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Targeted therapy after failure of two or more biologic or targeted synthetic DMARDs in axial spondyloarthritis: protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review stage at the time of initial registration - Piloting of the study selection process.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2026 and was last updated on 23 November 2026.

INTRODUCTION

Review question / Objective Primary objective: To estimate the outcomes of a b/tsDMARD started after failure of two or more previous distinct b/tsDMARDs (third or later line) in adults with axSpA. Secondary objectives: (1) Prognostic association: to compare these outcomes with those of patients who had one previous b/tsDMARD in the same study. This is a prognostic comparison, not a treatment effect. (2) Comparative effectiveness: to compare treatment options at third or later line (same class again versus new mechanism; TNF inhibitor, IL-17 inhibitor, JAK inhibitor); appropriately adjusted comparative estimates form the main evidence. (3) Efficacy versus placebo in randomised trials, where results for patients with two or more previous b/tsDMARDs are reported. (4) Outcomes in patients in whom both a TNF inhibitor and an IL-17 inhibitor have failed, and in cohorts meeting the ASAS D2M/treatment-refractory definition (prespecified subgroups). (5) Discontinuation because of inefficacy or adverse events, and serious adverse events.

Rationale Most evidence on switching in axial spondyloarthritis (axSpA) concerns the first change after a TNF inhibitor. Earlier systematic reviews are limited for the question addressed here. Navarro-Compán et al. (2017; PMID 29071119, DOI 10.1136/rmdopen-2017-000524) identified nine studies, with 1,956 patients on a second and only 170 on a third biologic, all third-line treatments being TNF inhibitors, and judged the third-line evidence insufficient. Yu et al. (2020; PMID 32946076, DOI 10.1007/s40259-020-00442-x) meta-analysed biologic drug survival in 39 real-world studies of ankylosing spondylitis up to May 2020 and assessed second and third lines together. Rana et al. (2026; PMID 42763066, DOI 10.1016/j.autrev.2026.104188) synthesised the prevalence and determinants of ASAS difficult-to-manage/treatment-refractory axSpA, not the outcomes of the next treatment, and is complementary. The 2025 British Society for

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Rheumatology axSpA guideline (PMID 40199504, DOI 10.1093/rheumatology/keaf089) identifies the safety and effectiveness of sequential targeted therapy as an important unmet research need. No dedicated, up-to-date systematic review has separately synthesised third- or later-line treatment outcomes across contemporary TNF, IL-17 and JAK inhibitor sequences in adults with axSpA after failure of at least two previous targeted therapies (PROSPERO and PubMed, checked 18 November 2026; INPLASY site search, checked 23 November 2026).

The main population is third-or-later-line treatment after multiple targeted-therapy failure. Failure of at least two b/tsDMARDs is part of the treatment-failure component of the ASAS 2025 difficult-to-manage (D2M) definition (Poddubnyy et al., Ann Rheum Dis 2025;84:538–546; PMID 39955166, DOI 10.1016/j.ard.2025.01.035) but is not D2M by itself: D2M also requires, unless contraindicated, different mechanisms of action, plus suboptimal disease control and signs or symptoms considered problematic by the patient or physician; treatment-refractory disease further requires objective inflammation and exclusion of non-inflammatory causes of non-response. The main population is therefore broader than D2M.

Condition being studied Axial spondyloarthritis (radiographic axial spondyloarthritis/ankylosing spondylitis and non-radiographic axial spondyloarthritis) after failure of two or more b/tsDMARDs, including the subgroup meeting the ASAS difficult-to-manage/treatment-refractory definition.

METHODS

Search strategy The searches are complete and are not repeated. No language limits.

