Supplementary data RECORD study

Index

1. Additional information on the search strategy

In general, the search string consisted of three parts: [IRDs] AND [drugs] AND [strategy]. The first part [IRDs] was identical for all strategies, and the second part [drugs] for every strategy except for route of administration, of which this part only focussed on drugs with multiple administration routes available (ABA, IFX, TCZ). Within each part, we combined both MeSH terms and title/abstract of the relevant keywords for PubMed, and Emtree terms and explode for Embase. If an additional search for RCTs was performed, only the relevant IRDs and drugs were included in the [IRDs] and [drugs] queries. For the SLR search, we filtered for 'systematic reviews' or 'reviews'. For the RCT search, we added the Cochrane maximum sensitivity search string.

2. Core searches

Search string for inflammatory rheumatic diseases

IRD – PubMed

(arthritis, rheumatoid[MeSH Terms]) OR (arthritis, psoriatic[MeSH Terms]) OR (ankylosing spondylitis[MeSH Terms]) OR (Rheumatoid arthritis[Title/Abstract]) OR (Psoriatic arthritis[Title/Abstract]) OR (axial spondyloarthritis[Title/Abstract]) OR (spondyloarthritis[Title/Abstract]) OR (ankylosing spondylitis[Title/Abstract]) OR (auto immune rheumatic disease*[Title/Abstract]) OR (immune-mediated inflammatory disease*[Title/Abstract])

IRD – Embase

1. rheumatoid arthritis/
2. exp rheumatoid arthritis/
3. psoriatic arthritis/
4. ankylosing spondylitis/
5. exp spondylarthritis/
6. rheumatoid arthritis.ti,ab,kw.
7. psoriatic arthritis.ti,ab,kw.
8. ankylos* spondyl*.ti,ab,kw.
9. spondyl?arthr*.ti,ab,kw.
10. AIRD.ti,ab,kw.
11. autoimmune rheumat* disease.ti,ab,kw.
12. IMID.ti,ab,kw.
13. immune-mediated inflammatory disease.ti,ab,kw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

Search string for b/tsDMARDs

The searches are divided in ‘drug name’ and ‘drug class’. For the part [drugs] we combined ‘drug name’ with ‘drug class’ using AND.

Drug name – PubMed

((((((((((((((((((((((((((((((((adalimumab[MeSH Terms]) OR (certolizumab pegol[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (ustekinumab[MeSH Terms])) OR (rituximab[MeSH Terms])) OR (abatacept[MeSH Terms])) OR (adalimumab[Title/Abstract])) OR (certolizumab[Title/Abstract])) OR (golimumab[Title/Abstract])) OR (infliximab[Title/Abstract])) OR (tocilizumab[Title/Abstract])) OR (sarilumab[Title/Abstract])) OR (ustekinumab[Title/Abstract])) OR (secukinumab[Title/Abstract])) OR (ixekizumab[Title/Abstract])) OR (rituximab[Title/Abstract])) OR (abatacept[Title/Abstract])) OR (tofacitinib[Title/Abstract])) OR (baricitinib[Title/Abstract])) OR (upadacitinib[Title/Abstract])) OR (filgotinib[Title/Abstract])) OR (apremilast[Title/Abstract])) OR (golimumab[Supplementary Concept])) OR (tocilizumab[Supplementary Concept])) OR (sarilumab[Supplementary Concept])) OR (secukinumab[Supplementary Concept])) OR (ixekizumab[Supplementary Concept])) OR (tofacitinib[Supplementary Concept])) OR (baricitinib[Supplementary Concept])) OR (upadacitinib[Supplementary Concept])) OR (filgotinib[Supplementary Concept])) OR (apremilast[Supplementary Concept])) OR (etanercept[Title/Abstract])

Drug class – PubMed

((tumor necrosis factor inhibitors[MeSH Terms]) OR (janus kinase inhibitors[MeSH Terms])) OR (phosphodiesterase 4 inhibitors[MeSH Terms])) OR (TNF inhibitor*[Title/Abstract])) OR (TNF Antagonist*[Title/Abstract])) OR (TNF blocker[Title/Abstract])) OR (bDMARD[Title/Abstract])) OR (tsDMARD[Title/Abstract])) OR (biological agent*[Title/Abstract]))

OR (biologicals[Title/Abstract])) OR (biological drug*[Title/Abstract])) OR (biological medication[Title/Abstract])) OR (biologics[Title/Abstract])) OR (targeted small molecules[Title/Abstract])) OR (janus kinase inhibitor*[Title/Abstract])) OR (JAK inhibitor*[Title/Abstract])) OR (Phosphodiesterase 4 inhibitor*[Title/Abstract])) OR (PDE 4 inhibitor*[Title/Abstract])) OR (PDE4 inhibitor[Title/Abstract])) OR (IL6R inhibitor*[Title/Abstract])) OR (IL-6R inhibitor*[Title/Abstract])) OR (IL6R blocker*[Title/Abstract])) OR (IL-6R blocker*[Title/Abstract])) OR (IL6R antagonist*[Title/Abstract])) OR (IL-6R antagonist*[Title/Abstract])) OR (anti IL6[Title/Abstract])) OR (anti IL-6[Title/Abstract])) OR (IL12/23 inhibitor*[Title/Abstract])) OR (IL-12/23 inhibitor*[Title/Abstract])) OR (IL12/IL23 inhibitor*[Title/Abstract])) OR (IL-12/IL-23 inhibitor*[Title/Abstract])) OR (IL12/23 blocker*[Title/Abstract])) OR (IL-12/23 blocker*[Title/Abstract])) OR (IL-12/IL-23 blocker*[Title/Abstract])) OR (IL12/23 antagonist*[Title/Abstract])) OR (IL-12/IL-23 antagonist*[Title/Abstract])) OR (anti IL12/23[Title/Abstract])) OR (anti IL-12/23[Title/Abstract])) OR (anti IL-12/IL-23[Title/Abstract])) OR (anti IL12/IL23[Title/Abstract])) OR (IL17 inhibitor*[Title/Abstract])) OR (IL-17 inhibitor*[Title/Abstract])) OR (IL17 blocker*[Title/Abstract])) OR (IL-17 blocker*[Title/Abstract])) OR (IL17 antagonist*[Title/Abstract])) OR (IL-17 antagonist*[Title/Abstract])) OR (anti IL17[Title/Abstract])) OR (anti IL-17[Title/Abstract])

Drug name – Embase

1. adalimumab.ti,ab,kw. or exp adalimumab/
2. etanercept.ti,ab,kw. or exp etanercept/
3. golimumab.ti,ab,kw. or exp golimumab/
4. infliximab.ti,ab,kw. or exp infliximab/
5. certolizumab pegol.ti,ab,kw. or exp certolizumab pegol/
6. certolizumab.ti,ab,kw.
7. tofacitinib.ti,ab,kw. or exp tofacitinib/
8. baricitinib.ti,ab,kw. or exp baricitinib/
9. filgotinib.ti,ab,kw. or exp filgotinib/
10. tocilizumab.ti,ab,kw. or exp tocilizumab/
11. sarilumab.ti,ab,kw. or exp sarilumab/
12. secukinumab.ti,ab,kw. or exp secukinumab/
13. ustekinumab.ti,ab,kw. or exp ustekinumab/
14. ixekizumab.ti,ab,kw. or exp ixekizumab/
15. abatacept.ti,ab,kw. or exp abatacept/
16. rituximab.ti,ab,kw. or exp rituximab/
17. upadacitinib.ti,ab,kw. or exp upadacitinib/
18. apremilast.ti,ab,kw. or exp apremilast/
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

