.6 µg/mL.²⁷ The authors estimated roughly a one-third drug saving.

A Danish trial in 239 patients with RA, psoriatic arthritis or axial spondyloarthritis extended this approach across three TNF inhibitors and reduced prescribed drug (infliximab dose down 12%, adalimumab interval lengthened 28%) without change in disease activity.²⁸ A Spanish pragmatic trial of TDM-guided adalimumab missed its flare endpoint (0.67 versus 0.90 persistent flares, $P=0.073$) yet was cheaper and gained 0.075 QALYs.²⁹ Infliximab data are older: concentration monitoring altered treatment decisions in half of 24 RA patients in a 2009 French study.³⁰

The 2023 EULAR points to consider weighed this literature and concluded that routine proactive TDM is not recommended in inflammatory rheumatic disease, while reactive testing could be considered at non-response, before tapering patients with high levels, and after hypersensitivity reactions.⁶ NOR-DRUM B, which included rheumatological diagnoses, is the main counterweight, but its disease-specific effects were not powered separately.²¹



Rheumatology thus has a usable de-escalation strategy and a weak case for routine proactive escalation.

which outcomes are worse; they do not prove that raising the level to that value will improve outcomes. Table 2 sets out the most widely used targets with their derivations.

6. Thresholds: what the numbers mean and where they came from

A threshold carries the design of the study that produced it. Values derived from cross-sectional associations in remission identify a level below

Table 2. Trough concentration thresholds for biologic TDM and the evidence behind each.

Agent and setting	Proposed threshold	Derivation	Source
Infliximab, IBD, week 14	7 mg/L	Level associated with remission at weeks 14 and 54 in a prospective cohort	PANTS [1]
Infliximab, IBD maintenance	≥5 µg/mL (reactive); 3-7 or 3-8 µg/mL (proactive)	Guideline evidence synthesis; trial targets	AGA [5]; TAXIT [16]; NOR-DRUM B [21]
Adalimumab, IBD, week 14	12 mg/L	Prospective cohort association	PANTS [1]
Adalimumab, IBD maintenance	≥7.5 µg/mL (adult reactive); ≥5 µg/mL (paediatric proactive)	Guideline synthesis; randomised target	AGA [5]; PAILOT [18]
Certolizumab pegol, IBD	≥20 µg/mL	Guideline synthesis	AGA [5]
Infliximab or adalimumab before abandoning for mechanistic failure	10-15 µg/mL	Delphi consensus	Cheifetz [7]
Drug adequate at loss of response	Infliximab >3.8; adalimumab >4.5 µg/mL	90% specificity for failure of escalation	Yanai [11]
High-titre ADA predicting failure of escalation	Infliximab >9; adalimumab >4 µg/mL-eq	Retrospective cohort, assay specific	Yanai [11]
Adalimumab, RA	5-8 mg/L effect plateau; >8 µg/mL candidate for interval extension	Concentration-effect curve; non-inferiority RCT	Pouw [26]; l'Ami [27]
Vedolizumab, ustekinumab	No validated proactive target	No completed proactive RCT	BSG 2025 [25]

µg/mL-eq, microgram-equivalents per millilitre; ADA in this table denotes anti-drug antibodies.

Three cautions apply before any number is entered into a protocol. Antibody units are not

interchangeable between assays, so a titre from one laboratory cannot be read against a cut-off



from another; the PANTS and Yanai values belong to specific platforms. Concomitant immunomodulators shift both drug level and antibody risk: in SONIC, antibodies to infliximab appeared in 0.9% of patients on combination therapy and 14.6% on infliximab alone, and median trough doubled.³¹ In PANTS, an immunomodulator reduced antibody formation by more than half for both agents.¹ Finally, targets for perianal fistulising disease and for mucosal healing sit higher than those for clinical remission, so a single maintenance target can under-dose the patient whose goal is endoscopic.

