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The 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDS

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The 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDS: executive summary

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Keywords: Psoriatic arthritis, biologics, targeted synthetic DMARDs, treatment, management, guideline, recommendations, psoriasis, enthesitis, dactylitis

Scope and Purpose

Need for guideline

Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease affecting approximately one quarter of people with the skin condition, psoriasis. PsA is a highly heterogeneous disease, encompassing diverse musculoskeletal manifestations or "domains" resulting from disease activity in different tissues. These include peripheral arthritis, spondylitis (axial inflammation), dactylitis (inflammation of the whole digit) and enthesitis (inflammation where a tendon, ligament or joint capsule insert to the bone). Unlike Rheumatoid Arthritis (RA) there is a significant variability in clinical presentation of PsA. Individuals with PsA may have different domains involved and drugs have different levels of effectiveness on each domain. The most recent British Society for Rheumatology (BSR) guidelines for the treatment of PsA were published in 2012[1]. and focussed specifically on TNF inhibitors as they were the only biologic DMARDs (bDMARDs) available. Since that time, there have been significant advances in therapeutic options available for PsA and drugs with different modes of action are now available, including interleukin (IL) IL17, IL12/23, IL23 p19, Cytotoxic T-lymphocyte-Associated antigen 4 (CTLA4), Phosphodiesterase-4 (PDE4) and Janus kinase (JAK) inhibition.

Objective of the guideline

To offer systematic and evidence-based recommendations to support UK clinicians in the prescription of bDMARD and tsDMARD therapies in adult patients with PsA. The guideline also includes guidance for managing those patients with extra-articular manifestations (uveitis and inflammatory bowel disease (IBD)), as well as those who smoke or are overweight.

Areas not covered

This guideline does not cover the use of conventional synthetic DMARDs, safety, use of biologics or tsDMARDs in pregnancy or juvenile idiopathic arthritis. We refer to the relevant BSR or other guideline recommended by the working group relating to these topics. For patients with psoriatic disease confined to the skin we recommend the British Association of Dermatologists guidelines for the management of psoriasis at https://www.bad.org.uk/healthcare-professionals/psoriasis.

Target audience

The guidelines have been developed to aid rheumatologists, dermatologists and other clinicians involved in the prescription of biologics and tsDMARDs for people with PsA. They will also assist specialist nurses and allied health professionals (AHPs) in the assessment of treatment response, drug

sequencing and switching and provide information to people with PsA who are receiving or moving towards biologic or tsDMARD therapy.

Stakeholder involvement

The guideline has been developed by a multidisciplinary working party set up by the British Society for Rheumatology (BSR), including rheumatologists, dermatologists, an ophthalmologist, a gastroenterologist, a general practitioner, an epidemiologist, a specialist nurse and patient representatives.

Rigour of development

This Guideline was developed in line with the British Society for Rheumatology's Guideline Protocol, which has National Institute for Health and Care Excellence (NICE) accreditation[2]. The evidence used to develop these guidelines was compiled from a systematic and comprehensive literature search, including electronic bibliographic databases (Medline and Embase) and the Cochrane Database of Systematic Reviews up to 10 December 2020.

Grading the evidence and strength of recommendation

The GRADE method was used to assess the quality of evidence and the strength of recommendation. Recommendations were categorized as either strong (denoted by 1) or weak (denoted by 2), according to the balance between benefits, risks, burden and cost. The quality of evidence was categorised as either high (A), moderate (B) or low/very low (C) quantifying estimates of benefits or harm. A strong recommendation (*to offer or not to offer)* something, where the benefits clearly outweigh the risks (or vice versa) for nearly all patients, is denoted by the number 1 in the guideline. A conditional recommendation (*to consider or not*), is made either when the risks and benefits are more closely balanced or are more uncertain and are denoted by the number 2 in this guideline.

GRADE recommends that where it is generally agreed by the medical community that certain principles of diagnosis and disease will do more good than harm (or vice versa), then these should be stated in terms of 'good practice statements'. The 'good practice statements' within this guideline are not necessarily evidence-based; however, are a description of generally accepted best medical practice agreed within our Guideline Working Group.

The Guideline

A summary algorithm for the use of b/tsDMARDs in the treatment of individuals with PsA can be found in Figure 1.

Overarching generic recommendations and levels of agreement

I. Therapeutic decisions need to be individualised and should be based on shared-decision making between people with psoriatic arthritis and their clinicians (strength of agreement SoA 98%).

II. All medication decisions in people with PsA should take into account: disease presentation with activity in the different domains below, previous medication use, associated conditions such as psoriasis, uveitis, and IBD, other comorbidities and patient preference (SoA 97%).

III. When a range of clinically suitable and equivalent treatments are being considered by people with psoriatic arthritis and their clinicians, select the least expensive, taking into account administration costs, dosage, price per dose and commercial arrangements (SoA 88%).

IV. If people with PsA have an inadequate response to a b/tsDMARDs, consider potential factors that could be addressed including: confirming correct diagnosis, adherence, pain due to other causes, drug levels and immunogenicity (SoA 95%).

Whilst discussions about treatments may be discussed with wider members of the rheumatology team, we suggest that commencing a bDMARD or tsDMARD for PsA remains a decision that should be made by a rheumatology consultant.

Treatment by domains:

Peripheral arthritis (mono, oligo and polyarthritis)

i) In people with active psoriatic arthritis*, with inadequate response or intolerance to one csDMARD, consider escalation to b/tsDMARDs *(defined as at least three tender and three swollen joints or those with fewer joints and either poor prognositic markers or severe disease impact defined as ≥2 domains involved, extraarticular involvement or impaired quality of life). (GRADE 2A, SoA 98%)

ii) In people with active peripheral psoriatic arthritis, with inadequate response or intolerance to csDMARDs, offer a bDMARD (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i). (GRADE 1A, 94%) When selecting therapy, consider using

TNFi, IL17i, or upadacitinib (UPA) ahead of IL12/23i or IL23i ahead of PDE4i ahead of CTLA4-Ig. (GRADE 2B, SoA 88%)

A summary of the results from RCTs of biologic and targeted synthetic DMARDs in PsA is shown in Table 1.

PsA with enthesitis

iii) In people with active psoriatic enthesitis, with inadequate response or intolerance to a csDMARD, offer any bDMARD (TNFi, IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i). (GRADE 1A, SoA 91%)

PsA with dactylitis

iv) In people with active psoriatic dactylitis, with inadequate response or intolerance to a csDMARD, offer any bDMARD (TNFi, IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i). (GRADE 1A, SoA 92%)

PsA with axial disease

v) In people with active psoriatic axial disease, with inadequate response or intolerance to at least 2 NSAIDs, offer any TNFi or IL-17i or consider a JAKi. (GRADE 1A, SoA 92%)

PsA with extra-articular manifestations (psoriasis, uveitis, inflammatory bowel disease)

vi) Where a person has associated conditions alongside their psoriatic arthritis, such as psoriasis, uveitis and/or IBD, a multidisciplinary and multispecialty approach should be taken for their care including timely discussions prior to systemic treatment changes. Be aware of other licensed indications and option for differential dosing of common medications in different indications to optimise doses for each individual. (GRADE 1B, SoA 98%)

vii) In the presence of psoriasis, offer concomitant topical therapy. (in line with NICE CG 153) (GRADE 1A, SoA 96%)

viii) In the presence of psoriasis and/or nail psoriasis, all currently licensed b/tsDMARDs can be offered but consider prioritising therapies recommended use for psoriasis: monoclonal TNFi, IL-17i, IL-12/23i or IL-23i summarised in publication[3]. (GRADE 1A, SoA 93%)

ix) In the presence of significant* psoriasis, be aware that IL-17i and IL23i have superior evidence of efficacy over TNFi *significant psoriasis is defined as extensive psoriasis (BSA≥10 or PASI≥10) or localised psoriasis associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites). (GRADE 1A, 92%)

x) In the presence of a mild relapse of anterior uveitis follow standard treatment with concomitant topical therapy. (GRADE 1A, SoA 94%)

xi) In the presence of moderate to severe sight threatening uveitis or multiple recurrent relapses, consider adalimumab or another monoclonal TNFi. (GRADE 1A, 97%)

xii) Refer to the global consensus guideline [4] or NHS England guideline[5] for additional advice on management of uveitis. (GRADE 1C, SoA 96%)

xiii) In the presence of a mild or suspected relapse of IBD, discuss with gastroenterology as a first step. (GRADE 1C, SoA 94%)

xiv) In the presence of moderate to severe Crohns disease, offer any bDMARD (Adalimumab, infliximab, certolizumab, ustekinumab) or consider IL-23i. (GRADE 1A, SoA 93%)

xv) In the presence of moderate to severe UC, offer any bDMARD (Adalimumab, Infliximab, Golimumab, ustekinumab) or tsDMARD (tofacitinib) or consider upadacitinib. (GRADE 1A, SoA 93%)

xvi) Prior to prescription of an IL-17i, consider GI referral for people with un-investigated persistent lower GI symptoms or people with a strong family history of IBD. (GRADE 2C, SoA 93%)

xvii) Do not use IL-17i in people with active Crohns disease. (GRADE 1B, SoA 88%)

xviii) IBD is not an absolute contraindication to commencement of an IL17i however Secukinumab and Ixekizumab are not recommended in individuals with IBD. Exercise caution and consult gastroenterology team before offering IL-17i to people with controlled UC or Crohns disease. If used, individuals and their clinicians should be regularly monitoring for symptoms compatible with IBD. (GRADE 1C, SoA 89%)

Treatment strategy

1. A treat-to-target strategy, whereby an individual's disease activity is proactively measured and treatment escalated accordingly, should be offered to all people with psoriatic arthritis who require treatment. (GRADE 1A, SoA 96%)

2. The treat to target strategy should aim for remission or alternatively low disease activity, taking into account patient goals, associated conditions and co-morbidities, and non-inflammatory causes of pain. (GRADE 1B, SoA 96%)
3. In people with psoriatic arthritis who are on treatment and in a stable low disease activity state across disease domains and associated conditions, consider dose reduction or dose spacing of medication following shared decision making with the patient and in consultation with the other specialists involved in their care. (GRADE 2B, SoA 98%)

Prescribing/ switching

1. When considering treatment with biosimilars for people with PsA, refer to the British Society for Rheumatology 2018 factsheet on Biosimilars. (GRADE 1C, SoA 96%)

2. In people with active psoriatic arthritis beginning b/tsDMARDs the routine use of concurrent csDMARDs is not required but concurrent csDMARDs may be required for the drug licence and may be considered to maximise effectiveness for skin disease, IBD or uveitis and/or to improve persistence with TNFi. (GRADE 1A, SoA 97%)

3. In people with active psoriatic arthritis, with inadequate response or intolerance to a b/tsDMARD, offer any of the current licensed b/tsDMARD treatments. (GRADE 1A, SoA 94%)

4. When selecting therapies, following an inadequate response or intolerance to a b/tsDMARD, consider the following (GRADE 2B, SoA 96%):

   a. The domains of disease relevant in that individual, previous medication use, and associated conditions such as psoriasis, uveitis, and IBD, as with first line b/tsDMARDS.
   b. In people who have primary inefficacy to a b/tsDMARD, consider a different mode of action for the next treatment.
   c. In people who have developed secondary inefficacy to a b/tsDMARD, consider drugs with the same mode of action first, however all currently licenced b/tsDMARDS, without limit to previous lines of therapy and including those previously discontinued can be considered.

Lifestyle choices

1. People with PsA should have their height, weight and BMI recorded. (GRADE 2B, SoA 94%). In people with PsA who are overweight or obese, offer weight loss support and signpost to relevant services to maximise response and long term medication effectiveness of biologics and targeted synthetic DMARDs. (GRADE 1A, SoA 98%)

2. In people with PsA, treatment selection should not be affected by a person's weight. (GRADE 2C, SoA 88%)
3. People with PsA should have their smoking status recorded. (GRADE 2B, SoA 97%)
4. In people with PsA who are smokers, signpost to smoking cessation support services to maximise treatment response, persistence and improve general health. (GRADE 1A, SoA 99%)
5. In people with PsA, treatment selection should not be affected by the person's smoking status although doses should be adjusted appropriately. (GRADE 2C, SoA 96%)

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Table 1 – Summary of key information relating to bDMARDs and tsDMARDS in PsA

	ADA	CZP	ETN	GOL	IFL	ABA	UST	SEC	IXE	GUS	TOFA	UPAD	APR[@]
Year of licence (UK)	2006	2014	2002	2009	2006	2017	2014	2015	2017	2021	2018	2021	2014
Licence in PsA	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü
Phase 3 data in AS/AxSpA	ü	ü	ü	ü	ü	X	ü	ü	ü	X	ü	ü	X
Licence in AS/AxSpA	ü	ü	ü	ü	ü	X	ü	ü	ü	X	X	X	X
Phase 3 data in IBD	ü	ü (CD)	X	ü (UC)	ü	X	ü	X	X	ü (CD)	ü (UC)	ü (UC)	X
Licence in IBD	ü	ü (CD)	X	ü (UC)	ü	X	ü	X	X	X	ü (UC)	X	X
Licence in uveitis	ü	X	X	X	X	X	X	X	X	X	X	X	X
ACR50 at week 12-16 (%)	PBO 3	PBO 12	PBO 4	PBO 2	PBO 2	N/A	N/A	PBO 9	PBO 5	N/A	PBO 10	PBO 13	PBO 7
	ADA 33	CZP 34	ETN 40	GOL 29	IFL 39	N/A	N/A	SEC 4	IXE 34	N/A	TOFA 28	UPAD 38	APR 13
ACR50 at week 24 (%)	PBO 6	PBO 15	PBO 4	PBO 4	PBO 4[$]	PBO 15	PBO 9	PBO 9	PBO 15	PBO 14	N/A	PBO 19	PBO 4
	ADA 40	CZP 42	ETN 37	GOL 35	IFL 41[$]	ABA 25	UST 26	SEC 46	IXE 40	GUS 31	TOFA 38	UPAD 52	APR 20
PASI75 at week 12-16 (%)	PBO 4	PBO 17	N/A	PBO 3	PBO 2	N/A	PBO 9	PBO 13	PBO 5	N/A	PBO 15	PBO 21	PBO 6
	ADA 49	CZP 43	N/A	GOL 49	IFL 65	N/A	UST 50	SEC 65	IXE 75	N/A	TOFA 43	UPAD 63	APR 22
PASI75 at week 24 (%)	PBO 1	PBO 20	PBO 3	PBO 1	PBO 1[$]	PBO 10	PBO 11	PBO 32	PBO 7	PBO 23	N/A	N/A	PBO 5
	ADA 59	CZP 56	ETN 23	GOL 59	IFL 60[$]	ABA 18	UST 60	SEC 72	IXE 71	GUS 79	TOFA 46	N/A	APR 21
Enthesitis efficacy vs placebo	N/A	ü	N/A	ü	ü	X	ü	ü	X	ü (pooled)	ü (pooled)	ü	ü (pooled)
Dactylitis efficacy vs placebo	N/A	ü	N/A	ü	ü	X	ü	ü	ü	ü (pooled)	ü (pooled)	X	ü (pooled)
MDA rates at week 24	PBO 6~	PBO 6	N/A	PBO 1	N/A	PBO 8*	N/A	PBO 15	PBO 15	PBO 11	PBO 19	PBO 12	N/A
	ADA 36~	CZP 33	N/A	GOL 28	N/A	ABA 12*	N/A	SEC 41	IXE 30	GUS 23	TOFA 26	UPAD 37	N/A
Contraindications	Demyelination NY class 3/4 Heart failure							IBD					
Key safety issues	Non-melanoma skin cancer Infections						Exfoliative dermatitis	Fungal infections including candida			Herpes zoster VTE/malignancy risk		Suicidal thought and behaviour