Drug class – Embase

1. tumor necrosis factor inhibitors.ti,ab,kw. or exp tumor necrosis factor inhibitor/
2. exp tumor necrosis factor antibody/
3. exp Janus kinase inhibitor/ or janus kinase inhibitor*.ti,ab,kw.
4. exp phosphodiesterase IV inhibitor/ or phosphodiesterase 4 inhibitor*.ti,ab,kw.
5. bDMARD*.ti,ab,kw.
6. tsDMARD*.ti,ab,kw.
7. biological*.ti,ab,kw.
8. biological drug*.ti,ab,kw.
9. biologics.ti,ab,kw.
10. JAK inhibitor*.ti,ab,kw.
11. PDE4 inhibitor*.ti,ab,kw.
12. IL6R inhibitor*.ti,ab,kw.

13. IL6R blocker*.ti,ab,kw.
14. IL6R antagonist*.ti,ab,kw.
15. anti IL6.ti,ab,kw.
16. exp interleukin 12 antibody/
17. IL 23 inhibitor*.ti,ab,kw.
18. IL17 inhibitor*.ti,ab,kw.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

Cochrane search for RCTs with maximum sensitivity

RCT search – PubMed

((((((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]))

RCT search – Embase

1. Randomized controlled trial/
2. Controlled clinical study/
3. random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. human experiment/
19. trial.ti.
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
23. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
24. (Systematic review not (trial or study)).ti.
25. (nonrandom$ not random$).ti,ab.
26. Random field$.ti,ab.
27. (random cluster adj3 sampl$).ti,ab.
28. (review.ab. and review.pt.) not trial.ti.
29. we searched.ab. and (review.ti. or review.pt.)

30. update review.ab.
31. (databases adj4 searched).ab.
32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
33. Animal experiment/ not (human experiment/ or human/)
34. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 20 not 34

3. Response prediction

Strategy specific search

PubMed search

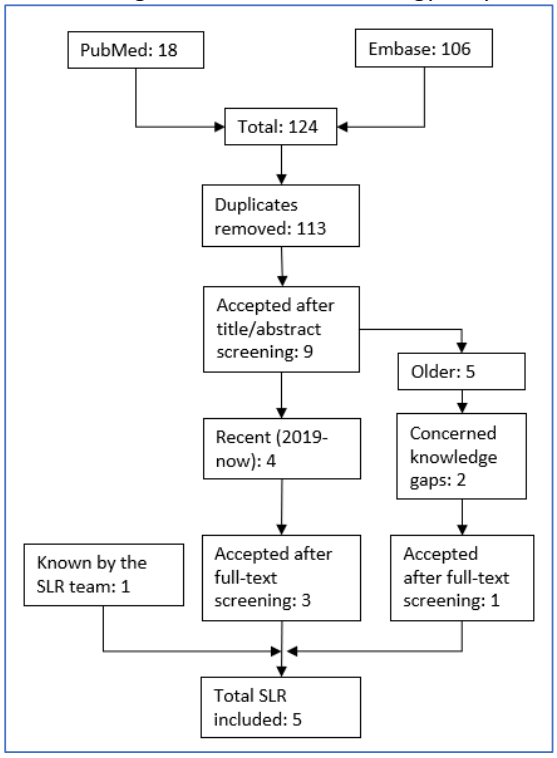
(predictive value of tests[MeSH Terms]) OR (response prediction[Title/Abstract]) OR (personalized treatment[Title/Abstract]) OR (prediction[Title/Abstract]) OR (drug monitoring, therapeutic[MeSH Terms]) OR (drug monitoring[MeSH Terms]) OR (therapeutic drug monitoring[Title/Abstract]) OR (drug level[Title/Abstract]) OR (serum level[Title/Abstract])

Embase search

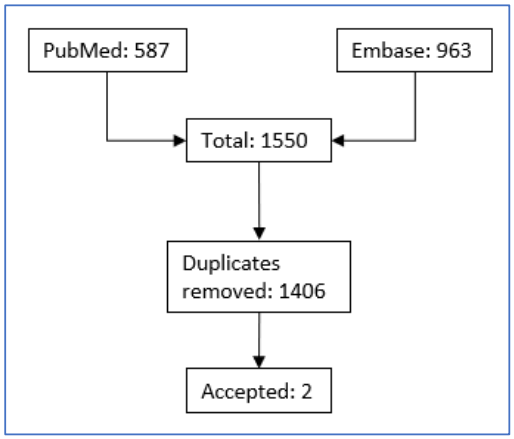
predictive value/ or response prediction.ti,ab,kw. or personalized treatment.ti,ab,kw. or predict*.ti,ab,kw. or drug monitoring/ or therapeutic drug monitoring.ti,ab,kw. or drug level.ti,ab,kw. or serum level.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for response prediction:



The flow diagram for the search strategy of randomized controlled trials for response prediction:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Tikhonova[1]	2021	P: patients with RA I: treatment decisions based on drug levels or anti-drug antibodies C: regular treatment O: clinical or patient related outcomes	anti-TNF	Moderate	1=yes, 2=yes, 3=no, 4=partial yes, 5=yes, 6=yes, 7=yes, 8=yes, 9=yes, 10=yes, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=yes
Pouw[2]	2019	P: patients with PsA I: biomarkers C: not clearly mentioned O: not clearly mentioned	bDMARDs	Low	1=no, 2=no, 3=no, 4=partial yes, 5=no, 6=no, 7=no, 8=no, 9=no, 10=no, 11=0, 12=0, 13=no, 14=no, 15=0, 16=yes.
Schlager[3]	2019	P: RA, receiving b/tsDMARD I: discontinuation of the b/tsDMARD in remission or LDA C: continuation O: % remaining in remission or LDA, to identify predictors.	bDMARDs	Critically low	1=yes, 2=no, 3=no, 4=no, 5=yes, 6=no, 7=no, 8=partial yes, 9=yes, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes
Tweehuysen[4]	2018	P: RA treated with bDMARD I: biomarker C: no biomarker O: successful dose reduction or discontinuation	bDMARDs	Moderate	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=yes, 7=partial yes, 8=partial yes, 9=0, 10=no, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=no.
Ingegnoli[5]	2011	P: RA starting an anti-TNF drug I: genetic polymorphism in TNF, interleukin, interferon gamma or TGF beta. C: not clearly mentioned O: not clearly mentioned.	anti-TNF	Critically low	1=no, 2=no, 3=no, 4=no, 5=no, 6=no, 7=no, 8=no, 9=no, 10=no, 11=0, 12=0, 13=no, 14=no, 15=0, 16=no.