7. Pharmacist-led implementation

Proactive TDM fails in practice for organisational reasons more often than pharmacological ones. Samples are drawn at the wrong time, results return after the next infusion has already been given at the old dose, antibody results are misread across assays, and nobody owns the follow-up level. Each of these is a medication-management task, and each falls within the training of a clinical pharmacist.

The most complete published model comes from Melbourne. Rentsch and colleagues placed pharmacists at the infusion chair with a point-of-care infliximab assay for 48 maintenance patients, targeting 3 to 7 µg/mL.³² Only 20% were in range at baseline; by weeks 24 and 48 the proportion had tripled. About half started above range and most were corrected with a single dose change without loss of disease control, while 29% of those below range needed

two or three adjustments. Drug cost fell by 4%, and the process added around 30 minutes per infusion. In Salamanca, a multidisciplinary early proactive programme run with the hospital pharmacy treated 81 IBD patients and compared them with 72 historical controls on empirical dosing.³³ Treatment failure (HR 0.51, 95% CI 0.27 to 0.92), surgery (HR 0.14) and hospitalisation (HR 0.38) were all lower. Neither study was randomised, and the Salamanca comparison is open to secular change in care.

Wider pharmacist involvement in IBD clinics has been linked to more steroid-free patients (63% versus 50%) and greater CRP reduction in a United States before-and-after comparison.³⁴ The weakness of this evidence base is uniform: single centres, historical controls, and process outcomes more often than disease outcomes.

Point-of-care testing is what makes infusion-chair dosing possible. A lateral-flow assay correlated closely with ELISA (Spearman 0.93 for infliximab, 0.88 for adalimumab), but it read infliximab systematically higher, and the dosing decision would have differed in 21.6% of samples.³⁵ A service must therefore use one platform per patient and re-derive targets if it changes method.

Cost decides adoption. A simulation of Crohn's disease estimated that proactive infliximab TDM cost US\$146,494 per QALY gained at 40% of list price, only marginally cost-effective, but became more attractive as the drug price fell.³⁶ That sensitivity matters for biosimilars. Where an infusion costs less, the value of each avoided flare stays the same while the cost of the extra



monitoring becomes proportionally larger, so proactive TDM is most defensible where it also enables dose reduction.

7.1 The Indian context

India's case is sharpest on access. A national survey of 101 gastroenterologists found that about one in five used TDM and proactive use was rare (5.3%); cost (71.2%), availability (67.8%) and delayed results (58.7%) were the named barriers, and almost all non-users said they would use it if these were removed.³⁷ TDM services in general remain concentrated in a few academic centres, and a national action plan with nodal laboratories has been proposed.³⁸ Biosimilar infliximab performed comparably to the originator in a North Indian IBD cohort, which also recorded 18 cases of tuberculosis over follow-up,³⁹ a reminder that a service optimising anti-TNF exposure in India must include tuberculosis screening and surveillance as standard steps.

No Indian study has yet reported outcomes from pharmacist-delivered biologic TDM. Pharm D graduates now work in tertiary hospitals across Karnataka and other states, and their role in antimicrobial and antiepileptic monitoring is established. Extending that role to biologics requires three things: a hospital protocol that authorises pharmacist-ordered troughs and dose recommendations within agreed limits, a laboratory arrangement with a fixed assay and a turnaround shorter than the infusion interval, and documentation that allows audit of time in target range.

Figure 2 sets out a pathway suited to this setting. Its proactive arm is restricted to maintenance infliximab, where the trial evidence lies, and to patients considered for de-escalation, where the rheumatology evidence lies. Every other test is reactive and objective-inflammation-triggered.