6. * Mixed population with some TNFi exposure
7. ~data on subset with all data available and baseline BSA>3%
8. $Data at 24 weeks from IMPACT2 study only
9. @ week 12 data based on PALACE 2 and 3, week 24 data based on PALACE 1, all trials mixed population with TNF exposure
10.
11. **Abbreviations:** ABA=abatacept, ACR50=American College of Rheumatology 50% response, ADA=adalimumab, APR=apremilast, AS=ankylosing spondylitis, AxSpA=axial spondyloarthritis, CD=Crohns disease, CZP=certolizumab pegol, ETN=etanercept, GOL=golimumab, GUS=guselkumab, IBD=inflammatory bowel disease, INF=infliximab, IXE=ixekizumab, MDA=minimal disease activity, PASI75=psoriasis area and severity index 75% response, PBO=placebo, SEC=secukinumab, TOFA=tofacitinib, UC=ulcerative colitis, UPAD=upadacitinib, UST=ustekinumab

Figure 1. Summary algorithm for the treatment of an individual with PsA with b/tsDMARDs.

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Background

Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease affecting approximately one quarter of people with the skin condition, psoriasis[1, 2]. PsA is a highly heterogeneous disease, encompassing diverse musculoskeletal manifestations or "domains" resulting from disease activity in different tissues. These include peripheral arthritis, spondylitis (axial inflammation), dactylitis (inflammation of the whole digit) and enthesitis (inflammation where a tendon, ligament or joint capsule insert to the bone). Unlike Rheumatoid Arthritis (RA) there is a significant variability in clinical presentation of PsA. Individuals with PsA may have different domains involved and drugs have different levels of effectiveness on each domain. It is therefore essential that clinical guidelines for the treatment selection in PsA include disease phenotype and differential effect of medication.

PsA is a potentially debilitating and destructive disease, with half of people developing irreversible joint damage within 2 years[3]. This results in significant functional limitations, depression and anxiety, as well as negatively impacting on education, work capacity and social participation[4-8]. Furthermore, PsA is associated with extra-articular manifestations, including inflammatory bowel disease (Crohn's disease and ulcerative colitis) and uveitis. In addition, metabolic syndrome (obesity, diabetes, hypertension, hyperlipidaemia, fatty liver disease) and cardiovascular disease are more common compared with the prevalence in the general population[7, 9, 10]. All of these factors may influence treatment selection[11] and potentially modifiable risk factors, such as obesity and smoking, which can impact therapeutic response and prognosis, should be addressed within the management plan.

There is strong evidence that a treat-to-target (T2T) approach to PsA management, aiming for remission or low disease activity, results in better clinical, radiographic and patient reported outcomes[15, 16]. Significant advances in therapeutic options available for PsA now mean a target of remission is an achievable goal. Despite PsA being a highly heterogenous disease, most physicians apply the same step-up therapy to all people with peripheral arthritis, owing to the lack of comparative evidence. Initially a single conventional systemic disease-modifying anti-rheumatic drug (csDMARD) is used, with methotrexate typically being prescribed first-line. This is followed by use of an alternative single csDMARD or combinations of csDMARDs, prior to biologic use if the previous treatment step is unsuccessful [11, 12]. Up to 50% of people with PsA require biologic or targeted synthetic b/ tsDMARD therapy[13] and treatment in the UK is governed by specific agencies, owing to the higher cost of these drugs. This includes recommendations in England from the National Institute for Health and Care Excellence (NICE) criteria and in Scotland from the Scottish Medicines

Consortium (SMC). In addition, non-steroidal anti-inflammatory drugs and local corticosteroids are frequently used, which although not optimal for long-term use, do offer quick, short-term symptomatic relief, whilst DMARDs take effect.

In practice, biologics require use for a minimum of 12 (e.g. TNFi) or 16 weeks (e.g. IL-17Ai), before response can be evaluated [14]. Unfortunately, a proportion of people do not respond to the first-line drug chosen (primary non-response), whilst other people respond well initially, but subsequently lose response (secondary non-response). For these reasons, as well as adverse events encountered by some people, switching therapy is required to achieve and maintain treatment targets.

Need for updating of guideline

The last British Society for Rheumatology (BSR) guideline for the treatment of PsA were published in 2012 [15] and focussed specifically on TNF inhibitors as they were the only biologic DMARDs (bDMARDs) available. Since that time, there have been significant advances in therapeutic options available for PsA and drugs with different modes of action are now available, including interleukin (IL) IL17, IL12/23, IL23 p19, Cytotoxic T-lymphocyte-Associated antigen 4 (CTLA4-Ig), Phosphodiesterase-4 (PDE4) and Janus kinase (JAK) inhibition (i).

We recognise existing high quality international treatment recommendations, which include those written by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in 2021, EULAR in 2020 and American College of Rheumatology in 2018[16-18]. However, these are generic to many international health settings and do not provide specific guidance for the UK, taking account of the health-care system and prescribing restrictions. This guideline aims to look at the evidence beyond current NICE technology appraisals and to provide advice for the management of people with PsA.

Objectives

This guideline offers systematic and evidence-based recommendations to support UK clinicians in the prescription of bDMARD and tsDMARD therapies in adults with PsA. The guideline also includes guidance for managing those patients with extra-articular manifestations (uveitis and inflammatory bowel disease (IBD)), as well as those who smoke or are overweight. The guideline provides a stepwise management plan giving clear advice on treatment, including drug eligibility, sequencing, switching and treatment strategy.

This guideline complements existing BSR guidelines and therefore do not include:

(i) Detailed assessment of the safety of biologic DMARDs

(ii) Biologic or tsDMARD therapies for juvenile idiopathic arthritis

(iii) Use of csDMARDs in PsA

(iv) Use of biologics or tsDMARDs in pregnancy

(v) Biologic or tsDMARD therapies for adults with psoriatic disease confined to the skin only (in this situation please refer to BAD guidelines for management of psoriasis at https://www.bad.org.uk/healthcare-professionals/psoriasis)

Target audience

The guideline has been developed to provide assistance to rheumatologists, dermatologists and other clinicians involved in the prescription of biologics and tsDMARDs for people with PsA. The guideline will also assist specialist nurses and allied health professionals (AHPs) in the assessment of treatment response, drug sequencing and switching and provide information to people with PsA who are receiving or moving towards biologic or tsDMARD therapy.

Stakeholder involvement

The guideline has been developed by a multidisciplinary guideline working group (GWG) set up by the British Society for Rheumatology (BSR), including rheumatologists, dermatologists, an ophthalmologist, a gastroenterologist, a general practitioner, an epidemiologist, a specialist nurse and patient representatives. Any conflicts of interest among the GWG were fully declared. Details of members of this working party and their declared conflicts of interest are included at the end of this article and are available on the BSR website. The guideline will be presented for comment at the BSR Annual Meeting in 2022 and was available for open consultation on the BSR website for a month prior to submission for publication. Opinions of key stakeholders, including members of the BSR, and Primary Care Rheumatology and Musculoskeletal Medicine Society (PCRMM), as well as patient members of the Psoriasis and Psoriatic Arthritis Alliance (PAPAA), were also sought.

Rigour of development

This guideline and recommendations were developed in line with the British Society for Rheumatology's Guidelines Protocol[19], which has National Institute for Health and Care Excellence (NICE) accreditation. The guideline and recommendations were underpinned with a systematic literature review.

Literature review

The evidence used to develop this guideline was compiled from a systematic literature review (SLR), including electronic bibliographic databases (Medline and Embase) and the Cochrane Database of Systematic Reviews up to 10 December 2020. Key terms for the search were the following: MeSH terms arthritis, psoriatic, psoriatic arthritis, psoriasis and arthritis in combination (independently) with biologic therapy mode of action, targeted synthetic mode of action or any biologic or tsDMARD drug name. Inclusion criteria for review were clinical outcomes in adults with PsA, published in English or in languages other than English with an English translation available. All titles and abstracts were screened by the BSR systematic literature reviewer and full papers of relevant material were obtained. In addition, data extraction and quality assessment undertaken by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)[20] was utilised to aid in the completion of this SLR. Reviews of the articles included were conducted to establish current evidence for the following topics: efficacy of TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, abatacept, apremilast or JAK inhibitors in different disease domains (peripheral arthritis, axial disease, enthesitis, dactylitis) as well as extra-articular diseases (psoriasis, uveitis and inflammatory bowel disease), the clinical effectiveness of a treat-to-target strategy, the impact of bDMARD or tsDMARD tapering and dose reduction in remission, switching to a biosimilar drug, use of concomitant csDMARDs, efficacy of biologic and tsDMARD therapies in people who are overweight or smoke and the clinical effects of weight loss and smoking cessation in adults with active PsA. These key questions were agreed by the GWG prior to the literature search and published in the guideline scope.[21]

In relation to efficacy, only randomized controlled trials (RCTs) of high quality were included for musculoskeletal and skin features of psoriatic disease, whereas in other areas, given the paucity of published data, wider data were included. Data from relevant articles were extracted using standardized literature evaluation forms in order to summarize evidence. Evidence for all aspects of the guideline was limited to articles published in peer-reviewed medical journals. There is a wealth of evidence concerning efficacy and safety of the bDMARDs and tsDMARDs available in PsA but a limited amount of evidence available to support recommendations on choice of therapy and treatment strategy.

Level of evidence

This guideline was developed in line with BSR's Guidelines Protocol (Ref). The GWG convened on five occasions to review evidence and formulate recommendations. A draft document of the guideline

was circulated to the full GWG for review. Each suggested recommendation in the final document was evaluated by all members and subjected to a vote relating to strength of agreement on a scale of 1 [total disagreement] to 10 [total agreement]. The strength of agreement across the GWG for each recommendation is presented as the mean of the members' individual strength of recommendation, expressed as a percentage (e.g. 100% implies all responses were 10/10). The recommendation statements are presented at the beginning of each section. The GRADE approach to assessing the quality and strength of recommendations was adopted[22]. In addition, and in accordance with the BSR protocol accompanying each recommendation in parenthesis is a statement reflecting the strength of recommendation and quality of supporting evidence.

Strength of the recommendation

A strong recommendation to offer (or not to offer) something, where the benefits clearly outweigh the risks (or vice versa) for nearly all patients, is denoted by the number 1 in the guideline. A conditional recommendation (to consider or not), is made either when the risks and benefits are more closely balanced or are more uncertain and are denoted by the number 2 in this guideline.

Quality of evidence:

Assessment of supporting evidence quality in GRADE reflects confidence in the estimates of benefits, harms and burdens. This guideline uses three levels and a letter (A, B, C) to reflect high, moderate or low/ very low quality of evidence.

High quality is where further research is very unlikely to change the confidence in the estimate of effect.

Moderate quality is where further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality is where further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low-quality : any estimate of effect is very uncertain.

Plan for review

The planned review date for this guideline will be in five years' time. However, important interim changes will be updated on the BSR website.

The guideline

Each of the seven sections of the guideline (overarching recommendations, treatment by disease domain, psoriasis and uveitis, IBD, treatment strategy, prescribing/ switching, lifestyle choices) will now be discussed in detail. For each statement, a review of the evidence will follow.

New treatment algorithm

The guideline includes a new and expanded treatment algorithm incorporating all the modes of action available. The algorithm is intended to be practical and accessible 'at a glance' to practicing clinicians. The algorithm is underpinned by the key principle of thorough disease assessment to adequately understand disease phenotype and therefore to facilitate selection of b/tsDMARDs based on the domains of disease. The step-up algorithm incorporates the treat to target approach, the importance of considering comorbidities and associated conditions. See figure 1 for the new treatment algorithm.

Overarching generic recommendations and levels of agreement

GRADE recommends that where it is generally agreed by the medical community that certain principles of diagnosis and disease will do more good than harm (or vice versa), then these should be stated in terms of 'good practice statements' or generic recommendations[23]. The generic recommendations within this guideline are not necessarily evidence-based; however, are a description of generally accepted best medical practice agreed within our Guideline Working Group.

I. Therapeutic decisions need to be individualised and should be based on shared-decision making between people with psoriatic arthritis and their clinicians (strength of agreement [SoA] 98%).
II. All medication decisions in people with PsA should take into account: disease presentation with activity in the different domains below, previous medication use, associated conditions such as psoriasis, uveitis, and IBD, other comorbidities and patient preference (SoA 97%).
III. When a range of clinically suitable and equivalent treatments are being considered by people with psoriatic arthritis and their clinicians, select the least expensive, taking into account administration costs, dosage, price per dose and commercial arrangements (SoA88%).
IV. If people with PsA have an inadequate response to a b/tsDMARD, consider potential factors that could be addressed including: confirming correct diagnosis, adherence, pain due to other causes, drug levels and immunogenicity (SoA 95%).