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Syversen[6]	2021	NOR-DRUM A	P: patients with RA, PsA, axSpA initiating IFX treatment I: IFX TDM: serum trough levels entered in eCRF which provides recommended dose and interval C: standard clinical practice O: % clinical remission at week 30	IFX	Some concerns

Tanaka[7]	2020	RRRR	P: RA, active disease despite MTX I: IFX dose reduction at 14 weeks based on TNF-a antigen level C: standard IFX, no dose reduction O: % patients who sustained discontinuation at week 54.	IFX	Some concerns

4. Drug formulary policy

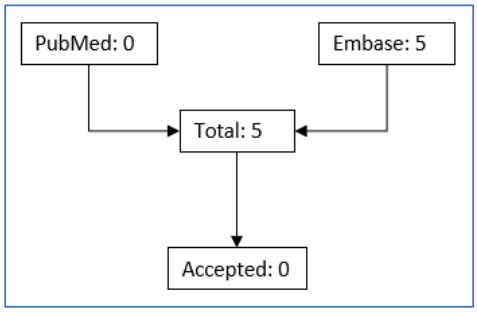
Strategy specific search

PubMed search
((drug formulary[title/abstract]) OR (drug policy[title/abstract]))

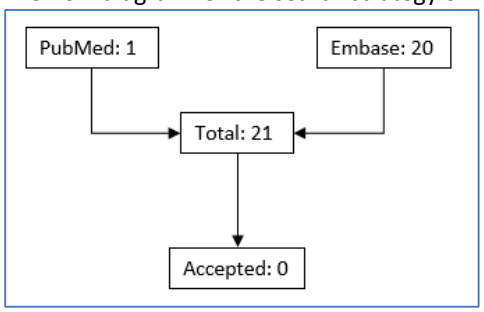
Embase search
exp drug formulary/ or exp health care policy/ or drug formulary policy.ti,ab,kw. or drug formulary.ti,ab,kw. or drug policy.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic reviews for 'drug formulary policy':



The flow diagram for the search strategy of randomized controlled trials for 'drug formulary policy':



Included SLRs
None of the found publications matched our research question and could be included.

Included RCTs
None of the found publications matched our research question and could be included.

5. Biosimilar/generic drug use

Strategy specific search

PubMed search

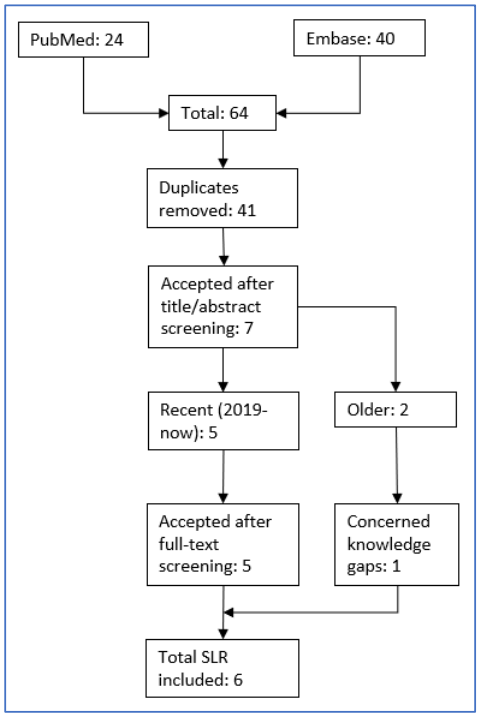
((biosimilar pharmaceuticals[MeSH Terms]) OR (biosimilar[Title/Abstract])) OR (follow-on biologics[Title/Abstract])

Embase search

exp biosimilar agent/ or biosimilar*.ti,ab,kw. or follow-on biologic*.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic reviews for 'Biosimilar/generic drug use':



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Kim[8]	2021	P: RA, PsA, axSpA I/C: not entirely clear, they mention the keywords: biosimilar, adalimumab, etanercept, infliximab, rituximab O: effectiveness	bDMARDs	Critically low	1=no, 2=no, 3=yes, 4=partial yes, 5=yes, 6=no, 7=partial yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes
Luttropp[9]	2020	P: inflammatory arthritis I/C: bio-originator to biosimilar switch, bio-originator to bio-originator or biosimilar to bio-originator. O: switch or discontinue treatment	bDMARDs	Low	1=yes, 2=no, 3=yes, 4=partial yes, 5=no, 6=no, 7=yes, 8=yes, 9=no, 10=no, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=yes
Feagan[10]	2019	P: RA, PsA, axSpA I/C: bio-originator to biosimilar switch, bio-originator to bio-originator or biosimilar to bio-originator. O: efficacy, safety, immunogenicity	IFX	Critically low	1=yes, 2=no, 3=yes, 4=partial yes, 5=no, 6=no, 7=partial yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes

Cantini[11]	2019	P: RA I/C: not entirely clear, they mention biosimilars of adalimumab, etanercept and infliximab O: efficacy and safety	ADA, ETN, IFX	Critically low	1=yes, 2=no, 3=yes, 4=no, 5=no, 6=no, 7=no, 8=no, 8=no, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes
Mezones-Holguin[12]	2019	P: RA, PsA, axSpA I: switch to biosimilar infliximab C: continuation with originator O: efficacy and safety	IFX	Critically low	1=yes, 2=no, 3=no, 4=no, 5=yes, 6=yes, 7=no, 8=partial yes, 9=yes, 1=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=no
Numan[13]	2018	P: RA, PsA, axSpA I/C: double-blind RCT in which multiple biosimilar/bio-originator switches are perfomed. O: immunogenicity, patient-level	anti-TNF	Critically low	1=no, 2=no, 3=yes, 4=no, 5=yes, 6=no, 7=partial yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=no

Included RCTs

None, our research question was answered after the SLR search.

6. Avoid dose loading

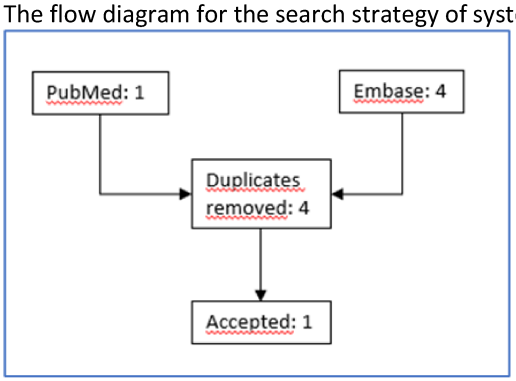
Strategy specific search

PubMed search
(dose loading[Title/Abstract]) OR (loading dose[Title/Abstract])

Embase search
(dose loading or loading dose).ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for dose loading:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Geurts-Voerman[14]	2020	P: RA, PsA, axSpA I: dose loading C: no dose loading O: efficacy (disease activity)	CER, IFX, ABA, SEC or UST	Critically low	1=yes, 2=no, 3=yes, 4=yes, 5=yes, 6=no, 7=yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes.