MEDLINE via PubMed (2 November 2026; 6,676 records):

("Spondylitis, Ankylosing"[Mesh] OR "Axial Spondyloarthritis"[Mesh] OR "Spondylarthritis"[Mesh] OR "ankylosing spondylitis"[tiab] OR "axial spondyloarthritis"[tiab] OR "axial spondylarthritis"[tiab] OR "axial spa"[tiab] OR axspa[tiab] OR spondyloarthrit*[tiab] OR spondylarthrit*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] OR bechterew*[tiab] OR bechterev*[tiab] OR bekhterev*[tiab] OR "Marie Strumpell"[tiab]) AND (switch*[tiab] OR swap*[tiab] OR cycl*[tiab] OR sequenc*[tiab] OR second-line[tiab] OR third-line[tiab] OR "drug survival"[tiab] OR retention[tiab] OR refractory[tiab] OR difficult-to-treat[tiab] OR difficult-to-manage[tiab] OR resistant[tiab] OR resistance[tiab] OR "inadequate response"[tiab] OR nonrespon*[tiab] OR non-respon*[tiab] OR discontinu*[tiab] OR experienced[tiab] OR "previously treated"[tiab] OR "prior exposure"[tiab] OR intoleran*[tiab] OR failure[tiab] OR failed[tiab] OR "second biologic*"[tiab] OR "subsequent biologic*"[tiab] OR "prior biologic*"[tiab] OR "previous biologic*"[tiab] OR "TNFi-IR"[tiab] OR "bDMARD-IR"[tiab] OR "TNF-IR"[tiab] OR "line of therapy"[tiab] OR "lines of therapy"[tiab] OR "treatment line*"[tiab] OR "loss of response"[tiab])

Embase via Embase.com (17 November 2026): the same blocks translated to Embase syntax (Emtree explode for 'ankylosing spondylitis', 'axial spondyloarthritis' and 'spondylarthritis'; all other terms in :ti,ab,kw). Embase's automatic term mapping added all-field free-text terms to the disease line; the strategy is reported as executed. 27,739 records in the interface; 27,736 in three publication-year exports (3 records outside the ranges); 26,824 unique records in the export files.

Cochrane CENTRAL via the Cochrane Library (2 November 2026; 4,668 trial records): #1 MeSH descriptor: [Spondylitis, Ankylosing] explode all trees; #3 [mh "Spondylarthritis"]; #4 [mh "Axial Spondyloarthritis"]; #5 ("axial spondyloarthritis" OR "axial spondylarthritis" OR "axial spa" OR axspa OR "ankylosing spondylitis" OR spondyloarthrit* OR spondylarthrit* OR spondyloarthropath* OR spondylarthropath* OR bechterew* OR bechterev* OR bekhterev* OR "Marie Strumpell" OR "Marie Struempell"):ti,ab,kw; #6 #1 OR #3 OR #4 OR #5.

Automated classification after the search (not part of the database strategies): an archived script (korpus_olc.py; code version, input and output identifiers and file hashes archived) deduplicates the exports and applies: publication year from 1998; the previous-treatment block to CENTRAL records; a targeted-drug or difficult-to-manage term in title/abstract; conference abstracts limited to 2025–2026; and whether an axial spondyloarthritis term appears in the title, abstract or a focused subject heading. Counts at each step are reported (PRISMA-S). Records set aside by the targeted-drug rule are checked in a random sample of 300 by one reviewer. Also: reference lists and forward citations of included studies and relevant systematic reviews.

Participant or population Adults (≥18 years) with axial spondyloarthritis (radiographic, non-radiographic or mixed) starting a b/tsDMARD after

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failure of two or more previous b/tsDMARDs (any mechanism; treatment line and failure as defined in the treatment-line rules). Cohorts meeting the ASAS D2M/treatment-refractory definition are eligible when they satisfy this criterion and form a prespecified subgroup. Studies of mixed diseases or mixed treatment lines are eligible only if results for this group are reported separately. Patients with one previous b/tsDMARD are not eligible on their own; they serve only as the within-study comparison group of secondary objective 1. Children are excluded.

Intervention Any b/tsDMARD started as third or later line: TNF inhibitors, IL-17 inhibitors, JAK inhibitors and other targeted agents. Dual targeted combinations are outside the scope.

Comparator Another treatment option at the same line; placebo; patients with one previous b/tsDMARD in the same study (prognostic comparison); none (single-arm cohorts, reported descriptively).

Study designs to be included Randomised controlled trials (including subgroup analyses and extensions) and prospective or retrospective cohort and registry studies with at least 10 patients in the eligible group.