Whilst discussions about treatments may be discussed with wider members of the rheumatology team, we suggest that commencing a bDMARD or tsDMARD for PsA remains a decision that should be made by a rheumatology consultant.

Treatment by domains:

Peripheral arthritis (mono, oligo and polyarthritis)

1. In people with active psoriatic arthritis*, with inadequate response or intolerance to one csDMARD, consider escalation to b/tsDMARDs *(defined as at least three tender and three swollen joints or those with fewer joints and either poor prognostic markers or severe disease impact defined as ≥2 domains involved, extraarticular involvement or impaired quality of life). (GRADE 2A, SoA 98%)

This recommendation refers to people with active peripheral PsA (at least three tender and three swollen joints or those with fewer joints but severe disease impact), with an inadequate response or intolerance to a csDMARD (methotrexate, leflunomide, sulfasalazine). In these individuals, escalation to a b/tsDMARD should be considered. This eligibility recommendation was made through group consensus and would bring the UK in line with the majority of European healthcare settings. However, the use of biologics after one csDMARD or for people with less than three tender/swollen joints is not currently permitted by NICE TAGs. A full assessment of evidence for csDMARD effectiveness was beyond the scope of this guideline, which focus on biologic and tsDMARD treatments. The GWG discussed the appropriateness of initiating a b/tsDMARD first-line, taking into consideration the efficacy, safety and cost effectiveness of conventional synthetic, biologic and tsDMARDS. Based on anecdotal and observational data supporting the efficacy of csDMARDs, especially methotrexate, in achieving low disease activity/ remission in PsA and from a cost-effective perspective, the group agreed that a csDMARD should be initiated first-line. There is little evidence to base a judgement on how many csDMARDs should be failed before considering a b/tsDMARD therapy; however, two relevant randomised controlled trials addressing eligibility for b/tsDMARDs were discussed: the SEAM-PsA and the CONTROL studies. The SEAM-PsA trial compared etanercept to etanercept plus methotrexate combination therapy and methotrexate monotherapy. The results demonstrated superiority of etanercept over methotrexate[24]. The CONTROL trial compared dose escalation of methotrexate to the addition of TNFi in people with inadequate disease control PsA after initial methotrexate therapy. A significantly higher proportion of individuals achieved minimal disease activity (MDA) at week 16 after introducing adalimumab compared to

dose escalation of methotrexate[25]. The guideline working group (GWG) therefore proposed earlier use of a b/tsDMARD therapy after failure of just one csDMARD be considered in those individuals with poor prognostic factors (polyarticular disease, high systemic inflammation levels, presence of radiographic erosions or significantly impaired functional ability)[6, 26-29] or severe active disease.

2. In people with active peripheral psoriatic arthritis, with inadequate response or intolerance to csDMARDs, offer a bDMARD (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i). (GRADE 1A, 94%) When selecting therapy, consider using TNFi, IL17i, or upadacitinib (UPA) ahead of IL12/23i or IL23i ahead of PDE4i ahead of CTLA4-Ig. (GRADE 2B, SoA 88%)

A summary of the results from RCTs of biologic and targeted synthetic DMARDs in PsA is shown in Table 1. The data supporting the first recommendation to offer a b/tsDMARDS was based on trials of medication versus placebo in the relevant domains of disease. There are no data to support optimal selection of drugs for individuals, but the guideline group developed a consensus recommendation to support biologic choice based on efficacy data, speed of onset and adverse events (table 1). TNF inhibitors remain the most widely used first line biologic in PsA and none of the other therapies have shown superiority to them for articular disease. Head to head studies now exist for IL-17i and upadacitinib showing non-inferiority to TNFi, hence their inclusion as potential first choices. Despite a lack of head to head data, there were concerns that clinical responses to IL12/23i, IL23i, PDE4i and CTLA4-Ig might be slightly lower and slower than TNFi. Physicians should be aware of the MHRA safety warning around the use of tofacitinib. [30]The safety data demonstrating increased rates of Venous Thromboembolic Disease (VTE), Major Cardiovascular Event (MACE) and malignancy with tofacitinib compared to TNFi available at the time of writing prompted the committee to differentiate between upadacitinib and tofacitinib in the recommendation.

PsA with enthesitis

3. In people with active psoriatic enthesitis, with inadequate response or intolerance to a csDMARD, offer any bDMARD (TNFi, IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i). (GRADE 1A, SoA 91%)

PsA with dactylitis

4. In people with active psoriatic dactylitis, with inadequate response or intolerance to a csDMARD, offer any bDMARD (TNFi, IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i). (GRADE 1A, SoA 92%).

Active enthesitis and dactylitis are seen in many PsA patients and are usually assessed clinically. Where any question as to the cause of pain, additional imaging (ultrasound or magnetic resonance imaging) may be helpful. Positive enthesitis and dactylitis outcomes were seen with all of the medications included in the SLR. Typically, these are as secondary outcomes in peripheral arthritis studies, although there are a small number of specific trials in enthesitis or dactylitis. Some older drugs (table 1) did not collect these outcomes in the initial phase 3 trials and therefore have poorer quality evidence. However, the group agreed that there was no evidence of differentiation within the drug classes and so all drugs within each class are recommended equally. However, we note that the use of biologics for people with less than three tender/swollen joints is not currently permitted by NICE TAGs which impede access to therapies for these indications.

PsA with axial disease

5. In people with active psoriatic axial disease, with inadequate response or intolerance to at least 2 NSAIDs, offer any TNFi or IL-17i or consider a JAKi. (GRADE 1A, SoA 92%)

In the literature search, evidence of an improvement in the Bath Ankylosing Spondylitis disease activity index (BASDAI) was seen in people with evidence of axial manifestations within the peripheral PsA trials. However, the group noted that the BASDAI is not specific to axial disease and is heavily influenced by disease activity in other domains of PsA. There was one specific axial study in a population with PsA who had physician-reported axial manifestations, and this found evidence of a clinical and imaging benefit for an IL-17Ai (secukinumab)[31]. The group also utilized results from ankylosing spondylitis (AS) and axial spondyloarthritis (aAxSpA) trials to support the recommendations. There are positive trials for TNFi, IL-17i, and JAKi in axial SpA. In contrast, there are trials for of an IL-12/23i that were stopped early, a negative trial for apremilast and a negative trial for an IL-23i. The group agreed to a practical approach, utilising what is known from AS / AxSpA studies to support the evidence found for small subgroups in the PsA trials and the single trial in PsA where all people had axial manifestations. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S1, available at *Rheumatology* online.

PsA with extra-articular manifestations (psoriasis, uveitis, inflammatory bowel disease)

6. Where a person has associated conditions alongside their psoriatic arthritis, such as psoriasis, uveitis and/or IBD, a multidisciplinary and multispecialty approach should be taken for their care including timely discussions prior to systemic treatment changes. Be aware of other licensed indications and option for differential dosing of common medications in different indications to optimise doses for each individual. (GRADE 1B, SoA 98%)

Psoriasis

7. In the presence of psoriasis, offer concomitant topical therapy. (in line with NICE CG 153) (GRADE 1A, SoA 96%)
8. In the presence of psoriasis and/or nail psoriasis, all currently licensed b/tsDMARDs can be offered but consider prioritising therapies recommended use for psoriasis: monoclonal TNFi, IL-17i, IL-12/23i or IL-23i summarised in publication[32]. (GRADE 1A, SoA 93%)
9. In the presence of significant* psoriasis, be aware that IL-17i and IL23i have superior evidence of efficacy over TNFi *significant psoriasis is defined as extensive psoriasis (BSA≥10 or PASI≥10) or localised psoriasis associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites). (GRADE 1A, SoA 92%).

The studies included in the SLR often reported psoriasis outcomes in people with 3% or more body surface area (BSA) plaque psoriasis. The SLR found a benefit for all of the bDMARDs and tsDMARDS included. In the dermatology literature, there are an increasing number of head-to-head trials comparing bDMARDs in psoriasis with evidence of superior efficacy for IL-17i and IL-23i over TNFi. However, the guideline group agreed that psoriasis tends to be less severe in rheumatology clinics and it is unlikely that such large disparities will exist in this population. Where psoriasis is more severe, then the discussion between the multidisciplinary team is important to select therapy. Further support is available in the clinical implementation toolkit developed by the British Association of Dermatologists.

Uveitis

10. In the presence of a mild relapse of anterior uveitis follow standard treatment with concomitant topical therapy. (GRADE 1A, SoA 94%)
11. In the presence of moderate to severe sight threatening uveitis or multiple recurrent relapses, consider adalimumab or another monoclonal TNFi. (GRADE 1A, SoA 97%)

12. Refer to the global consensus guideline [33] or NHS England guideline[34] for additional advice on management of uveitis. (GRADE 1C, SoA 96%)

There is little evidence for the management of uveitis specifically in people with psoriatic arthritis but there are many trials in wider populations of either people with uveitis or those with uveitis and spondyloarthritis. The guideline group therefore considered evidence from this wider population within existing ophthalmology guidelines and pathways. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S2, available at *Rheumatology* online.

IBD

13. In the presence of suspected relapse of IBD, discuss with gastroenterology as a first step. (GRADE 1C, SoA 94%)
14. In the presence of moderate to severe Crohn's disease, offer any of Adalimumab, infliximab, certolizumab, ustekinumab or consider IL-23i. (GRADE 1A, SoA 93%)
15. In the presence of moderate to severe UC, offer any of Adalimumab, Infliximab, Golimumab, ustekinumab or tofacitinib, or consider upadacitinib. (GRADE 1A, SoA 93%)
16. Prior to prescription of an IL-17i, consider GI referral for people with un-investigated persistent lower GI symptoms or people with a strong family history of IBD. (GRADE 2C, SoA 93%)
17. Do not use IL-17i in people with active Crohn's disease. (GRADE 1B, SoA 88%)
18. IBD is not an absolute contraindication to commencement of an IL17i however Secukinumab and Ixekizumab are not recommended in individuals with IBD. Exercise caution and consult gastroenterology team before offering IL-17i to people with controlled UC or Crohn's disease. If used, individuals and their clinicians should be regularly monitoring for symptoms compatible with IBD. (GRADE 1C, SoA 89%)

As for uveitis, there was no evidence to support the literature search specific to people with PsA and IBD. This guideline therefore considered evidence for relevant bDMARDs and tsDMARDs in trials of people with IBD to allow rheumatologists to understand their effectiveness. Conditional recommendations are included where recent evidence support efficacy in a phase 3 trial. The evidence for the adverse IBD effects of IL-17i has led to a cautious approach in this guideline. They are not universally excluded but should only be prescribed where other possible options have failed, and the person has well controlled IBD. Further information is available in guidelines published by the British Society of Gastroenterology[35]and the European Crohn's and Colitis Organisation[36].

The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S3, available at *Rheumatology* online.

Treatment strategy

19. A treat-to-target strategy, whereby an individual's disease activity is proactively measured and treatment escalated accordingly, should be offered to all people with psoriatic arthritis who require treatment. (GRADE 1A, SoA 96%)
20. The treat to target strategy should aim for remission or alternatively low disease activity, taking into account patient goals, associated conditions and co-morbidities, and non-inflammatory causes of pain. (GRADE 1B, SoA 96%)

The evidence from the TICOPA trial indicated that a treat to target strategy was effective across a range of disease domains and this was supported by the group's own experiences. Therefore, a recommendation was made to offer this strategy to people with PsA utilising regular and validated measurements of disease activity. A second recommendation was made based on consensus in the group that limiting the target to a single measure did not account for the totality of the disease effects. Therefore, the group recommended a disease activity target whilst also indicating that physicians should consider the patient goals they established early in the process, a person's co-morbidities, and other possible causes of pain. Incorporating this approach would keep the person's experiences at the centre of the care. Further advice on treat-to-target in PsA is available in specific International recommendations.[14] The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S4, available at *Rheumatology* online.

21. In people with psoriatic arthritis who are on treatment and in a stable low disease activity state across disease domains and associated conditions, consider dose reduction or dose spacing of medication following shared decision making with the patient and in consultation with the other specialists involved in their care. (GRADE 2B, SoA 98%)

The literature search identified one RCT of treatment withdrawal involving 17 people with PsA and was graded as low quality. However, the clinicians on the guideline group all indicated that they utilised some form of dose tapering in some cases within their usual practice. Given that many bDMARDs and tsDMARDs have standard doses, this is often done by stretching out the interval between doses e.g. taking adalimumab 40mg every 3 weeks. Shared decision making is thought to be very important for this process. People should not be forced to taper if they are unwilling as the evidence for a benefit is not strong enough. If considering tapering, there should be meaningful

involvement of all the specialists involved in the care of an individual in this decision. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S5, available at *Rheumatology* online.

Prescribing/ switching

22. When considering treatment with biosimilars for people with PsA, refer to the British Society for Rheumatology 2018 factsheet on Biosimilars.[37] (GRADE 1C, SoA 96%)
23. In people with active psoriatic arthritis beginning b/tsDMARDs the routine use of concurrent csDMARDs is not required but concurrent csDMARDs may be required for the drug licence and may be considered to maximise effectiveness for skin disease, IBD or uveitis and/or to improve persistence with TNFi. (GRADE 1A, SoA 97%)
24. In people with active psoriatic arthritis, with inadequate response or intolerance to a b/tsDMARD, offer any of the current licensed b/tsDMARD treatments. (GRADE 1A, SoA 94%)
25. When selecting therapies, following an inadequate response or intolerance to a b/tsDMARD, consider the following (GRADE 2B, SoA 96%):
    a. The domains of disease relevant in that individual, previous medication use, and associated conditions such as psoriasis, uveitis, and IBD, as with first line b/tsDMARDS.
    b. In people who have primary inefficacy to a b/tsDMARD, consider a different mode of action for the next treatment.
    c. In people who have developed secondary inefficacy to a b/tsDMARD, consider drugs with the same mode of action first, however all currently licenced b/tsDMARDS, without limit to previous lines of therapy and including those previously discontinued can be considered.

Large scale switches to biosimilar medications have occurred and continue to occur as more biosimilar medications become available. These are decisions rooted in finance rather than formal efficacy and there is very little evidence for or against switching. This guideline is utilising the recommendations held within the 2018 BSR factsheet on biosimilars. It is a consensus document and among its key recommendations, it states that people should be offered the most cost-effective biologic medications, encouraging shared decision-making and integration of the wider treatment group in decision-making, and not undertaking sequential switching. The guideline recommends that people can switch back to the originator if they lose efficacy or there are safety issues with the

new biosimilar. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S6, available at *Rheumatology* online.