Included RCTs
None. The SLR covered our research question regarding bDMARDs. We performed an additional search regarding tsDMARDs but found no hits in either PubMed or Embase.

7. Initial lower dose

Strategy specific search

PubMed search

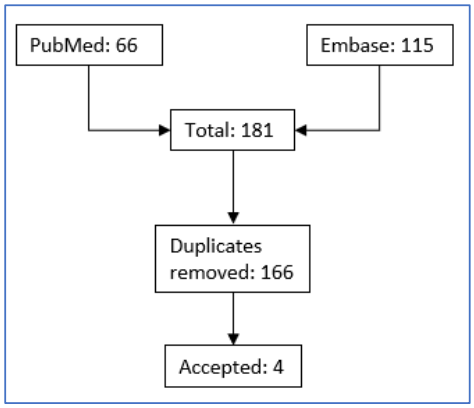
(low-dose*[Title/Abstract]) OR (low-dosage*[Title/Abstract]) OR (reduced-dose*[Title/Abstract]) OR (reduced-dosage*[Title/Abstract]) OR (half-dose*[Title/Abstract])

Embase search

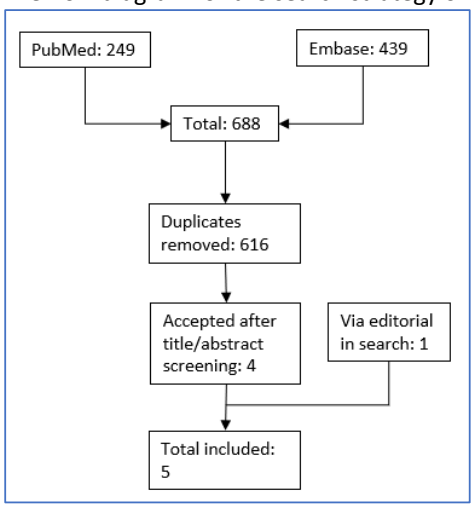
1. (low adj3 dose?).ti,ab,kw.
2. (reduc* adj3 dose?).ti,ab,kw.
3. (low* adj3 dosage?).ti,ab,kw.
4. (reduc* adj3 dosage?).ti,ab,kw.
5. (half adj3 dose?).ti,ab,kw.
6. 1 or 2 or 3 or 4 or 5
7. exp low dose/
8. 6 or 7
9. limit 8 to (human and english language and embase)

Strategy output

The flow diagram for the search strategy of systematic literature reviews for initial lower dose:



The flow diagram for the search strategy of randomized controlled trials for initial lower dose:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Weng[15]	2021	P: RA with inadequate response to at least one DMARD I: JAK-inhibitors (including bari 2 & 4) C: bDMARDs O: efficacy and safety	BARI	Critically low	1=yes, 2=yes, 3=no, 4=no, 5=yes, 6=yes, 7=no, 8=partial yes, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes
Bae[16]	2018	P: RA I: SAR 200 mg (mono or with MTX) C: SAR 150 mg + MTX, other bDMARD, or MTX mono O: Clinical efficacy and tolerability	SAR	Low	1=yes, 2=no, 3=yes, 4=partial yes, 5=no, 6=yes, 7=no, 8=partial yes, 9=no, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=yes.
Bredemeier (update)[17]	2015	P: RA I: low-dose RTX (1*1000 or 2*500) C: registered dose RTX (2*1000) O: efficacy	RTX	Critically low	1=yes, 2=no, 3=no, 4=yes, 5=yes, 6=yes, 7=no, 8=no, 9=yes, 10=no, 11=yes,12=yes, 13=yes, 14=yes, 15=yes, 16=yes
Bredemeier[18]	2014	P: RA I: low-dose RTX (1*1000 or 2*500) C: registered dose RTX (2*1000) O: efficacy	RTX	Critically low	1=yes, 2=no, 3=no, 4=yes, 5=yes, 6=yes, 7=no, 8=no, 9=yes, 10=no, 11=yes,12=yes, 13=yes, 14=yes, 15=yes, 16=yes

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Tada[19]	2012	PRECEPT	P: RA I: ETN 25 mg/week C: ETN 50 mg/week O: radiographic damage at week 52	ETN	Low
Tanaka[20]	2011	-	P: RA and inadequate response to MTX I: TOFA 2dd 1, 3, 5 or 10 mg + MTX C: placebo + MTX O: ACR20 response rate at week 12	TOFA	Some concerns
Smolen[21]	2008	OPTION	P: RA and inadequate response to MTX I: TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX C: placebo + MTX O: ACR20 response rate at week 24	TCZ	Some concerns
Maini[22]	2006	CHARISMA	P: RA and inadequate response to MTX I: TCZ 2 mg/kg + MTX, TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX C: placebo + MTX O: ACR20 response rate at week 16	TCZ	Some concerns

8. Optimizing pharmacokinetic exposure

Strategy specific search

PubMed search

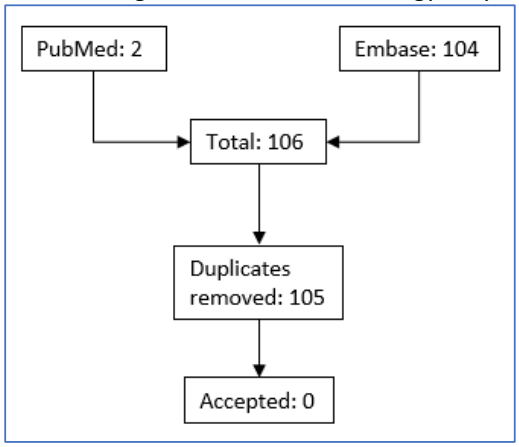
(((bioavailability[MeSH Terms]) OR (drug metabolism[Title/Abstract]) OR (drug excretion[Title/Abstract]) OR (drug absorption[Title/Abstract]) OR (drug distribution[Title/Abstract])) OR (pharmacokinetics[MeSH Terms]))

Embase search

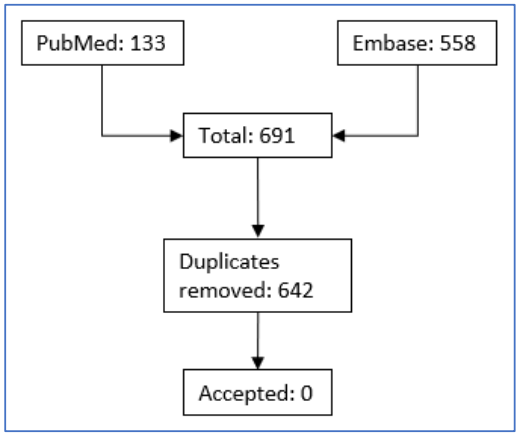
exp drug bioavailability/ or exp pharmacokinetics/ or exp drug metabolism/ or exp drug absorption/ or exp drug distribution/ or exp drug excretion/ or bioavailability.ti,ab,kw. or pharmacokinetics.ti,ab,kw. or drug metabolism.ti,ab,kw. or drug absorption.ti,ab,kw. or drug distribution.ti,ab,kw. or drug excretion.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for pharmacokinetics:



The flow diagram for the search strategy of randomized controlled trials for pharmacokinetics:



Included SLRs

None of the found publications matched our research question and could be included.