Eligibility criteria Full articles published from 1 January 1998 (year of the first TNF-inhibitor approvals); conference abstracts from 2025–2026 (older abstracts only as additional reports of an included study). No language restriction. At title/abstract stage, studies in which all patients are biologic-naive, or all are at second line, are excluded. Excluded designs: case reports, case series with fewer than 10 patients, reviews, editorials, guidelines and laboratory studies.

Treatment-line rules. (a) A new line is counted only when a different active agent is started. (b) Non-medical switching between an originator and its biosimilar, or between biosimilars of the same active substance, is neither a new line nor a failure. (c) A temporary interruption or restart of the same agent, with no other targeted agent in between, is not a new line. (d) Inefficacy, loss of response, intolerance or an adverse event counts as failure; remission, pregnancy, supply or reimbursement reasons and purely administrative changes do not. (e) If a study reports third-line treatment but the reasons for stopping the two previous agents are unclear, this is recorded; such patients stay in the main analysis and are removed in a sensitivity analysis restricted to documented failures.

Information sources MEDLINE (PubMed), Embase (Embase.com; accessed through a collaborating researcher's institutional subscription) and Cochrane CENTRAL (includes trial-registry records); reference lists and forward citations. Study authors are contacted once by e-mail when a denominator or an eligible-subgroup result is missing; the analysis does not wait for replies. Broad Scopus, EBSCO MEDLINE and CINAHL exports obtained earlier for scoping were not used as sources; this is reported as a limitation.

Main outcome(s) Observational studies: drug retention at 12 months (Kaplan–Meier estimate or crude proportion; the type is recorded and the two are not mixed). Drug retention is interpreted as a proxy for overall effectiveness and tolerability (persistence), not as efficacy. Randomised trials: ASAS40 response at week 16 (or the assessment in weeks 12–14 closest to week 16).

Additional outcome(s) BASDAI50 and ASDAS clinically important improvement (kept separate, never converted into each other); ASDAS below 2.1 and below 1.3; discontinuation because of inefficacy; discontinuation because of adverse events; serious adverse events. The exact assessment week is recorded for every result.

Data management Reviewers are trained with a written handbook and a one-hour session, then independently screen 30 records from a predefined calibration set; records they saw in the earlier diagnostic pilot are not used. The calibration pass criteria are, in every reviewer pair, at least 80% overall agreement, at least 70% positive agreement and at least 80% negative agreement, and that all three reviewers mark every predefined known advanced-line report as include or unclear. If any condition fails, the guide is clarified and a second round of 30 previously unseen records is completed. If any condition still fails, formal screening does not start and the methodological lead and guarantor decide on further training. Kappa is reported but is not used as a gate. Records with an axial spondyloarthritis term are screened at title/abstract by two of three reviewers independently (balanced, blinded pairs). The remaining records are screened by one reviewer with a liberal rule; records marked include or unclear go to a second reviewer, and a random 10% is screened independently by a second reviewer. Full texts are assessed by two reviewers independently. Disagreements at title/abstract are decided by the guarantor; at full text, data extraction and risk of bias by the methodological lead. Primary outcomes, denominators and

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subgroup counts are extracted independently by two reviewers; other items by one reviewer and checked against the source by a second. AI tools prepare forms, remove duplicates and compute agreement; they make no eligibility decision. Rules clarified during the review are recorded in a dated decision log.

Quality assessment / Risk of bias analysis RoB 2 for randomised trials; ROBINS-I for comparative effectiveness in observational studies; QUIPS for the prognostic association with the number of previous b/tsDMARDs; JBI checklist for single-arm cohort studies. Two reviewers independently. Randomised subgroup credibility. For subgroups with two or more previous b/tsDMARDs we extract whether the subgroup was prespecified, how it was defined at baseline, whether randomisation was stratified by it, any interaction test, and the risk of selective reporting. Post hoc subgroup results are labelled exploratory. ICEMAN is used if an effect-modification claim is made. Certainty of evidence: GRADE per outcome and comparison, assessed by the guarantor and the methodological lead.

