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Which DMARD should be de-escalated first in rheumatoid arthritis at target on combination therapy? Protocol for a systematic review and meta-analysis of randomized order-of-de-escalation trials

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026100014

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 October 2026 and was last updated on 2 October 2026.

INTRODUCTION

Review question / Objective In adults with rheumatoid arthritis who are in remission or low disease activity on a csDMARD combined with a bDMARD or tsDMARD, does de-escalating the csDMARD first (b/tsDMARD maintained) differ from de-escalating the b/tsDMARD first (csDMARD maintained) in maintaining disease control? The primary outcome is cumulative flare/failure within 48–52 weeks. Secondary objectives are remission and low disease activity, recapture after flare, function, radiographic progression and safety.

Condition being studied Rheumatoid arthritis in sustained remission or low disease activity (trial-defined, e.g. DAS28, DAS44, SDAI, CDAI or Boolean criteria) on csDMARD + b/tsDMARD combination therapy. De-escalation includes dose reduction, interval spacing, stepwise taper to discontinuation and immediate withdrawal.

METHODS

Participant or population Adults (≥ 18 years) with RA on ≥ 1 csDMARD plus one bDMARD or tsDMARD who are in remission or LDA by trial definition at randomization. Early and established RA are both eligible. Trials that randomized the future withdrawal strategy before target attainment, applying it only to those who later reached the target, are conditionally eligible (sensitivity analysis only).

Intervention csDMARD-first de-escalation (dose reduction, taper to stop or immediate withdrawal of the csDMARD) while the b/tsDMARD is maintained.

Comparator b/tsDMARD-first de-escalation (dose reduction, interval spacing, taper to stop or immediate withdrawal of the b/tsDMARD) while the csDMARD is maintained.

Study designs to be included Randomized controlled trials, including multi-arm trials and randomized strategy trials. Observational studies are excluded.

Eligibility criteria Any language, publication status (full paper, abstract, registry results) or year. Multiple reports of one randomized cohort are grouped as one trial family. Excluded:

- trials comparing de-escalation of one class with continuation only;
- withdrawal at treatment start in active disease;
- temporary interruptions (surgery, vaccination, pregnancy, adverse events);
- biosimilar switching;
- trials randomizing only the induction regimen.

Eligible trials without available results are listed as awaiting classification.

Information sources - Databases: PubMed ; Embase, CENTRAL, Web of Science and Scopus.
 - Registries: ClinicalTrials.gov, WHO ICTRP (including jRCT/UMIN/ChiCTR/NTR), EU CTR/CTIS and ISRCTN.
 - Conference abstracts: ACR Convergence archive; EULAR abstracts via Embase/Web of Science.

Main outcome(s) Cumulative flare/failure within 48–52 weeks after the start of de-escalation: at least one protocol-defined flare, disease worsening, relapse, or loss of target requiring rescue. Hierarchy: ITT/FAS counts from the full report, then per-protocol counts (with ITT imputation sensitivity), then registry results. Kaplan–Meier percentages are not converted into counts. Effect measure: risk ratio, csDMARD-first vs b/tsDMARD-first.

Quality assessment / Risk of bias analysis RoB 2 (assignment effect) will be assessed for each outcome contributing to synthesis. GRADE will be applied to the primary outcome, remission, serious adverse events and radiographic progression. Non-reporting of eligible registered trials will be considered under publication bias.

Strategy of data synthesis The primary model is a Bayesian random-effects normal-normal hierarchical model on log RR, with a half-normal(0.5) prior on τ and a uniform prior on the mean, computed by exact numerical integration. Results will be reported as posterior median, 95% CrI, $\Pr(RR < 1)$ and 95% prediction interval. Frequentist models (REML with Hartung–Knapp and modified Hartung–Knapp, DerSimonian–Laird, Mantel–Haenszel) and risk differences are sensitivity analyses. Multi-arm trials contribute only

their two order arms. No funnel plots or small-study tests will be used (fewer than 10 trials expected). The primary analysis set comprises all trials randomized after target attainment.

Subgroup analysis If available, comparison by:

- de-escalation intensity: complete or taper-to-stop vs partial;
- targeted drug class: TNFi vs other.

Sensitivity analysis - Adding conditionally eligible trials;

- leave-one-out;
- ITT imputation of per-protocol exclusions;
- excluding trials at high risk of bias.

Country(ies) involved China.

Keywords rheumatoid arthritis; treatment de-escalation; tapering; methotrexate; biologic DMARD; JAK inhibitor; remission; meta-analysis.

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