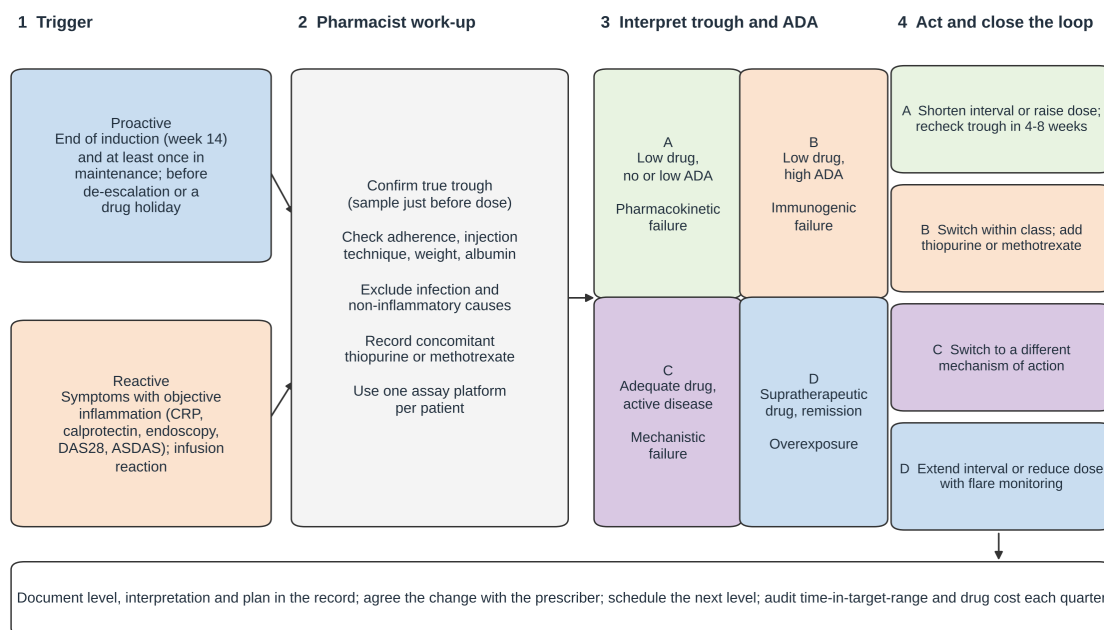




Figure 2. Proposed pharmacist-led pathway for biologic TDM. Proactive testing is restricted to the end of infliximab induction, at least one maintenance check and assessment before de-escalation; reactive testing follows symptoms with objective inflammation. After pharmacist work-up, trough drug and anti-drug antibody (ADA) results fall into four phenotypes (A to D), each mapped by letter and shade to its action. Thresholds for each phenotype are given in Table 2. CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ASDAS, Ankylosing Spondylitis Disease Activity Score.

8. Discussion

The weight of evidence supports proactive TDM in one setting: intravenous infliximab maintenance, where one large pragmatic trial, one Bayesian dosing trial and a pooled estimate point the same way. It does not support proactive escalation during induction, and in adult adalimumab maintenance the single randomised comparison was null. In rheumatology, the strongest use of a trough level is to identify patients who can safely receive less drug.

The trials have shared weaknesses. All were open-label, which matters when the primary endpoint includes patient-reported symptoms. Targets differed between trials, so a negative result may reflect a low target rather than a failed strategy. Comparator arms varied from purely symptom-driven dosing to reactive testing, which changes what "standard care" means. Follow-up rarely exceeded one year, while the outcomes that justify the cost (surgery, hospitalisation, loss of a drug class) accrue over longer periods. The observational cohorts that generated the original enthusiasm are larger in effect and weaker in design.

The next informative trial is not another comparison of proactive against standard care in infliximab maintenance. It is a randomised comparison of model-informed (Bayesian)

dosing against fixed-target proactive TDM in subcutaneous infliximab, adalimumab and ustekinumab, with endoscopic co-primary endpoints, two-year follow-up and a prespecified cost analysis. For India, a pragmatic stepped-wedge implementation study of a pharmacist-led service across several hospitals would answer the questions that matter locally: turnaround time, time in range, flare rate and net drug cost under biosimilar pricing.

9. Conclusion

Proactive TDM is justified for maintenance infliximab and for de-escalation in patients with high trough concentrations; elsewhere, reactive TDM interpreted with a structured matrix remains the defensible standard. Clinical pharmacists can run both, and in Indian hospitals the barrier is protocol and laboratory turnaround rather than knowledge.

Declarations

Conflicts of interest: None declared.

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