One RCT and two observational studies related to concurrent use of csDMARDs were identified in the literature search. All of these studied TNF inhibitors and indicated that there was no clinically important benefit for the routine use of csDMARDs. However, the group discussed other data outside the SLR particularly related to longevity of medications in national biologics registries. The group also raised the issue of csDMARD use for other indications such as psoriasis or related SpA conditions. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S7, available at *Rheumatology* online.

Lack or loss of response to advanced therapies is a relatively common problem in PsA. Whilst there are an increasing number of trials addressing efficacy of treatments in populations who are TNFi experienced, there is little evidence to guide optimal therapy selection for individuals. There are no studies looking at efficacy in people who have lost response to drugs with other modes of action. Therefore, no specific treatment class recommendations are made. Generally, the guideline group felt that after primary inefficacy to a particular drug, it would not make sense to try another drug from the same class, but an alternative mode of action should usually be selected in the first instance, reserving them for future lines of therapy. In contrast, after secondary inefficacy the same mode of action may be the most effective treatment. However, further studies around treatment sequencing are urgently needed to guide this approach. Pending data to the contrary the committee felt that all licenced b/tsDMARDS, without limit to previous lines of therapy, including those previously discontinued should remain available as treatment options. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary file S8, available at *Rheumatology* online.

Lifestyle choices

26. People with PsA should have their height, weight and BMI recorded. (GRADE 2B, 94%). In people with PsA who are overweight or obese, offer weight loss support and signpost to relevant services to maximise response and long term medication effectiveness of biologics and targeted synthetic DMARDs. (GRADE 1A, SoA 98%)
27. In people with PsA, treatment selection should not be affected by a person's weight. (GRADE 2C, SoA 88%)

The SLR showed similar efficacy for the medications versus placebo, but there were not enough data to differentiate between treatments. Therefore, the group agreed that treatment options for overweight/obese adults with PsA were identical to those offered to the general PsA population. In obese individuals, clinicians should prescribe the appropriate dose for any medication with weight-based dosing (e.g. infliximab, golimumab). It is important to note that people with PsA who are overweight/obese outnumber those of normal weight in the trials reviewed in the literature, so the data contain significant representation from this group. In the SLR, there were no studies addressing weight loss, but the group were aware of additional studies examining the benefits of weight loss in PsA. In both cases they broadly indicated a benefit of weight loss in the population[38, 39]. The group agreed weight loss is an issue that the clinical team should raise with people with PsA where required. This is due to an understanding that being overweight or obese has a negative impact on disease severity and is thought to lessen the efficacy of treatment. It is also known to be linked to more general medical problems such as metabolic syndrome and depression. There is a key role for other specialities and allied health professionals including dieticians, physiotherapists, occupational therapists and podiatrists in supporting interventions around diet and exercise/activity for people who are overweight. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary files S9 and S10, available at *Rheumatology* online.

28. People with PsA should have their smoking status recorded. (GRADE 2B, SoA 97%)
29. In people with PsA who are smokers, signpost to smoking cessation support services to maximise treatment response, persistence and improve general health. (GRADE 1A, SoA 99%)
30. In people with PsA, treatment selection should not be affected by the person's smoking status although doses should be adjusted appropriately. (GRADE 2C, SoA 96%)

There was little clinical effectiveness evidence for b/tsDMARDs comparing smokers and non-smokers so no recommendation was made prioritising any b/tsDMARD treatment over another. For general health benefits, particularly in people with PsA who often have other risk factors for cardiovascular disease, appropriate smoking cessation support was recommended. The evidence from the systematic literature review supporting these recommendations can be viewed in supplementary files .S11 and S12, available at *Rheumatology* online.

Applicability and utility

This guideline represent a framework to support clinicians prescribing bDMARDs and tsDMARDs for psoriatic arthritis. As in all guidelines, we recognise that individual patient circumstances will have

an important influence on clinical decision-making and clinicians should continue to implement shared care approaches alongside their patients. Failure to adhere to this guideline should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

As in other BSR guidelines, we recommend that biologic or targeted synthetic DMARD initiation should only take place under the supervision of a rheumatologist. This guideline does make recommendations on widening access to bDMARDs and tsDMARDs beyond the scope of current NICE TAGs. We recognise that currently this may not be possible to implement, but believe that our recommendations are evidence-based.

Audit tool

A model audit tool is available via the BSR website and in supplementary material S13, available at *Rheumatology* online.

Summary and conclusions

Since 2012, there has been a rapid expansion in the advanced therapies licensed for the treatment of PsA. Whilst this is clearly of benefit to people with PsA, it does bring additional challenges for clinicians in selecting the best therapy for individuals. This guideline aim to provide practical support to rheumatology clinicians to support the prescription of bDMARDs and tsDMARDs in PsA.

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Data availability statement: See OUP's website for more information: https://academic.oup.com/journals/pages/authors/preparing_your_manuscript/research-data-policy

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Figure 1 - Summary algorithm for the treatment of an individual with PsA with b/tsDMARDS.

Table 1 – Summary of key information relating to bDMARDs and tsDMARDS in PsA.

	ADA	CZP	ETN	GOL	IFL	ABA	UST	SEC	IXE	GUS	TOFA	UPAD	APR@
Year of licence (UK)	2006	2014	2002	2009	2006	2017	2014	2015	2017	2021	2018	2021	2014
Licence in PsA	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü
Phase 3 data in AS/AxSpA	ü	ü	ü	ü	ü	X	ü	ü	ü	X	ü	ü	X
Licence in AS/AxSpA	ü	ü	ü	ü	ü	X	ü	ü	ü	X	X	X	X
Phase 3 data in IBD	ü	ü (CD)	X	ü (UC)	ü	X	ü	X	X	ü (CD)	ü (UC)	ü (UC)	X
Licence in IBD	ü	ü^ (CD)	X	ü (UC)	ü	X	ü	X	X	X	ü (UC)	ü^ (UC)	X
Licence in uveitis	ü	X	X	X	X	X	X	X	X	X	X	X	X
ACR50 at week 12-16 (%)	PBO 3	PBO 12	PBO 4	PBO 2	PBO 2	N/A	N/A	PBO 9	PBO 5	N/A	PBO 10	PBO 13	PBO 7
	ADA 33	CZP 34	ETN 40	GOL 29	IFL 39	N/A	N/A	SEC 4	IXE 34	N/A	TOFA 28	UPAD 38	APR 13
ACR50 at week 24 (%)	PBO 6	PBO 15	PBO 4	PBO 4	PBO 4$	PBO 15	PBO 9	PBO 9	PBO 15	PBO 14	N/A	PBO 19	PBO 4
	ADA 40	CZP 42	ETN 37	GOL 35	IFL 41$	ABA 25	UST 26	SEC 46	IXE 40	GUS 31	TOFA 38	UPAD 52	APR 20
PASI75 at week 12-16 (%)	PBO 4	PBO 17	N/A	PBO 3	PBO 2	N/A	PBO 9	PBO 13	PBO 5	N/A	PBO 15	PBO 21	PBO 6
	ADA 49	CZP 43	N/A	GOL 49	IFL 65	N/A	UST 50	SEC 65	IXE 75	N/A	TOFA 43	UPAD 63	APR 22
PASI75 at week 24 (%)	PBO 1	PBO 20	PBO 3	PBO 1	PBO 1$	PBO 10	PBO 11	PBO 32	PBO 7	PBO 23	N/A	N/A	PBO 5
	ADA 59	CZP 56	ETN 23	GOL 59	IFL 60$	ABA 18	UST 60	SEC 72	IXE 71	GUS 79	TOFA 46	N/A	APR 21
Enthesitis efficacy vs placebo	N/A	ü	N/A	ü	ü	X	ü	ü	X	ü (pooled)	ü (pooled)	ü	ü (pooled)
Dactylitis efficacy vs placebo	N/A	ü	N/A	ü	ü	X	ü	ü	ü	ü (pooled)	ü (pooled)	X	ü (pooled)
MDA rates at week 24	PBO 6~	PBO 6	N/A	PBO 1	N/A	PBO 8*	N/A	PBO 15	PBO 15	PBO 11	PBO 19	PBO 12	N/A
	ADA 36~	CZP 33	N/A	GOL 28	N/A	ABA 12*	N/A	SEC 41	IXE 30	GUS 23	TOFA 26	UPAD 37	N/A
Contraindications	Demyelination NY class 3/4 Heart failure							IBD					
Key safety issues	Non-melanoma skin cancer Infections						Exfoliative dermatitis	Fungal infections including candida			Herpes zoster VTE/malignancy risk		Suicidal thought and behaviour

*Mixed population with some TNFi exposure
~data on subset with all data available and baseline BSA>3%
$Data at 24 weeks from IMPACT2 study only
@ week 12 data based on PALACE 2 and 3, week 24 data based on PALACE 1, all trials mixed population with TNF exposure
^ licensed in some countries but not currently in the UK

Abbreviations: ABA=abatacept, ACR50=American College of Rheumatology 50% response, ADA=adalimumab, APR=apremilast, AS=ankylosing spondylitis, AxSpA=axial spondyloarthritis, CD=Crohn's disease, CZP=certolizumab pegol, ETN=etanercept, GOL=golimumab, GUS=guselkumab, IBD=inflammatory bowel disease, INF=infliximab, IXE=ixekizumab, MDA=minimal disease activity, PASI75=psoriasis area and severity index 75% response, PBO=placebo, SEC=secukinumab, TOFA=tofacitinib, UC=ulcerative colitis, UPAD=upadacitinib, UST=ustekinumab

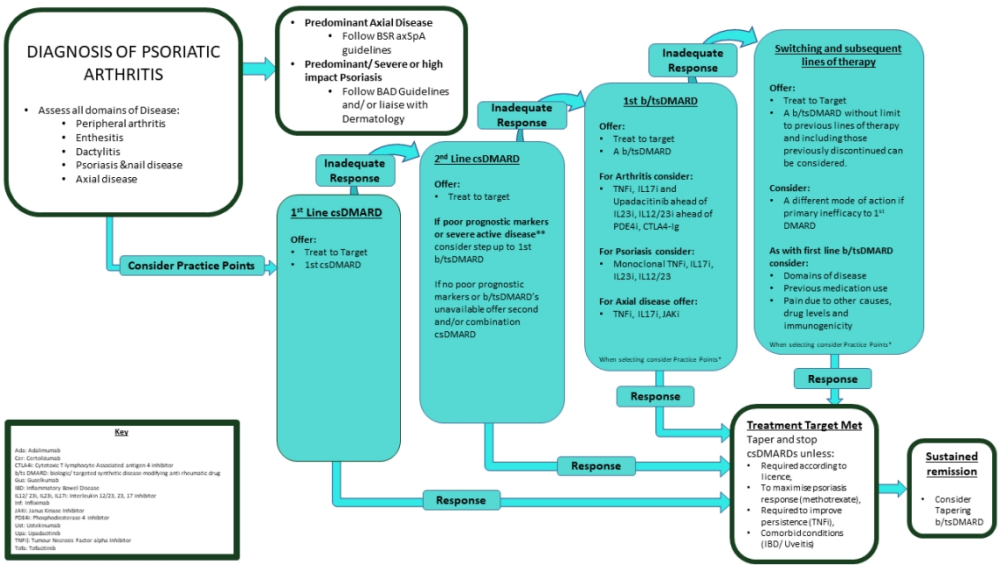

Figure 1 - Summary Algorithm for the treatment of an individual with PsA with b/tsDMARDS

338x190mm (96 x 96 DPI)

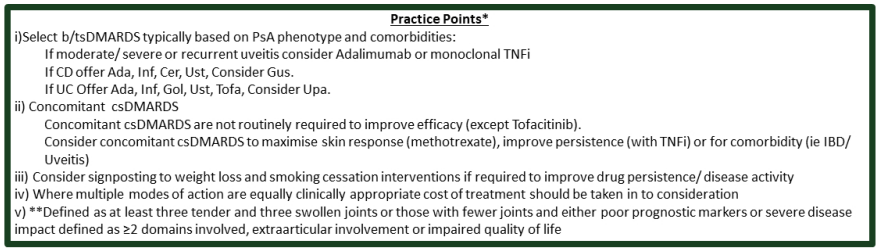

Figure 1 - Summary Algorithm for the treatment of an individual with PsA with b/tsDMARDS

338x190mm (96 x 96 DPI)

BSR Guidelines for Psoriatic Arthritis Audit Tool

The purpose of this audit tool is to ensure that the BSR Psoriatic Arthritis guideline criteria for biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARD) are being met. The tool is not intended to be an exhaustive representation of the guideline, the tool can be supplemented in order to address finer points of the guideline. The audit should be undertaken on a sample of all PsA patients attending clinic.