Included RCTs

None of the found publications matched our research question and could be included.

9. Combination therapy

Strategy specific search

PubMed search

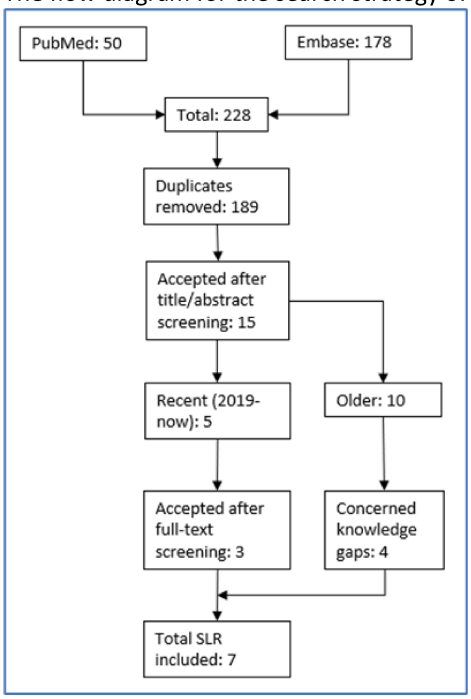
((Combination therapy[Title/Abstract]) OR (Combin*[Title/Abstract])) AND ((methotrexate[Title/Abstract]) OR (leflunomide[Title/Abstract]) OR (sulfasalazine[Title/Abstract]) OR (hydroxychloroquine[Title/Abstract]) OR (azathioprine[Title/Abstract]) OR (methotrexate[MeSH Terms]) OR (leflunomide[MeSH Terms]) OR (sulfasalazine[MeSH Terms]) OR (hydroxychloroquine[MeSH Terms]) OR (azathioprine[MeSH Terms]) (sulfasalazine[Title/Abstract]) OR (hydroxychloroquine[Title/Abstract]) OR (azathioprine[Title/Abstract]) OR (methotrexate[MeSH Terms]) OR (leflunomide[MeSH Terms]) OR (sulfasalazine[MeSH Terms]) OR (hydroxychloroquine[MeSH Terms]) OR (azathioprine[MeSH Terms]))

Embase search

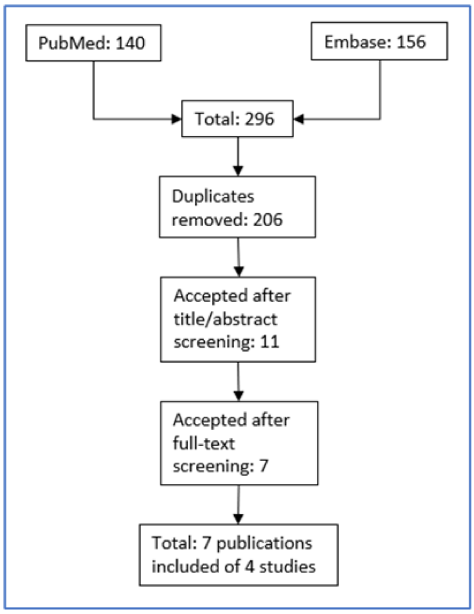
1. exp methotrexate/ or exp leflunomide/ or exp salazosulfapyridine/ or exp hydroxychloroquine/ or exp azathioprine/ or methotrexate.ti,ab,kw. or leflunomide.ti,ab,kw. or salazosulfapyridine.ti,ab,kw. or hydroxychloroquine.ti,ab,kw. or azathioprine.ti,ab,kw.
2. (combination therapy or combin*).ti,ab,kw.
3. 1 and 2

Strategy output

The flow diagram for the search strategy of systematic reviews for 'Combination therapy':



The flow diagram for the search strategy of randomised controlled trials for 'Combination therapy':



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Paul[23]	2020	P: RA I: monotherapy of ABA C: combination therapy of ABA + csDMARD or multiple csDMARDs O: efficacy and safety	ABA	Critically low	1=yes, 2=no, 3=no, 4=partial yes, 5=yes, 6=yes, 7=partial yes, 8=partial yes, 9=yes/no, 10=no, 11=no, 12=yes, 13=no, 14=no, 15=no, 16=no.
Donahue[24]	2019	P: RA I/C: head-to-head RCTs, nRCTs and prospective controlled cohort studies on bDMARD monotherapy or combination therapy for a network meta-analysis. O: Efficacy, PROMs, safety	bDMARDs	Critically low	1=yes, 2=no, 3=yes, 4=no, 5=yes, 6=yes, 7=yes, 8=partial yes, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes, 16=yes.
Tarp[25]	2019	P: RA I: combination therapy of bDMARD + MTX C: monotherapy of bDMARD O: ACR50, AEs	bDMARDs + tofa	Low	1=yes, 2=no, 3=no, 4=partial yes, 5=yes, 6=yes, 7=yes, 8=no, 9=yes, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=yes
Teitsma[26]	2016	P: RA I: TCZ monotherapy C: TCZ combination therapy O: efficacy and safety	TCZ	Critically low	1=yes, 2=no, 3=no, 4=no, 5=yes, 6=yes, 7=no, 8=yes, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes, 16=yes.
Behrens[27]	2015	P: PsA I: TNFi + MTX C: TNF monotherapy O: efficacy, safety, immunogenicity	anti-TNF	Critically low	1=yes, 2=no, 3=no, 4=no, 5=no, 6=no, 7=no, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=no, 15=0, 16=no
Lin[28]	2014	P: axSpA I: TNFi + MTX C: TNFi monotherapy or TNFi + placebo O: efficacy, safety, PROMs, radiographic damage	anti-TNF	Low	1=yes, 2=no, 3=no, 4=no, 5=no, 6=yes, 7=no, 8=partial yes, 9=yes, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=yes.

Jansen[29]	2014	P: RA I/C: bDMARD monotherapy and combiniation therapy or placebo O: PROMs	bDMARDs	Critically low	1=yes, 2=no, 3=no, 4=no, 5=no, 6=no, 7=no, 8=no, 9=no, 10=no, 11=yes, 12=no, 13=no, 14=no, 15=no, 16=no

Included RCTs

An additional RCT search was performed for the following questions:

- Combination therapy of tsDMARDs
- Recent information on PsA (from 2015)
- Recent information on axSpA (from 2015)

Author	**Year**	**Acronym**	**PICO**	**Drugs**	**RoB-2 conclusion**
Westhovens[30]	2021	FINCH-3	P: active RA, no DMARDs used I: FIL 200 mg + MTX, FIL 200 mg mono or FIL 100 mg + MTX C: MTX O: ACR20 response rate at week 24	FILG	Some concerns
Mease[31]	2019	SEAM-PsA	P: active PsA, no DMARDs used I: ETN + MTX or ETN + placebo C: MTX + placebo O: ACR20 response rate at week 24	ETN	Low
Strand[32]	2019	ORAL strategy	P: active RA despite MTX therapy I: TOFA 2dd 5 mg mono or + MTX C: ADA + MTX O: ACR50 response rate at 6 months (F), PROMs (S)	TOFA	Low
Fleischmann[33]	2017				
Van der Heijde[34]	2018	RA-BEGIN	P: active RA, no DMARDs used I: BARI 4 mg monotherapy or + MTX C: MTX monotherapy O: ACR20 response rate at week 24 (F), PROMs (S), radiographic damage (vdH)	BARI	Some concerns
Schiff[35]	2017				
Fleischmann[36]	2017				

10.Route of administration

Strategy specific search

For this strategy, we only sought for articles concerning infliximab, abatacept and tocilizumab, since those drugs both have an intravenous and subcutaneous route of administration registered.