Strategy of data synthesis Results are pooled only when at least three independent studies share the comparison, outcome definition, time point, estimand and effect measure. Risk ratios, odds ratios and hazard ratios are never mixed; adjusted and unadjusted estimates are kept separate. Random-effects models (REML) with Hartung–Knapp confidence intervals; 95% prediction intervals when three or more studies are pooled (labelled exploratory with three or four). Single-arm proportions form a separate descriptive layer (binomial-normal model) and are not used to compare treatments. For the prognostic comparison (two or more versus one previous b/tsDMARD) adjusted estimates are primary and no causal language is used; without compatible adjusted estimates, results are not pooled. If pooling is not possible, results are summarised following SWiM. Heterogeneity: τ^2, I^2 and prediction intervals; small-study effects only with at least 10 studies. R (meta, metafor); a second analyst reproduces all calculations independently.

Study families and cohort overlap. Reports are linked to one study family. An overlap matrix records country/registry, centre, inclusion period, treatment line and patient numbers. For the same outcome and time point, among substantially overlapping cohorts the most comprehensive and suitable report is selected. Complementary outcomes may come from different reports, but the same patients never enter one meta-analysis twice. Independent subcohorts are used separately when they can be separated; otherwise an alternative report is tried in a sensitivity analysis.

Selection of adjusted estimates. When a report presents several models, we select the authors' primary model or the prespecified model with the most appropriate confounders and no post-treatment mediators. Selection never depends on the size or direction of the result. The confounder set and target estimand are recorded.

Subgroup analysis Mechanism of the new drug; same class versus new mechanism; failure of both a TNF inhibitor and an IL-17 inhibitor; cohorts meeting the ASAS D2M/treatment-refractory definition; radiographic versus non-radiographic disease. Subgroup claims rest on interaction estimates.

Sensitivity analysis Without conference abstracts; without studies at high risk of bias; prognostic comparison with unadjusted estimates; restricted to patients with both previous discontinuations documented as failures; alternative report for overlapping cohorts that cannot be separated.

Language restriction No. No language limits are imposed on the search.

Country(ies) involved Türkiye.

Other relevant information Related review from the same institution: PROSPERO CRD420251275329 (failure of a first b/tsDMARD; within-class switch versus mechanism swap; ACR Convergence 2026 abstract 2311). This review addresses later lines only; reports included in both reviews will be disclosed. Stage at submission: Preliminary searches: completed (database exports obtained on 2 and 17 November 2026). Piloting of the study selection process: started. Three reviewers independently completed a 100-record diagnostic pilot under an earlier, broader, unregistered draft (v0.4.7); agreement did not meet that draft's prespecified criteria, and these decisions will not be used as review data or as calibration for the current protocol. Calibration against the current eligibility criteria has not been completed. Formal screening, data extraction, risk of bias assessment and data analysis: not started. AI-assisted pilots for method development were seen during protocol development; they are not review data. Reporting: PRISMA-P for this protocol; PRISMA 2020 and PRISMA-S for the final review. JBI items are reported individually, without a summary score or low/moderate/high cut-offs.

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Limiting conference abstracts to 2025–2026 is a pragmatic, resource-based decision that may miss older unique abstracts and is reported as a limitation. This protocol (v0.5.2) replaces unregistered drafts before formal screening; all changes are listed with reasons in the protocol amendment tables. The change from v0.5.0 to v0.5.1 (calibration process and stage wording) was prompted by the process and agreement data of the diagnostic pilot; no effect result was used, and the review question, eligibility criteria, outcomes and analysis did not change. The change from v0.5.1 to v0.5.2 followed methodological review before registration and formal screening. It corrects the rationale and the population label and adds rules for treatment lines, study overlap, subgroup credibility, model selection, the calibration safety gate and reporting. No eligibility decision or effect result of any report was used, and the review question did not change. Search strings, scripts, screening decisions and extracted data will be made public at publication.

Keywords axial spondyloarthritis; difficult-to-manage; treatment-refractory; biologic DMARD; JAK inhibitor; treatment line; drug retention; meta-analysis.

Dissemination plans Peer-reviewed journal article; conference presentation; public repository of data and code at publication.

Contributions of each author

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