SECTION A		**YES**	**NO**	
1.	Does that patient have a diagnosis of PsA?			
2.	How long has the patient had PsA?			No. of years
3.	Does the patient have predominant/ severe or high impact Psoriasis?			If no, skip to Q5
4.	Has the patient been referred to/seen by dermatology?			
5.	Does the patient have Peripheral arthritis?			
6.	Does the patient have dactylitis?			
7.	Does the patient have nail psoriasis?			
8.	Does the patient have predominantly axial disease?			If yes, please refer t axSpA guideline auc
9.	Have comorbidities been assessed to address Practice Points?			
10.	If the patient smokes have smoking cessation interventions been offered?			
11.	If the patient has an elevated BMI have weight loss interventions been offered?			
SECTION B – peripheral disease		**YES**	**NO**	
1.	Has the patient been offered Treat to Target?			
2.	What was the first csDMARD prescribed?			
	Methotrexate	Leflunomide	Sulfasalazine	Ciclosporin	Other
3.	Was treatment target achieved?			If yes, go to Q2 If no, go to Q4
4.	What was the reason for failing the first DMARD?			
	Inefficacy	Raised LFTs	Rash	Other	
		YES	**NO**	
5.	Does the patient have any adverse prognostic indicators?			If yes, go to Q9
	Defined as at least three tender and three swollen joints or those with fewer joints and either poor prognostic markers or severe disease impact defined as ≥2 domains involved, extraarticular involvement or impaired quality of life			
6.	What was the second/ another line of csDMARD prescribed?			
	Methotrexate	Leflunomide	Sulfasalazine	Ciclosporin	Other
7.	Was treatment target achieved?			If yes, go to Q2 If no, go to Q 6
8.	What was the reason for failing the second DMARD?			
	Inefficacy	Raised LFTs	Rash	Other	

		YES	NO	
9.	Has the patient been offered Treat to Target?			
10.	Was the patient eligible for b/tsDMARD therapy (≥3 Tender/ Swollen Joints)?			
11.	If active arthritis was (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i) offered?			If yes, go to Q12 If no, go to Q13
12.	If b/tsDMARD was TNFi, IL17i, or upadacitinib (UPA) considered ahead of IL12/23i or IL23i ahead of PDE4i ahead of CTLA4-Ig.			
13.	If active enthesitis was TNFi (IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i) offered?			
14.	If active dactylitis was (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i) offered?			
15.	If active axial disease and intolerance/ inadequate response to 2 NSAIDS was TNFi or IL-17i offered or JAKi considered?			
16.	Was the patient prescribed a b/tsDMARD therapy?			If no, go to Q17 If yes, go to Q18
17.	What b/tsDMARD therapy was prescribed?			

	Adalimumab		Etanercept		Certolizumab		Golimumab	
	Secukinumab		Ixekizumab		Ustekinumab		Guselkumab	
	Tofacitinib		Upadacitinib		Apremilast		Abatacept	

18.	Why was b/tsDMARD therapy not prescribed?								
	Patient refused		Previous cancer		Infections		Other		

		YES	NO	
19.	Was response to b/tsDMARD therapy assessed at 12 / 16 weeks?			
20.	Was PsARC assessment used?			
21.	Was treatment target achieved?			If no, go to Q 23 If yes, go to Q 24
22.	If partial response, was patient reassessed at 6 months?			
23	Have further lines of b/tsDMARD been offered without limit to previous lines of therapy and including those previously discontinued can be considered?			
24.	If the patient has achieved remission has tapering/ cessation of the csDMARDS been considered?			
25.	If the patient has achieved sustained remission has dose optimisation/ tapering of b/tsDMARDS been considered?			

Abbreviations: PsA - Psoriatic Arthritis, Ps – Psoriasis, BSA - Body Surface Area, PASI – psoriasis area and severity index, PsARC – Psoriatic Arthritis Response Criteria, BASDAI – Bath Ankylosing Spondylitis Disease Activity Index, VAS – Visual analogue scale, b/tsDMARD - biologic and targeted synthetic disease-modifying anti-rheumatic drugs. CTLA4i: Cytotoxic T-lymphocyte-Associated antigen 4 inhibitor, IL12/ 23i, IL23i, IL17i: Interleukin 12/23, 23, 17 inhibitor, JAKi: Janus Kinase Inhibitor, PDE4i: Phosphodiesterase-4 inhibitor, Upa: Upadacitinib, TNFi): Tumour Necrosis Factor alpha Inhibitor

British Society for Rheumatology

Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on initial biologic and targeted synthetic DMARD treatment

BSR Guideline

Intervention evidence review

October 2020

Contents

1Initial biologic and targeted synthetic DMARDs treatment

1.1 Review questions:

In adults with active peripheral psoriatic arthritis, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo?

In adults with active psoriatic arthritis-related dactylitis, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo?

In adults with active psoriatic arthritis-related enthesitis what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo?

In adults with active psoriatic arthritis-related axial disease that is not responding to NSAIDs, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitor, IL23 inhibitors, IL17 inhibitors, JAK inhibitors, apremilast or abatacept, in comparison to each other or placebo?

1.2 INTRODUCTION

People may be offered biologic or targeted synthetic (b/ts) DMARD treatment after conventional DMARDs are not effective or are not suitable. This review seeks to ascertain which b/tsDMARD should be offered initially given a person's disease manifestations.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with active peripheral psoriatic arthritis who are biologic and targeted synthetic DMARDs naïve
Interventions	• TNF inhibitors • IL12/23 inhibitors

	• IL23 inhibitors • IL17 inhibitors • Abatacept • Apremilast • JAK inhibitors
Comparison	Comparison of interventions or to placebo
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life including SF-36, PsAQoL (continuous) Arthritis • American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) Enthesitis in those with enthesitis at baseline • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Dactylitis in those with dactylitis at baseline • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis in those with axial disease at baseline • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis in those with psoriasis at baseline • Psoriasis score (PASI / IGA / BSA) (continuous) **Important** Arthritis • Radiological progression (continuous) Adverse Events • Serious adverse events (dichotomous) **The outcomes below are extracted if studies do not report ACR response.** • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • PsARC score • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous), • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)

Study design	Randomised Controlled Trails If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search we conducted to find studies comparing a person with psoriatic arthritis (PsA) initial biologic and targeted synthetic DMARDs (b/tsDMARDs) treatment. In addition data extraction and quality assessment undertaken by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was utilised to aid in the completion of this review.

34 RCTs were included in the review. These studies covered 7 comparisons versus placebo and 3 active control comparisons.

Active control comparisons:

- IL-17 inhibitor versus TNF inhibitor: 3 RCTs
- IL-12/23 inhibitor versus TNF inhibitor: 1 RCT
- JAK inhibitor versus TNF inhibitor: 1 RCT

Comparisons versus placebo:

- Abatacept versus placebo: 2 RCTs
- Apemiliast versus placebo: 5 RCTs
- IL12/23 inhibitors versus placebo: 2 RCTs
- IL-17 inhibitor versus placebo: 8 RCTs
- IL-23 inhibitors versus placebo: 1 RCT
- JAK inhibitor versus placebo: 2 RCTs
- TNF inhibitors versus placebo: 13 RCTs

1.4.2 Excluded studies

See the list of excluded studies in 0 Excluded studies

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of active controlled studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
IL-17 inhibitor versus TNF inhibitor				
EXCEED: McInnes 2020(37)	Secukinumab versus adalimumab for 52 weeks. Concurrent csDMARD treatment not permitted but a stable dose of corticosteroids was permitted.	N=853 Adults with active PsA and inadequate response or intolerance to csDMARDs.	- Mortality at 52 weeks - ACR20 at 52 weeks - ACR50 at 52 weeks - Minimal disease activity after 52 weeks - Absence of enthesitis at 52 weeks - Absence of dactylitis at 52 weeks - PASI response: ≥90% improvement at week 52 - Serious adverse events at 52 weeks	Multicentre study across Europe, North America, Asia, and Australasia. Funding: Novartis
SPIRIT-P1: Mease 2017(20)	Ixekizumab (n=210) versus adalimumab (n=101) Stable doses of cDMARDs, oral corticosteroids, opiates and/or NSAIDs were permitted	N=417 Adults with active PsA who were naïve to bDMARD treatment.	- ACR20 at 12 weeks - ACR50 at 12 weeks - ACR70 at 12 weeks - Dactylitis resolution (LDI-B = 0) at 12 weeks - Enthesitis absence (LEI=0) at 12 weeks - PASI response: ≥75% improvement at week 12 - Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks	Multicentre study in North America, South America, Asia, and Europe. Funding: Eli Lilly and Company.

Study	Intervention and comparison	Population	Outcomes	Comments
			- Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks - Serious adverse events at 24 weeks	
SPIRIT-H2H: Mease 2020(38)	Ixekizumab (n=283) versus adalimumab (n=283) Stable doses of cDMARDs, oral corticosteroids, opiates and/or NSAIDs were permitted	N=417 Adults with active PsA who were naïve to bDMARD treatment.	- Mortality at 24 weeks. - ACR20 response at 24 weeks. - ACR50 response at 24 weeks. - ACR70 response at 24 weeks. - PASI response: ≥75% improvement at week - Minimal disease activity at 12 weeks. - Dactylitis resolution at 24 weeks in people with dactylitis at baseline. - Enthesitis resolution at week 24 in people with enthesitis at baseline. - Serious adverse events at 24 weeks. RoB: h	Multicentre study in North America, South America, Asia, Africa, and Europe. Funding: Eli Lilly and Company.
IL-12/23 inhibitor versus TNF inhibitor				
ECLIPSA**:** Araujo 201**7**(39)	Ustekinumab versus TNF inhibitors (Adalimumab n=10, Cetolizumab n=6; Etanercept n=5; Infliximab n=3) for 24 weeks Glucocorticoids of less than 5 mg prednisolone/day were allowed	N=51 Adults active PsA and were methotrexate (MTX) IR. People were bDMARD naïve.	- Complete resolution of enthesitis, arthritis and skin at 24 weeks - Presence or absence of enthesitis	Single centre study in Germany. No external funding

Study	Intervention and comparison	Population	Outcomes	Comments
	during the study. Symptomatic treatment with NSAIDs was also allowed,		- BASDAI: Bath Ankylosing Spondylitis Disease Activity Index at 24 weeks. - DAPSA: Disease Activity Index for Psoriatic Arthritis at 24 weeks. - Short Form-36 Health Survey, Physical Component Score at 24 weeks - Short Form-36 Health Survey, Mental Component Summary at 24 weeks - Minimal disease activity (7 of 7 criteria) at 24 weeks. - PASI response: 100% improvement at week 24.	
JAK inhibitor versus TNF inhibitor				
OPAL Broaden: Mease 2017(23)	Tofacitinib (n=211) versus adalimumab (n=104) People received a stable dose of a conventional DMARD.	N=422 Adults with active PsA and inadequate response to at least 1 csDMARD.	- ACR20 at week 12 - ACR50 at week 12 - ACR70 at week 12 - Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks - Enthesitis absence at 12 weeks - Dactylitis resolution at 12 weeks - PASI response: ≥75% improvement at week 12 - Serious adverse events at 12 weeks - LEI: Leeds Enthesitis Index in at 12 weeks	11 (3%) were previously exposed to b/tsDMARDs. Multicentre study across North America, South America, Australasia, Europe, and Asia. Finding: Pfizer

Table 3: Summary of placebo controlled studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Abatacept versus placebo				
ASTRAEA: Mease 2017(1), Strand 2018(2)	Abatacept (n=129) versus placebo (n=130) for 24 weeks csDMARD and corticosteroid treatment allowed. In the placebo group early escape possible at week 16.	N=424 overall Data extracted for N=159 who were bDMARD naïve. Adults with active PsA and inadequate response or intolerance to at least one non-biologic DMARD. They were required to active plaque psoriasis.	- ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks	Multicentre study across Europe, North America, South America, Asia, and Africa. Funding: Bristol-Myers Squibb.
NCT00534313: Mease 2011(3)	Abatacept (n=95) versus placebo (n=30) for 24 weeks Stable doses of methotrexate, NSAIDs and corticosteroids were permitted	N=170 Data extracted for N=125 who were TNF inhibitors naïve. Adult with active PsA and plaque psoriasis who had inadequate response to DMARDs	- ACR20 at week 24.	Multicentre study in North America, South America, Austrasia, Europe, and Africa
Apremilast versus placebo				
ACTIVE Nash 2018(4)	Apremilast (n=110) versus placebo (n=109) for 24 weeks.	N=219 Adults with active PsA who were biologic naïve and discontinued their current csDMARD treatment prior to entering the study.	- Mortality at 24 weeks - ACR20 at 16 weeks - ACR50 at 16 weeks - ACR70 at 16 weeks - Enthesitis resolution at 24 weeks - Serious adverse events at 24 weeks	Multicentre study across Europe, North America, South America, and Australasia. Funding: Celgene Corporation.

Study	Intervention and comparison	Population	Outcomes	Comments
PALACE 1: Kavanaugh 2014(5)	Apremilast (n=253) versus placebo (n=120) for 24 weeks. Concurrent stable treatment with csDMARDs, NSAIDs and corticosteroids was permitted. Early escape possible for people in either group at week 16.	N=504 Data extracted for N=373 (74%) who were bDMARD naïve. Adults with active PsA despite previous treatment with csDMARDs and/or bDMARDs.	- ACR20 at week 16.	Multicentre study in North America, Australasia, Europe, and Africa. Funding: Study sponsored by Celgene Corp.
PALACE 2: Cutolo 2016(6)	Apremilast (n=269) versus placebo (n=135) for 24 weeks. Concurrent stable treatment with csDMARDs, NSAIDs and corticosteroids was permitted. Early escape possible for people in either group at week 16.	N=484 Data extracted for N=404 (83%) who were bDMARD naïve. Adults with active PsA despite previous treatment with csDMARDs and/or bDMARDs.	- Mortality at week 16 - ACR20 at week 16	Multicentre study in North America, Asia, Europe, and Africa. Funding: Study sponsored by Celgene Corp.
PALACE 3: Edwards 2016(7)	Apremilast (n=336) versus placebo (n=169) for 24 weeks. Concurrent stable treatment with csDMARDs, NSAIDs and corticosteroids was permitted. Early escape possible for people in either group at week 16.	N=505 Data extracted for N=364 (72%) who were bDMARD naïve. Adults with active PsA despite previous treatment with csDMARDs and/or bDMARDs.	- ACR20 at 16 weeks - Mortality at 16 weeks	Multicentre study in North America, Australasia, and Europe. Funding: Study sponsored by Celgene Corp.
PALACE 4: Wells 2018(8)	Apremilast (n=409) versus placebo (n=108) for 24 weeks. Stable doses of oral corticosteroids and NSAIDs were permitted.	N=527 Data extracted for N=363 (72%) who were bDMARD naïve.	- Mortality at 24 weeks - SF36 physical component score at 16 weeks - SF36 mental component score at 16 weeks - ACR20 at 24 weeks	Multicentre study in North America, Australasia, Europe, and Asia. Funding: Celgene Corp.