PubMed search (add this search to 'IRD')

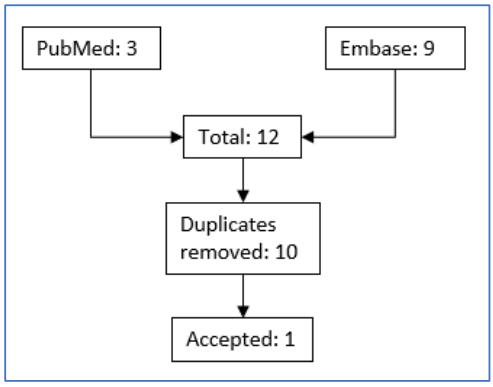
(((subcutan*[title/abstract]) AND (intraven*[title/abstract])) AND ((((((infliximab[MeSH Terms]) OR (abatacept[MeSH Terms])) OR (tocilizumab[Supplementary Concept])) OR (infliximab[Title/Abstract])) OR (abatacept[Title/Abstract])) OR (tocilizumab[Title/Abstract])))

Embase search (add this search to 'IRD')

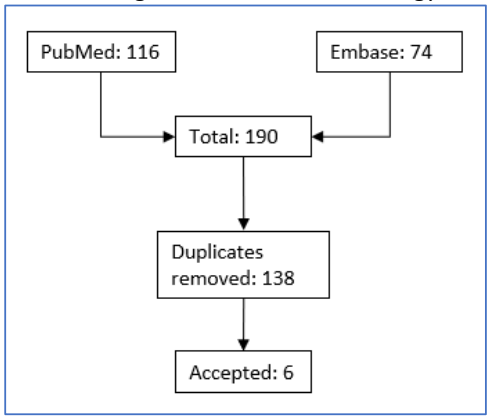
1. exp infliximab/ or exp abatacept/ or exp tocilizumab/ or infliximab.ti,ab,kw. or abatacept.ti,ab,kw. or tocilizumab.ti,ab,kw.
2. exp subcutaneous drug administration/ or subcutan*.ti,ab,kw.
3. exp intravenous drug administration/ or intraven*.ti,ab,kw.
4. 1 and 2 and 3

Strategy output

The flow diagram for the search strategy of systematic literature reviews for route of administration:



The flow diagram for the search strategy of randomized controlled trials for route of administration:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Caporali[37]	2021	P: RA I/C: combine efficacy and safety data of IFX sc with historical data on IFX iv, ADA, ETN O: Efficacy, safety	IFX	Moderate	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=no, 7=yes, 8=partial yes, 9=yes, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=no.

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Westhovens[38]	2021	-	P: active RA and inadequate response to MTX I: IFX sc 120 mg every 2 weeks from week 6 (after IV loading dose on week 0 and 2) C: IFX IV 3 mg/kg every 8 weeks O: Efficacy, PROMs, pharmacokinetics	IFX	Low
Burmester[39]	2016	SUMMACTA extension	P: SUMMACTA participants I/C: SC group: randomization 11:1 to continue sc or switch to iv; IV group: randomization 2:1 to continuation of iv or switch to sc.	TCZ	Some concerns
Ogata[40]	2014	MUSASHI	P: active RA and inadequate response to previous tx I: TCZ sc 162 mg every 2 weeks C: TCZ iv 8 mg/kg every 4 weeks O: ACR20 response rate	TCZ	Some concerns
Burmester[41]	2014	SUMMACTA	P: active RA and inadequate response to csDMARD I: TCZ sc 162 mg once weekly C: TCZ iv 8 mg/kg every 4 weeks O: ACR20 response rate	TCZ	Low
Iwahashi[42]	2014	-	P: RA and inadequate response to MTX I: ABA sc 125 mg/week C: ABA iv 10 mg/kg every 4 weeks O: ACR20 response rate, safety, pharmacokinetics and immunogenicity.	ABA	Low
Genovese[43]	2011	ACQUIRE	P: active RA and inadequate response to MTX I: ABA sc 125 mg/week C: ABA iv 10 mg/kg every 4 weeks O: ACR20 response rate, safety, immunogenicity.	ABA	Low

11.Drug wastage

Strategy specific search

PubMed search

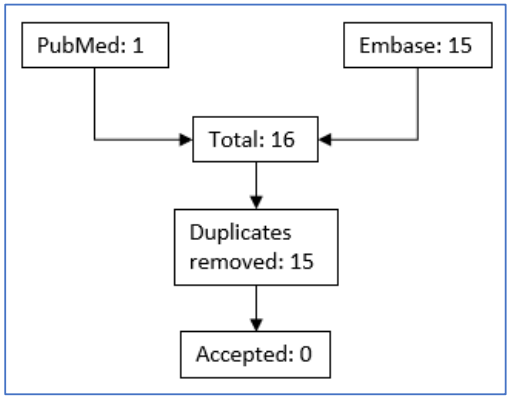
(redispens*[Title/Abstract]) OR (waste[Title/Abstract]) OR (wastage[Title/Abstract]) OR (compounding[Title/Abstract]) OR (dispens*[Title/Abstract]) OR (spillage[Title/Abstract]) OR (reuse[title/abstract]) OR (unused[title/abstract])

Embase search

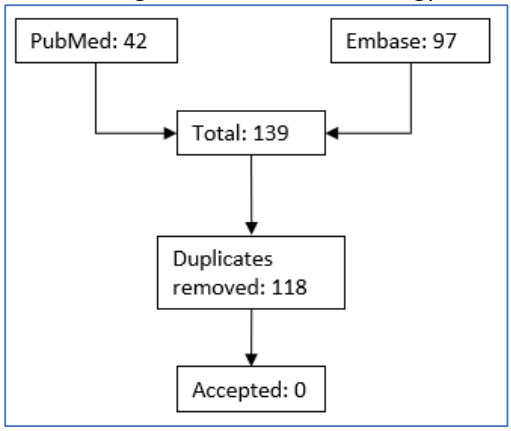
(redispens or waste or wastage or compound* or dispens* or spillage or reuse or unused).ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for drug wastage:



The flow diagram for the search strategy of randomized controlled trials for drug wastage:



Included SLRs

None of the found publications matched our research question and could be included.

Included RCTs

None of the found publications matched our research question and could be included.

12.Medication adherence

Strategy specific search

PubMed search

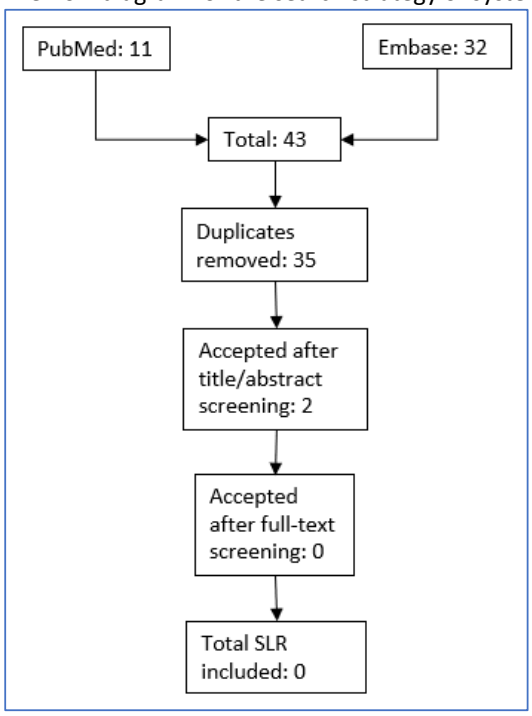
(medication adherence[MeSH Terms]) OR (medication adherence[Title/Abstract]) OR (drug adherence[Title/Abstract]) OR (adherence[Title/Abstract]) OR (patient compliance[Title/Abstract]) OR (medication compliance[Title/Abstract]) OR (drug compliance[Title/Abstract]) OR (non adherence[Title/Abstract]) OR (medication persistence[Title/Abstract]) OR (drug persistence[Title/Abstract]) OR (administration, self[MeSH Terms]) OR (self injection[Title/Abstract]) OR (self administration[Title/Abstract])

Embase search

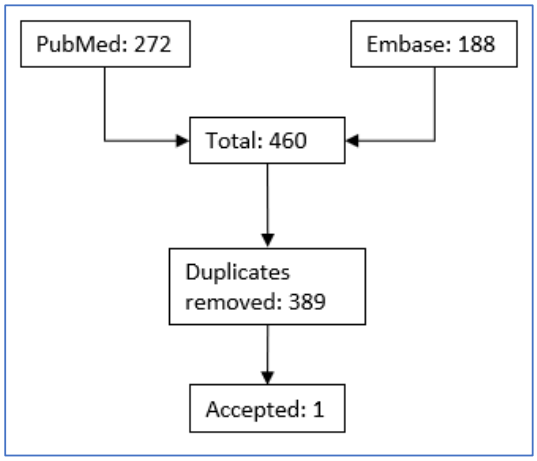
medication compliance/ or adherence.ti,ab,kw. or patient compliance.ti,ab,kw. or compliance.ti,ab,kw. or non adherence.ti,ab,kw. or medication persistence.ti,ab,kw. or drug persistence.ti,ab,kw. or self administration.ti,ab,kw. or self injection.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for medication adherence:



The flow diagram for the search strategy of randomized controlled trials for medication adherence:



Included SLRs

None. None of the found publications matched our research question and could be included.

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Gutermann[44]	2021	-	P: axSpA patients with stable disease activity for 6 months and treatment with sc bDMARD I: Pharmacist' educational interview C: Regular care O: Change in patients' knowledge score about sc bDMARD management at month 6, change in medication possession rate.	bDMARD	Low

We formed an expert opinion point-to-consider only, referring to the current EULAR points to consider for management of non-adherence, because the evidence we found was very limited and not general enough to form a point-to-consider by itself.

13.Disease activity guided dose optimisation (DAGDO)

Strategy specific search

PubMed search

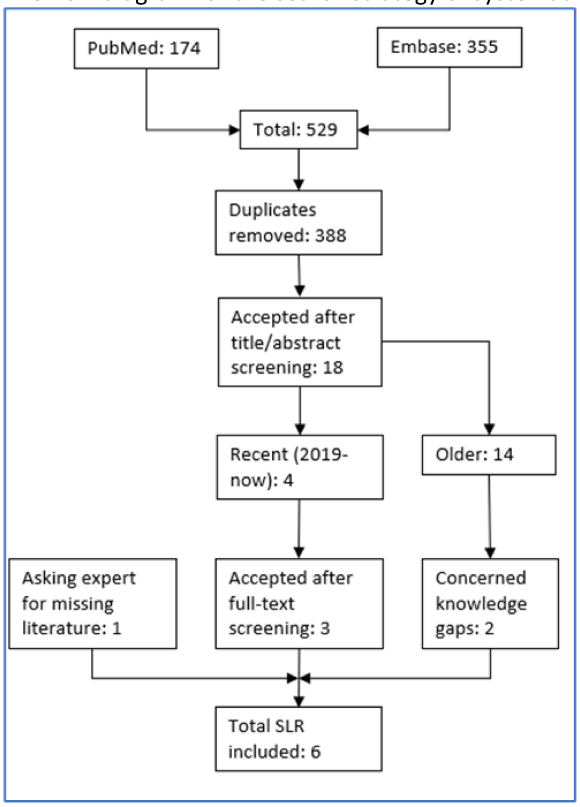
((((((((((((titrat*[Title/Abstract]) OR (down titrat*[Title/Abstract])) OR (reduc*[Title/Abstract])) OR (dose reduc*[Title/Abstract])) OR (dose de-escalat*[Title/Abstract])) OR (discontinu*[Title/Abstract])) OR (dose taper*[Title/Abstract])) OR (taper*[Title/Abstract])) OR (spac*[Title/Abstract])) OR (cessat*[Title/Abstract])) OR (stop*[Title/Abstract])) OR (withdraw*[Title/Abstract])) OR (dose titrat*[Title/Abstract])) OR (interval widen*[Title/Abstract])

Embase search

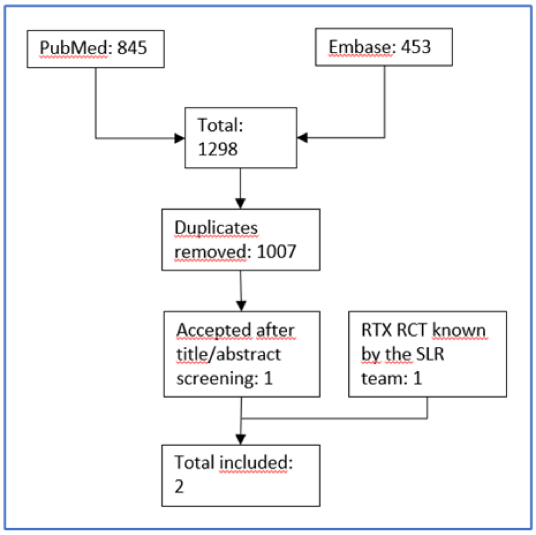
exp drug dose reduction/ or taper*.ti,ab,kw. or dose reduc*.ti,ab,kw. or down titrat*.ti,ab,kw. or reduc*.ti,ab,kw. or dose de-escalat*.ti,ab,kw. or discontinu*.ti,ab,kw. or dose taper*.ti,ab,kw. or spac*.ti,ab,kw. or cessat*.ti,ab,kw. or stop*.ti,ab,kw. or withdraw*.ti,ab,kw. or dose titrat*.ti,ab,kw. or interval widen*.ti,ab,kw.