Study	Intervention and comparison	Population	Outcomes	Comments
	Early escape possible for people in either group at week 16.	Adults with active PsA despite previous treatment with csDMARDs and/or bDMARDs.	- ACR50 at 24 weeks - ACR70 at 24 weeks - Dactylitis presence at 24 weeks - Change in dactylitis count at 16 weeks in people with dactylitis at baseline - Enthesitis presence at 24 weeks - PASI response: ≥55% improvement at week 24 - PASI response: ≥75% improvement at week 24 - Serious adverse events at 24 weeks	
IL12/23 inhibitor versus placebo				
PSUMMIT 1: McInnes 2013(9)	Ustekinumab (n=409) versus placebo (n=206) for 24 weeks Stable doses of csDMARDs, oral corticosteroids and NSAIDs were permitted. Early escape possible at week 16.	N=615 Adults with active PsA who were IR / intolerant to previous csDMARD or NSAID treatment.	- Mortality at 24 weeks - ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks - Dactylitis presence at 24 weeks - Enthesitis presence at 24 weeks - PASI response: ≥75% improvement at week 24 - BASDAI20 response at 24 weeks - Serious adverse events at 24 weeks	Multicentre study in North America, Australasia, and Europe. Funding: Janssen Research & Development
PSUMMIT 2: Richlin 2014(10)	Ustekinumab (n=208) versus placebo (n=104) for 24 weeks	N=312	- ACR20 at 24 weeks - PASI response: ≥75% improvement at week 24	Multicentre study in North America and Europe.

Study	Intervention and comparison	Population	Outcomes	Comments
	Stable doses of methotrexate, oral corticosteroids and NSAIDs were permitted. Early escape possible at week 16.	Adults with active PsA who were IR / intolerant to previous csDMARD or NSAID treatment.		Funding: Janssen Research & Development
IL-17 inhibitor versus placebo				
DISCOVER 1: Deodhar 2020(11)	Guselkumab (n=176) versus placebo (n=87) for 24 weeks. Background treatment with csDMARDs, corticosteroids, or NSAIDs allowed. Early escape possible for people in either group at week 16.	N=381 overall Data extracted for N=239 who were bDMARD naïve. People with active PsA with inadequate response (IR) to conventional treatment.	- ACR20 at 24 weeks - ACR50 at 24 weeks - ACR75 at 24 weeks	Multicentre study across Europe, North America, South America, and Asia. Funding: Janssen Research and Development.
FUTURE 1: Mease 2015(12)	Secukinumab (n=285) versus placebo (n=143) for 24 weeks. Concomitant use of oral glucocorticoids or MTX permitted.	N=606 Data extracted for N=428 people who were TNF inhibitor naïve. Adults with active PsA despite previous treatment with csDMARDs, NSAIDs or TNF inhibitors.	- ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks - Change in mTSS/SHS: van der Heijde modified Total Sharp Score at 24 weeks	Multicentre study across Europe, North America, Australasia and Asia. Funding: Novartis
FUTURE 2. McInnes 2015(13), Kavanaugh 2016(14), Coates 2018(15)	Secukinumab (n=195) versus placebo (n=63) for 24 weeks. Concomitant use of MTX permitted.	N=397 Data extracted for N=258 people who were TNF inhibitor naïve. Adults with active PsA despite previous treatment with conventional therapy.	- Mortality at 24 weeks. - MDA: Minimal disease activity (≥ 5 of 7 criteria) at 16 weeks - ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks - Enthesitis resolution at 24 weeks	Multicentre study across Europe, North America, Australasia and Asia. Funding: Novartis

Study	Intervention and comparison	Population	Outcomes	Comments
			- Dactylitis resolution at 24 weeks - PASI response: ≥90% improvement at week at 24 weeks - PASI response: ≥75% improvement at week at 24 week	
FUTURE 3: Nash 2018(16)	Secukinumab (n=189) versus placebo (n=93) for 24 weeks. Concomitant use of oral glucocorticoids or MTX permitted.	N=414 Data extracted for N=282 people who were TNF inhibitor naïve. Adults with active PsA despite previous treatment with csDMARDs, NSAIDs or TNF inhibitors.	- ACR20 at 24 weeks - ACR50 at 24 weeks	Multicentre study across Europe, North America, and Australasia. Funding: Novartis
FUTURE 4: Kivitz 2019(17)	Secukinumab (n=173) versus placebo (n=87) for 24 weeks. Concomitant use of NSAIDs, oral glucocorticoids or MTX permitted. At week 16 people in the placebo group could have early escape to secukinumab treatment.	N=341 Data extracted for N=260 people who were TNF inhibitor naïve. Adults with active PsA despite previous treatment with cs/bDMARDs and/or NSAIDs.	- ACR20 at 16 weeks - ACR50 at 16 weeks	Multicentre study across Europe, North America, and Australasia. Funding: Novartis
FUTURE 5: Mease 2018(18)	Secukinumab (n=469) versus placebo (n=234) for 24 weeks. Concomitant use of NSAIDs, oral glucocorticoids or MTX permitted.	N=996 Data extracted for N=701 people who were TNF inhibitor naïve. Adults with active PsA despite previous treatment with	- ACR20 at 16 weeks. - ACR50 at 16 weeks. - ACR70 at 16 weeks.	Multicentre study across Europe, North America, South America, and Asia. Funding: Novartis

Study	Intervention and comparison	Population	Outcomes	Comments
	At week 16 people in the placebo group could have early escape to secukinumab treatment.	csDMARDs, NSAIDs or TNF inhibitors.		
NCT01516957: Mease 2014(19)	Brodalumab (n=52) versus placebo (n=40) for 12 weeks NSAIDs could be used to treat flares. It was unclear whether previous cDMARDs were continued.	N=168 Outcomes were extracted where reported for people without prior exposure to biologics: N= 92 (55%) Adults up to 75 years old with active PsA.	- ACR20 at 12 weeks. - ACR50 at 12 weeks. - ACR70 at 12 weeks.	Multicentre study in USA and Canada. Funding: Amgen
SPIRIT-P1: Mease 2017(20)	Ixekizumab (n=210) versus Placebo (n=101) Stable doses of cDMARDs, oral corticosteroids, opiates and/or NSAIDs were permitted	N=417 Adults with active PsA who were naïve to bDMARD treatment.	- ACR20 at 12 weeks - ACR50 at 12 weeks - ACR70 at 12 weeks - Dactylitis resolution (LDI-B = 0) at 12 weeks - Enthesitis absence (LEI=0) at 12 weeks - PASI response: ≥75% improvement at week 12 - Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks - Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks - Serious adverse events at 24 weeks	Multicentre study in North America, South America, Asia, and Europe. Funding: Eli Lilly and Company.
IL-23 inhibitor versus placebo				
NCT02319759: Deodhar 2018(21)	Guselkumab (n=91) versus placebo (n=44) for 24 weeks	N=149	- Mortality at 24 weeks - ACR20 at 24 weeks	Multicentre study in North America and Europe.

Study	Intervention and comparison	Population	Outcomes	Comments
	Stable doses of methotrexate, NSAIDs, or corticosteroids were permitted.	Outcomes extracted for people who were TNF inhibitor naïve (n=135) Adults with active PsA and inadequate response to conventional treatment.		Funding: Janssen Research & Development.
JAK inhibitor versus placebo				
EQUATOR: Mease 2018(22)	Filgotinib (n=54) versus placebo (n=57) for 16 weeks Concurrent csDMARD treatment allowed.	N=131 Data extracted for N=111 who were TNF inhibitor naïve People with active moderate to severe PsA with documented history of plaque psoriasis, and an IR or intolerant to a csDMARD.	- ACR20 at week 16	Multicentre study across Europe Funding: Galapagos and Gilead Sciences.
OPAL Broaden: Mease 2017(23)	Tofacitinib (n=211) versus placebo (n=104) People received a stable dose of a conventional DMARD.	N=422 Adults with active PsA and inadequate response to at least 1 csDMARD.	- ACR20 at week 12 - ACR50 at week 12 - ACR70 at week 12 - Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks - Enthesitis absence at 12 weeks - Dactylitis resolution at 12 weeks - PASI response: ≥75% improvement at week 12 - Serious adverse events at 12 weeks - LEI: Leeds Enthesitis Index in at 12 weeks	11 (3%) were previously exposed to b/tsDMARDs. Multicentre study across North America, South America, Australasia, Europe, and Asia. Finding: Pfizer

Study	Intervention and comparison	Population	Outcomes	Comments
TNF inhibitor versus placebo				
ADEPT: MEASE 2005(24), Gladman 2007(25)	Adalimumab (n=151) versus placebo (n=162) for 24 weeks Concurrent MTX and corticosteroids allowed.	N=313 Adults with moderate to severely active PsA. They were TNF inhibitor naïve.	- ACR20 at week 12. - ACR50 at week 12. - ACR70 at week 12 - PASI response: ≥50% improvement at week 12 - PASI response: ≥75% improvement at week 12 - Serious adverse events at 24 weeks - Change in SF-36 physical component at 12 weeks - Change in SF-36 mental component at 12 weeks	Multicentre study across Europe and North America. Funding: Bristol-Myers Squibb.
Genovese 2007(26)	Adalimumab (n=50) versus placebo (n=50) for 12 weeks Concurrent of csDMARDs was permitted.	N=100 Adults with active PsA and psoriasis or history of psoriasis. They were using csDMARDs or csDMARDs IR. Previous use of TNF inhibitors was not permitted.	- ACR20 at 12 weeks - ACR50 at 12 weeks - ACR70 at 12 weeks - People achieving clear/almost clear psoriasis status at 12 weeks - SF-36 physical component score at 12 weeks - SF-36 mental component score at 12 weeks - Serious adverse events at 12 weeks	Multicentre study in USA and Canada. Funding: no external finding
GO-DACT: Viera-Sousa 2020(27)	Golimumab + methotrexate (n=195) versus placebo + methotrexate (n=63) for 24 weeks Concurrent use of other csDMARD treatment was not permitted.	N=397 Adults with active PsA, dactylitis, and at least one other site of active	- ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks - Minimal disease activity (≥ 5 of 7 criteria) at 24 weeks.	Multicentre study conducted in Portugal. Funding: no external funding.

Study	Intervention and comparison	Population	Outcomes	Comments
	However a stable dose of NSAIDs was allowed.	inflammation. They were naïve to MTX and bDMARDs.	- Enthesitis resolution at 24 weeks - Dactylitis resolution at 24 weeks - PASI response: ≥50% improvement at week at 24 weeks. - PASI response: ≥90% improvement at week at 24 weeks. - PASI response: ≥75% improvement at week at 24 weeks.	
GO-REVEAL: Kavanaugh 2009(28)	Golimumab (n=292) versus placebo (n=113) for 24 weeks. Stable doses of methotrexate, NSAIDs, or corticosteroids were permitted. Early escape from either group permitted at week 16.	N=405 People with active PsA despite therapy with cDMARD or NSAIDs. Prior use anti-TNF agents, rituximab, natalizumab, or cytotoxic agents not allowed.	- ACR20 response at week 14 - PASI response: ≥75% improvement at week 14 in people with psoriasis at baseline - Serious adverse events at 24 weeks - Change in SF-36 mental component score at 14 weeks - Change in SF-36 physical component score at 12/14/16/24 weeks	Multicentre study conducted in Europe and North America. Funding: Centocor Research and Development, Inc. and Schering-Plough.
GO-VIBRANT: Kavanaugh 2017(29), Kavanaugh 2019(30)	Golimumab (n=241) versus placebo (n=239) for 24 weeks. Stable doses of methotrexate, NSAIDs, or corticosteroids were permitted.	N=480 People with active PsA despite. Prior use anti-TNF agents, rituximab, natalizumab, or cytotoxic agents were not allowed.	- Mortality at week 24. - Change in SF-36 mental component score at 14 weeks - Change in SF-36 physical component score at 14 weeks	Multicentre study conducted in Europe and North America. Funding: Janssen Research & Development LLC

Study	Intervention and comparison	Population	Outcomes	Comments
	Early escape from either group permitted at week 16.		- ACR20 at week 14 - ACR50 at week 14 - ACR70 at week 14 - BASDAI20 response at 14 weeks in people with spondylitis and peripheral joint involvement. - LEI: Leeds Enthesitis Index in perople with enthesitis at baseline. - mTSS/SHS: van der Heijde modified Total Sharp Score at 24 weeks. - PASI response: ≥75% improvement at week 14. - PASI response: ≥90% improvement at week 14. - Serious adverse events at 24 weeks.	
IMPACT 1: Antoni 2005(31)	Infliximab (n=52) versus placebo (n=52) for 16 weeks Concomitant stable therapy with csDMARDs, corticosteroids, and NSAIDs were permitted.	N=104 People with active PsA who had been unresponsive to at least one csDMARD treatment.	- ACR20 at week 16 - ACR50 at week 16. - ACR70 at week 16 - Dactylitis score over 0 at week 16 - Enthesitis at week 16 - PASI response: ≥75% improvement at week 14 PASI response: ≥50% improvement at week 14 - Serious adverse events at week 16	Multicentre study conducted in Europe and North America. Funding: Schering-Plough Research Institute.
IMPACT 2: Antoni 2005(32)	Infliximab (n=100) versus placebo (n=100) for 24 weeks	N=200	- Quality of life: Change in SF-36 physical component at week 14.	Multicentre study conducted in Europe and North America.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant stable therapy with methotrexate or corticosteroids were permitted.	People with active PsA who had been unresponsive to csDMARDs or NSAID treatment.	- Quality of life: Change in SF-36 mental component at week 14. - ACR20 at week 14. - ACR50 at week 14. - ACR70 at week 14. - ≥1 dactylitis digits at week 14. - Enthesopathy at week 14 - PASI response: ≥50% improvement at week 14	Funding: Centocor, Inc, and Schering-Plough.
Mease 2000(33)	Etanercept (n=30) versus placebo (n=30) for 12 weeks Prior use of methotrexate was allowed to continue as was corticosteroid use.	N=200 People with active PsA who had been unresponsive to NSAID treatment.	- ACR20 response at week 12 - ACR50 response at week 12 - ACR70 response at week 12 - PASI response: ≥75% improvement at week 12 - Serious adverse events at 12 weeks	Unclear but appears to be single centre in the USA. Funding: grant support from the Immunex Corporation
NCT01871649: van Mens 2019(34)	Golimumab + methotrexate (n=26) versus placebo + methotrexate (n=25)	N=51 Adults up to 70 years old with active PsA. No previous treatment with DMARDs was permitted.	- ACR20 at 22 weeks - ACR50 at 22 weeks - ACR70 at 22 weeks - MDA: Minimal disease activity at 22 weeks. - Median (IQR) BASDAI: Bath Ankylosing Spondylitis Disease Activity Index at 22 weeks - Serious adverse events	Multicentre study in the Netherlands Funding: grant from MSD
OPAL Broaden: Mease 2017(23)	Adalimumab (n=104) versus placebo (n=104)	N=422	- ACR20 at week 12 - ACR50 at week 12	11 (3%) were previously exposed to b/tsDMARDs.