Strategy output

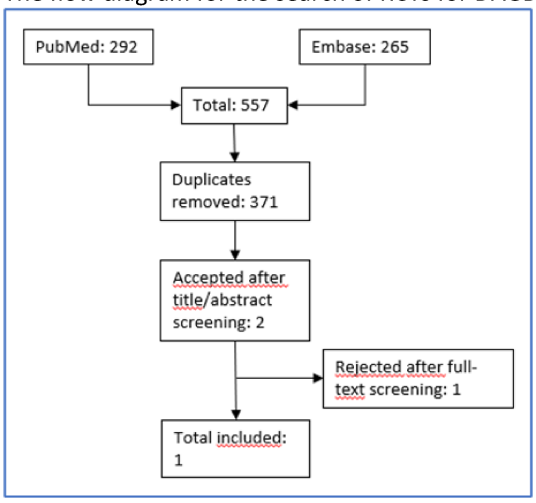
The flow diagram for the search strategy of systematic reviews for 'DAGDO':



The flow diagram for the search of RCTs for 'DAGDO in PsA, with the addition of the RTX RCT':



The flow diagram for the search of RCTs for DAGDO of tsDMARDs:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Lawson[45]	2021	P: axSpA treated with TNFi I: dose reduction C: maintenance of standard dose O: efficacy, safety, QoL	TNFi	High	1=yes, 2=yes, 3=yes, 4=yes, 5=yes, 6=yes, 7=partial yes, 8=yes, 9=yes, 10=yes, 11=yes, 12=no, 13=yes, 14=yes, 15=yes, 16=yes
Vasconcelos[46]	2020	P: RA I: reducing or spacing bDMARD C: dose maintenance of bDMARD O: efficacy, safety, radiographic progression	ABA, ADA, CER, ETN, TCZ	Moderate	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=yes, 7=partial yes, 8=yes, 9=yes, 10=yes, 11=yes, 12=yes, 13=yes, 14=yes, 15=yes, 16=yes
Vinson[47]	2020	P: RA I: tapering (dose reduction or spacing) C: continuation O: serious infections and AEs	bDMARDs, JAKi	Critically low	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=no, 7=yes, 8=no, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes, 16=yes

Verhoef[48]	2019	P: RA and LDA I: down-titration of anti-TNF C: usual care O: efficacy, functioning, costs, safety and radiographic progression	anti-TNF	Moderate	1=yes, 2=no, 3=yes, 4=yes, 5=yes, 6=yes, 7=yes, 8=yes, 9=yes, 10=yes, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=yes.
Edwards[49]	2017	P: RA, PsA, axSpA I: tapering C: not clearly mentioned O: efficacy, patient perspective	bDMARDs	Critically low	1=no, 2=no, 3=no, 4=partial yes, 5=yes, 6=yes, 7=no, 8=no, 9=no,10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=no
Navarro-Compan[50]	2016	P: axSpA I: discontinuation or tapering C: maintaining dose of anti-TNF O: flare or change on disease activity parameters.	ADA, ETN, IFX	Critically low	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=yes, 7=yes, 8=yes, 9=no, 10=no, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=no

Included RCTs

Author	**Year**	**Acronym**	**PICO**	**Drugs**	**RoB-2 conclusion**
Coates[51]	2021	SPIRIT-P3	P: participant in the SPIRIT-P3 study (PsA, biologic-naïve, treated with IXE in the study for 36 weeks) I: continuation of IXE 80 mg/2 weeks C: switch to placebo O: time to relapse	IXE	Low
Verhoef[52]	2019	REDO	P: RA patients on RTX with low disease activity for at least 6 months I: dose reduction to 200 mg or 500 mg RTX C: continuation of 1000 mg RTX O: change from baseline in DAS28-CRP at 3 and 6 months	RTX	Low
Takeuchi[53]	2018	-	P: RA, treated with BARI 4 mg in phase 3 trials I: dose reduction to BARI 2 mg C: continuation of BARI 4 mg O: proportion maintaining CDAI ≤ 10 at 3 months	BARI	Some concerns

14.Non-medical drug switching

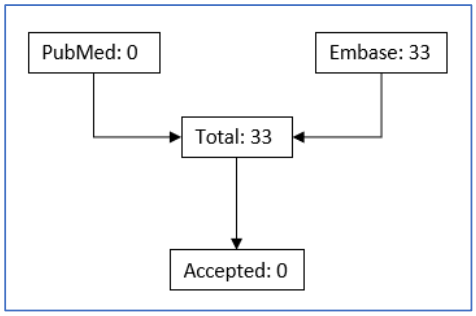
Strategy specific search

PubMed search
(drug switch*[Title/Abstract]) OR (drug transition*[Title/Abstract])

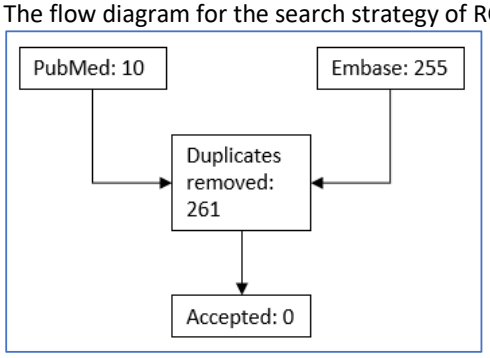
Embase search
drug substitution/ or drug switch*.ti,ab,kw. or drug transition*.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic reviews for 'nonmedical drug switching':



The flow diagram for the search strategy of RCTs for 'nonmedical drug switching':



Included SLRs
None of the found publications matched our research question and could be included.

Included RCTs
None of the found publications matched our research question and could be included.

15. Research agenda

Supplementary box 1. Research agenda
1. Is optimizing pharmacokinetic exposure of b/tsDMARDs possible? 2. Does the use of a drug formulary policy contribute to cost-effectiveness? 3. How can wastage of b/tsDMARDs be reduced? 4. Is non-medical drug switching efficacious, safe and acceptable for patients? 5. What are effective strategies to improve medication adherence of b/tsDMARDs? 6. What predictors for choosing or tapering a b/tsDMARD are effective? 7. Does combination therapy of non-TNFi with MTX (or another csDMARD) for PsA and axSpA have additional value on efficacy and drug survival, compared to monotherapy? 8. Does combination therapy of sarilumab with MTX (or another csDMARD) in RA have additional value on efficacy and drug survival, compared to monotherapy? 9. Is switching from intravenous to subcutaneous administration or vice versa of infliximab effective and safe? 10. Is subcutaneous administration of rituximab effective and safe in RA? 11. What is the most effective DAGDO strategy in IRD? 12. What is the long-term effectiveness and safety of DAGDO in IRD?

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