Study	Intervention and comparison	Population	Outcomes	Comments
	People received a stable dose of a conventional DMARD.	Adults with active PsA and inadequate response to at least 1 csDMARD.	- ACR70 at week 12 - Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks - Enthesitis absence at 12 weeks - Dactylitis resolution at 12 weeks - PASI response: ≥75% improvement at week 12 - Serious adverse events at 12 weeks - LEI: Leeds Enthesitis Index in at 12 weeks	Multicentre study across North America, South America, Australasia, Europe, and Asia. Finding: Pfizer
RAPID-PsA: Mease 2014(35)	Certolizumab (n=219) versus placebo (n=110) Use of single csDMARDs was permitted.	N=409 Data extracted for N=229 who were TNF inhibitor naïve Adults with active PsA and psoriasis or history of psoriasis.	- ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks	Multicentre study across North America, South America, Australasia, and Europe. Funding: UCB Pharma
SEAM-PsA: Mease 2019(36)	Etanercept + methotrexate (n=284) versus placebo + methotrexate (n=284) Stable doses or oral corticosteroids and NSAIDs were permitted.	N=851 Adults with active PsA who were naïve to bDMARDs and no prior use of methotrexate for PsA.	- Mortality at 48 weeks - SF36 physical component score at 24 weeks - SF36 mental component score at 24 weeks - ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks - Minimal disease activity at 24 wees - Dactylitis resolution at 24 weeks	Multicentre study across North America, South America, Africa, and Europe. Funding: Amgen

Study	Intervention and comparison	Population	Outcomes	Comments
			- Enthesitis resolution at 24 weeks - People achieving clear/almost clear on sPGA-psoriasis at 24 weeks - Serious adverse events at 48 weeks - Radiological progression at 48 weeks - SPARCC Enthesitis Index at 24 weeks	
SPIRIT-P1: Mease 2017(20)	Adalimumab (n=101) versus placebo (n=101) Stable doses of cDMARDs, oral corticosteroids, opiates and/or NSAIDs were permitted	N=417 Adults with active PsA who were naïve to bDMARD treatment.	- ACR20 at 12 weeks - ACR50 at 12 weeks - ACR70 at 12 weeks - Dactylitis resolution (LDI-B = 0) at 12 weeks - Enthesitis absence (LEI=0) at 12 weeks - PASI response: ≥75% improvement at week 12 - Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks - Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks - Serious adverse events at 24 weeks	Multicentre study in North America, South America, Asia, and Europe. Funding: Eli Lilly and Company.

1.4.4 Quality assessment of clinical studies included in the evidence review

1.4.4.1 Head to head comparisons

Table 4: IL-17 inhibitor versus TNF inhibitor

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 16 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	1/919 (0.1%)	0/811 (0.0%)	**RD 0.0** (0.0 to 0.1)	**0 fewer per 1,000** (from 10 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow up: 12 weeks; assessed with: Change in Short Form-36 Health Survey, Physical Component Score)												
1	randomised trials	not serious	not serious	not serious	not serious	none	107	101	-	MD **0.8 higher** (1.48 lower to 3.08 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow up: 12 weeks; assessed with: Change in Short Form-36 Health Survey, Mental Component Score)												
1	randomised trials	not serious	not serious	not serious	not serious	none	107	101	-	MD **1.1 lower** (3.79 lower to 1.59 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR20 response (follow up: range 12 weeks to 52 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	603/919 (65.6%)	521/811 (64.2%)	**RR 1.04** (0.97 to 1.11)	**26 more per 1,000** (from 19 fewer to 71 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
ACR50 response (follow up: range 12 weeks to 52 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	429/919 (46.7%)	354/811 (43.6%)	**RR 1.10** (0.99 to 1.23)	**44 more per 1,000** (from 4 fewer to 100 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR70 response (follow up: 12 weeks)												
2	randomised trials	not serious	very serious [a]	not serious	serious [b]	none	123/493 (24.9%)	91/384 (23.7%)	**RR 1.15** (0.91 to 1.45)	**36 more per 1,000** (from 21 fewer to 107 more)	⊕◯◯◯ VERY LOW	CRITICAL
Minimal disease activity (follow up: range 12 weeks to 52 weeks; assessed with: 78/76 joints)												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	265/709 (37.4%)	235/710 (33.1%)	**RR 1.13** (0.98 to 1.30)	**43 more per 1,000** (from 7 fewer to 99 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Dactylitis resolution in people with dactylitis at baseline (follow up: range 12 weeks to 52 weeks)												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	252/374 (67.4%)	184/326 (56.4%)	**RR 1.18** (1.05 to 1.33)	**102 more per 1,000** (from 28 more to 186 more)	⊕⊕◯◯ LOW	CRITICAL
Enthesitis resolution in people with enthesitis at baseline (follow up: range 16 weeks to 52 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [a]	not serious	not serious	not serious	none	228/401 (56.9%)	213/355 (60.0%)	**RR 1.04** (0.93 to 1.17)	**24 more per 1,000** (from 42 fewer to 102 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Psoriasis score in people with ≥3% BSA affected with psoriasis at baseline (follow up: range 12 weeks to 24 weeks; assessed with: PASI response: ≥75% improvement)												
2	randomised trials	very serious [a]	very serious [c]	not serious	serious [b]	none	323/415 (77.8%)	218/351 (62.1%)	**RR 1.30** (1.17 to 1.43)	**186 more per 1,000** (from 106 more to 267 more)	⊕◯◯◯ VERY LOW	CRITICAL
Psoriasis score in people with ≥3% BSA affected with psoriasis at baseline (follow up: range 12 weeks to 52 weeks; assessed with: PASI response: ≥100% improvement)												
3	randomised trials	very serious [a]	not serious	not serious	not serious	none	307/630 (48.7%)	164/553 (29.7%)	**RR 1.71** (1.47 to 1.99)	**211 more per 1,000** (from 139 more to 294 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse events at 24/52 weeks												
3	randomised trials	not serious	not serious	not serious	not serious	none	36/918 (3.9%)	61/811 (7.5%)	**RR 0.52** (0.35 to 0.79)	**36 fewer per 1,000** (from 49 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
c. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

Table 5: IL-12/23 inhibitor versus TNF inhibitor

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-12/23 inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 24 weeks; assessed with: Short Form-36 Health Survey, Mental Component Summary. 0-100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Median (IQR): IL-12/23 inhibitors - 52.9 (4.9). TNF Inhibitors: - 48.2 (11.1)				⊕⊕◯◯ LOW	CRITICAL
Quality of life (follow up: 24 weeks; assessed with: Short Form-36 Health Survey, Physical Component Score. 0-100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Median (IQR): IL-12/23 inhibitors: 52.8 (6.1). TNF Inhibitors: 46 (11.6).				⊕⊕◯◯ LOW	CRITICAL
Complete resolution of enthesitis, arthritis and skin (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	4/23 (17.4%)	2/24 (8.3%)	**RR 2.09** (0.42 to 10.32)	**91 more per 1,000** (from 48 fewer to 777 more)	⊕◯◯◯ VERY LOW	CRITICAL
Disease Activity Index for Psoriatic Arthritis (DAPSA) (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Median (IQR) change was 3.61 for IL-12/23 inhibitors and 6.8 (6.22) for TNF inhibitors.				⊕⊕◯◯ LOW	CRITICAL
Minimal disease activity (follow up: 24 weeks; assessed with: 7 of 7 criteria)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	10/23 (43.5%)	5/24 (20.8%)	**RR 2.09** (0.84 to 5.18)	**227 more per 1,000** (from 33 fewer to 871 more)	⊕⊕◯◯ LOW	CRITICAL
Enthesitis resolution (follow up: 24 weeks; assessed with: LEI = 0, SPARCC = 0, MASES = 0)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-12/23 inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	18/23 (78.3%)	7/24 (29.2%)	**RR 2.68** (1.39 to 5.19)	**490 more per 1,000** (from 114 more to 1,000 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (follow up: 24 weeks; assessed with: 0-10)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Median (IQR) change IL-12/23 inhibitors: 0.19 (0.37) TNF inhibitors: 1.4 (1.28)				⨁⨁◯◯ LOW	CRITICAL
Psoriasis score (follow up: 24 weeks; assessed with: PASI response: 100% improvement)												
1	randomised trials	serious [a]	serious [a]	not serious	serious [c]	none	14/23 (60.9%)	7/24 (29.2%)	**RR 2.09** (1.03 to 4.22)	**318 more per 1,000** (from 9 more to 939 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Imprecision could not be assessed for this measure of effect
c. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: JAK inhibitors versus TNF inhibitors

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
ACR20 response (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	not serious	none	117/211 (55.5%)	35/106 (33.0%)	**RR 1.68** (1.25 to 2.26)	**225 more per 1,000** (from 83 more to 416 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR50 response (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72/211 (34.1%)	10/106 (9.4%)	**RR 3.62** (1.95 to 6.72)	**247 more per 1,000** (from 90 more to 540 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR70 response (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	33/211 (15.6%)	5/106 (4.7%)	**RR 3.32** (1.33 to 8.25)	**109 more per 1,000** (from 16 more to 342 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Minimal disease activity (follow up: 12 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	55/211 (26.1%)	27/106 (25.5%)	**RR 1.02** (0.69 to 1.52)	**5 more per 1,000** (from 79 fewer to 132 more)	⨁◯◯◯ VERY LOW	CRITICAL
Enthesitis absence in people with enthesitis at baseline (follow up: 12 weeks)												
1	randomised trials	serious [c]	not serious	serious [a]	serious [b]	none	51/139 (36.7%)	36/76 (47.4%)	**RR 0.77** (0.56 to 1.07)	**109 fewer per 1,000** (from 208 fewer to 33 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
LEI: Leeds Enthesitis Index in people with enthesitis at baseline												
2	randomised trials	not serious	very serious [d]	serious [a]	not serious	none	315	246	-	MD **0.05 lower** (0.73 lower to 0.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Dactylitis resolution in people with dactylitis at baseline. (follow up: 12 weeks)												
1	randomised trials	serious [c]	not serious	serious [a]	very serious [b]	none	57/121 (47.1%)	27/58 (46.6%)	**RR 1.01** (0.72 to 1.41)	**5 more per 1,000** (from 130 fewer to 191 more)	⨁◯◯◯ VERY LOW	CRITICAL
Psoriasis score (follow up: 12 weeks; assessed with: PASI response: ≥75% improvement)												
1	randomised trials	serious [c]	not serious	serious [a]	serious [b]	none	66/152 (43.4%)	30/77 (39.0%)	**RR 1.11** (0.80 to 1.56)	**43 more per 1,000** (from 78 fewer to 218 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	4/211 (1.9%)	1/106 (0.9%)	**RR 2.01** (0.23 to 17.76)	**10 more per 1,000** (from 7 fewer to 158 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. 11 (3%) people in the study were previously exposed to b/tsDMARDs.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
c. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
d. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

1.4.4.2 Comparison versus placebo

Table 7 Abatacept versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abatacept	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response (follow up: range 16 weeks to 24 weeks)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	66/135 (48.9%)	20/93 (21.5%)	**RR 2.20** (1.40 to 3.45)	**258 more per 1,000** (from 86 more to 527 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	21/84 (25.0%)	12/81 (14.8%)	**RR 1.69** (0.89 to 3.20)	**102 more per 1,000** (from 16 fewer to 326 more)	⊕⊕◯◯ LOW	CRITICAL
ACR70 response (follow up: 16 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abatacept	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	10/84 (11.9%)	7/81 (8.6%)	**RR 1.38** (0.55 to 3.44)	**33 more per 1,000** (from 39 fewer to 211 more)	⊕◯◯◯ VERY LOW	CRITICAL
Psoriasis score (follow up: 24 weeks; assessed with: PASI50 response)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	27/84 (32.1%)	22/81 (27.2%)	**RR 1.18** (0.74 to 1.90)	**49 more per 1,000** (from 71 fewer to 244 more)	⊕◯◯◯ VERY LOW	CRITICAL
Psoriasis score (follow up: 24 weeks; assessed with: PASI75 response)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	15/84 (17.9%)	8/81 (9.9%)	**RR 1.81** (0.81 to 4.03)	**80 more per 1,000** (from 19 fewer to 299 more)	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 8: Apremilast versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apremilast	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 16 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	0/459 (0.0%)	0/285 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life (follow up: 16 weeks; assessed with: Change in SF36 physical component score)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	351	176	-	MD **2.64 higher** (1.34 higher to 3.95 higher)	⊕⊕◯◯ LOW	CRITICAL
ACR20 response (follow up: 16 weeks)												
5	randomised trials	very serious [a]	not serious	not serious	not serious	none	515/1216 (42.4%)	131/659 (19.9%)	**RR 2.12** (1.79 to 2.51)	**223 more per 1,000** (from 157 more to 300 more)	⊕⊕◯◯ LOW	CRITICAL
ACR50 response (follow up: 16 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	50/460 (10.9%)	13/285 (4.6%)	**RR 2.34** (1.28 to 4.28)	**61 more per 1,000** (from 13 more to 150 more)	⊕⊕◯◯ LOW	CRITICAL
ACR70 response (follow up: 16 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apremilast	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	21/460 (4.6%)	2/285 (0.7%)	**RR 5.32** (1.51 to 18.73)	**30 more per 1,000** (from 4 more to 124 more)	⨁⨁◯◯ LOW	CRITICAL
Enthesitis resolution in people with enthesitis at baseline (follow up: 16 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	90/284 (31.7%)	39/166 (23.5%)	**RR 1.44** (1.04 to 1.99)	**103 more per 1,000** (from 9 more to 233 more)	⨁◯◯◯ VERY LOW	CRITICAL
Dactylitis resolution in people with dactylitis at baseline (follow up: 16 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	70/173 (40.5%)	28/90 (31.1%)	**RR 1.30** (0.91 to 1.86)	**93 more per 1,000** (from 28 fewer to 268 more)	⨁◯◯◯ VERY LOW	CRITICAL
Change in dactylitis count in people with dactylitis at baseline (follow up: 16 weeks; Scale from: 0 to 20)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	173	90	-	MD **0.95 lower** (1.72 lower to 0.17 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Psoriasis score in people with psoriasis at baseline (follow up: 16 weeks; assessed with: PASI50 response)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	96/213 (45.1%)	18/93 (19.4%)	**RR 2.33** (1.50 to 3.62)	**257 more per 1,000** (from 97 more to 507 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apremilast	placebo	Relative (95% CI)	Absolute (95% CI)		
Psoriasis score in people with psoriasis at baseline (follow up: 16 weeks; assessed with: PASI75 response)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	46/213 (21.6%)	10/93 (10.8%)	**RR 2.01** (1.06 to 3.81)	**109 more per 1,000** (from 6 more to 302 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow up: 24 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7/459 (1.5%)	10/285 (3.5%)	**RR 0.49** (0.19 to 1.26)	**18 fewer per 1,000** (from 28 fewer to 9 more)	⊕◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

Table 9: IL-12/23 inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-12/23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/409 (0.0%)	0/205 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR20 response (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-12/23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	not serious	none	237/580 (40.9%)	59/247 (23.9%)	**RR 1.72** (1.35 to 2.19)	**172 more per 1,000** (from 84 more to 284 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ACR50 response (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	108/409 (26.4%)	18/206 (8.7%)	**RR 3.02** (1.89 to 4.84)	**177 more per 1,000** (from 78 more to 336 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ACR70 response (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	54/409 (13.2%)	5/205 (2.4%)	**RR 5.41** (2.20 to 13.32)	**108 more per 1,000** (from 29 more to 300 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Enthesitis presence in people with enthesitis at baseline (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	186/288 (64.6%)	111/137 (81.0%)	**RR 0.80** (0.71 to 0.90)	**162 fewer per 1,000** (from 235 fewer to 81 fewer)	⨁⨁◯◯ LOW	CRITICAL
Bath Ankylosing Spondylitis Disease activity Index in people with spondylitis at baseline (follow up: 24 weeks; assessed with: BASDAI20 response)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	60/111 (54.1%)	16/61 (26.2%)	**RR 2.06** (1.31 to 3.25)	**278 more per 1,000** (from 81 more to 590 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-12/23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Psoriasis score in people with ≥3% BSA affected with psoriasis at baseline (follow up: range 12 weeks to 24 weeks; assessed with: PASI response: ≥75% improvement)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	222/370 (60.0%)	19/176 (10.8%)	**RR 5.56** (3.61 to 8.58)	**492 more per 1,000** (from 282 more to 818 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: 16 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	7/409 (1.7%)	4/205 (2.0%)	**RR 0.88** (0.26 to 2.96)	**2 fewer per 1,000** (from 14 fewer to 38 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 10: IL-17 inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 24 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	0/405 (0.0%)	0/169 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Change in quality of life (follow up: 12 weeks; assessed with: Short Form-36 Health Survey, Mental Component Score)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	107	106	-	MD **1.1 higher** (1.75 lower to 3.95 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	107	106	-	MD **3.9 higher** (1.73 higher to 6.07 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response (follow up: range 12 weeks to 24 weeks)												
7	randomised trials	serious [b]	not serious	not serious	not serious	none	870/1571 (55.4%)	183/756 (24.2%)	**RR 2.30** (2.01 to 2.63)	**315 more per 1,000** (from 244 more to 395 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response (follow up: range 12 weeks to 24 weeks)												
7	randomised trials	serious [b]	serious [c]	not serious	not serious	none	469/1572 (29.8%)	59/756 (7.8%)	**RR 3.66** (2.37 to 5.66)	**208 more per 1,000** (from 107 more to 364 more)	⊕⊕◯◯ LOW	CRITICAL
ACR70 response (follow up: range 12 weeks to 24 weeks)												
5	randomised trials	serious [b]	not serious	not serious	not serious	none	310/1209 (25.6%)	14/576 (2.4%)	**RR 10.02** (6.02 to 16.65)	**219 more per 1,000** (from 122 more to 380 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Minimal disease activity (follow up: 16 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	42/128 (32.8%)	8/60 (13.3%)	**RR 2.46** (1.23 to 4.91)	**195 more per 1,000** (from 31 more to 521 more)	⨁⨁◯◯ LOW	CRITICAL
Enthesitis absence/resolution in people with enthesitis at baseline (follow up: range 12 weeks to 24 weeks)												
2	randomised trials	serious [b]	not serious	not serious	serious [a]	none	96/244 (39.3%)	28/99 (28.3%)	**RR 1.38** (0.97 to 1.96)	**107 more per 1,000** (from 8 fewer to 272 more)	⨁⨁◯◯ LOW	CRITICAL
Dactylitis resolution in people with dactylitis at baseline. (follow up: range 12 weeks to 24 weeks)												
2	randomised trials	serious [b]	not serious	not serious	not serious	none	84/133 (63.2%)	18/45 (40.0%)	**RR 1.81** (1.25 to 2.63)	**324 more per 1,000** (from 100 more to 652 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Psoriasis score (follow up: range 12 weeks to 24 weeks; assessed with: PASI response: ≥75% improvement)												
2	randomised trials	serious [b]	serious [c]	not serious	not serious	none	145/231 (62.8%)	11/98 (11.2%)	**RR 4.92** (1.25 to 19.32)	**440 more per 1,000** (from 28 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Radiological progression (follow up: 24 weeks; assessed with: mTSS/SHS: van der Heijde modified Total Sharp Score)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [b]	serious [c]	not serious	serious [a]	none	263	129	-	MD **0.78 lower** (1.29 lower to 0.27 lower)	⊕◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	9/209 (4.3%)	2/106 (1.9%)	**RR 2.28** (0.50 to 10.38)	**24 more per 1,000** (from 9 fewer to 177 more)	⊕⊕◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
c. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

Table 11: IL-23 inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	0/91 (0.0%)	0/48 (0.0%)	**RD 0.00** (-0.03 to 0.03)	**0 fewer per 1,000** (from 30 fewer to 30 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	not serious	none	149/267 (55.8%)	30/135 (22.2%)	**RR 2.51** (1.80 to 3.50)	**336 more per 1,000** (from 178 more to 556 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ACR50 response (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	60/176 (34.1%)	9/87 (10.3%)	**RR 3.30** (1.72 to 6.32)	**238 more per 1,000** (from 74 more to 550 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ACR70 response at week 24												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	32/176 (18.2%)	6/87 (6.9%)	**RR 2.64** (1.15 to 6.07)	**113 more per 1,000** (from 10 more to 350 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 12: JAK inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious [a]	not serious	none	159/268 (59.3%)	55/162 (34.0%)	**RR 1.79** (1.42 to 2.27)	**268 more per 1,000** (from 143 more to 431 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR50 response (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	72/211 (34.1%)	10/105 (9.5%)	**RR 3.58** (1.93 to 6.65)	**246 more per 1,000** (from 89 more to 538 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR70 response at week 12												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	33/211 (15.6%)	5/105 (4.8%)	**RR 3.28** (1.32 to 8.17)	**109 more per 1,000** (from 15 more to 341 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Minimal disease activity (follow up: 12 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	55/211 (26.1%)	7/105 (6.7%)	**RR 3.91** (1.85 to 8.28)	**194 more per 1,000** (from 57 more to 485 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Enthesitis absence in people with enthesitis at baseline (follow up: 12 weeks)												
1	randomised trials	serious [c]	not serious	serious [b]	serious [d]	none	51/139 (36.7%)	14/65 (21.5%)	**RR 1.70** (1.02 to 2.84)	**151 more per 1,000** (from 4 more to 396 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Enthesitis score in people with enthesitis at baseline (follow up: range 12 weeks to 14 weeks; assessed with: Leeds Enthesitis Index)												
2	randomised trials	serious [c]	serious [e]	not serious	serious [d]	none	315	237	-	MD **0.75 lower** (1.23 lower to 0.27 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Dactylitis resolution in people with dactylitis at baseline (follow up: 12 weeks)												
1	randomised trials	serious [c]	not serious	serious [b]	serious [d]	none	57/121 (47.1%)	19/58 (32.8%)	**RR 1.44** (0.95 to 2.18)	**144 more per 1,000** (from 16 fewer to 387 more)	⨁◯◯◯ VERY LOW	CRITICAL
Psoriasis score in people with ≥3% BSA affected with psoriasis at baseline (follow up: 12 weeks; assessed with: PASI response: ≥75% improvement)												
1	randomised trials	serious [c]	not serious	serious [b]	serious [d]	none	66/152 (43.4%)	30/77 (39.0%)	**RR 1.11** (0.80 to 1.56)	**43 more per 1,000** (from 78 fewer to 218 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	serious [b]	very serious [d]	none	4/111 (3.6%)	1/105 (1.0%)	**RR 3.78** (0.43 to 33.31)	**26 more per 1,000** (from 5 fewer to 308 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. 11 people in one study were previously exposed to b/tsDMARDs.
b. 11 (3%) people were previously exposed to b/tsDMARDs.
c. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
d. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
e. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

Table 13: TNF inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality at 16/24 weeks (follow up: range 16 weeks to 24 weeks)												
4	randomised trials	not serious	not serious	not serious	not serious	none	0/726 (0.0%)	2/727 (0.3%)	**RD 0.00** (-0.01 to 0.00)	**0 fewer per 1,000** (from 0 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in SF-36 mental component score at 12/14/16/24 weeks												
8	randomised trials	not serious	very serious [a]	not serious	serious [b]	none	1182	1101	-	MD **2.68 higher** (0.8 higher to 4.56 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Change in SF-36 physical component score at 12/14/16/24 weeks												
8	randomised trials	not serious	very serious [a]	not serious	not serious	none	1182	1101	-	MD **5.04 higher** (3.51 higher to 6.57 higher)	⊕⊕◯◯ LOW	CRITICAL
ACR20 response (follow up: range 12 weeks to 24 weeks)												
13	randomised trials	not serious	very serious [a]	not serious	not serious	none	1090/1722 (63.3%)	376/1331 (28.2%)	**RR 2.75** (1.95 to 3.88)	**494 more per 1,000** (from 268 more to 814 more)	⊕⊕◯◯ LOW	CRITICAL
ACR50 response (follow up: range 12 weeks to 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
12	randomised trials	not serious	very serious [a]	not serious	not serious	none	602/1455 (41.4%)	150/1250 (12.0%)	**RR 3.45** (2.94 to 4.05)	**294 more per 1,000** (from 233 more to 366 more)	⊕⊕◯◯ LOW	CRITICAL
ACR70 response (follow up: range 12 weeks to 24 weeks)												
12	randomised trials	not serious	very serious [a]	not serious	not serious	none	367/1457 (25.2%)	64/1252 (5.1%)	**RR 6.26** (3.29 to 11.90)	**269 more per 1,000** (from 117 more to 557 more)	⊕⊕◯◯ LOW	CRITICAL
Minimal disease activity (follow up: range 12 weeks to 24 weeks; assessed with: ≥ 5 of 7 criteria)												
4	randomised trials	not serious	serious [a]	not serious	not serious	none	188/536 (35.1%)	88/434 (20.3%)	**RR 2.10** (1.38 to 3.18)	**223 more per 1,000** (from 77 more to 442 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Dactylitis presence (follow up: range 14 weeks to 16 weeks; assessed with: ≥1 dactylitis digits/dactylitis score over 0)												
3	randomised trials	very serious [c]	not serious	not serious	not serious	none	35/178 (19.7%)	70/176 (39.8%)	**RR 0.50** (0.36 to 0.70)	**199 fewer per 1,000** (from 255 fewer to 119 fewer)	⊕⊕◯◯ LOW	CRITICAL
Dactylitis resolution in people with dactylitis at baseline (follow up: range 12 weeks to 24 weeks)												
4	randomised trials	serious [c]	not serious	not serious	serious [b]	none	113/183 (61.7%)	96/198 (48.5%)	**RR 1.27** (1.07 to 1.51)	**131 more per 1,000** (from 34 more to 247 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Enthesitis presence (follow up: range 14 weeks to 16 weeks; assessed with: Enthesopathy/enthesitis)												
2	randomised trials	serious [c]	not serious	not serious	serious [b]	none	29/152 (19.1%)	50/152 (32.9%)	**RR 0.58** (0.39 to 0.86)	**138 fewer per 1,000** (from 201 fewer to 46 fewer)	⊕⊕◯◯ LOW	CRITICAL
Enthesitis resolution at week 16/24 in people with enthesitis at baseline												
4	randomised trials	serious [c]	serious [a]	not serious	serious [b]	none	149/320 (46.6%)	112/301 (37.2%)	**RR 1.25** (0.92 to 1.71)	**93 more per 1,000** (from 30 fewer to 264 more)	⊕◯◯◯ VERY LOW	CRITICAL
Enthesitis score in people with enthesitis at baseline (follow up: range 12 weeks to 24 weeks; assessed with: LEI / SPAECC Enthesitis index)												
3	randomised trials	serious [c]	very serious [a]	not serious	serious [b]	none	434	403	-	SMD **0.29 SD lower** (0.69 lower to 0.1 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Bath Ankylosing Spondylitis Disease activity Index in people with spondylitis and peripheral joint involvement (follow up: 14 weeks; assessed with: BASDAI20 response)												
1	randomised trials	serious [c]	not serious	not serious	not serious	none	41/61 (67.2%)	12/57 (21.1%)	**RR 3.19** (1.87 to 5.44)	**461 more per 1,000** (from 183 more to 935 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Psoriasis score (follow up: range 12 weeks to 14 weeks; assessed with: PASI response: ≥50% improvement)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [c]	very serious [a]	not serious	not serious	none	134/172 (77.9%)	28/178 (15.7%)	**RR 4.21** (1.48 to 11.98)	**505 more per 1,000** (from 76 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Psoriasis score (follow up: range 12 weeks to 14 weeks; assessed with: PASI response: ≥75% improvement)												
9	randomised trials	serious [c]	serious [a]	not serious	not serious	none	413/801 (51.6%)	59/741 (8.0%)	**RR 6.74** (5.15 to 8.81)	**457 more per 1,000** (from 330 more to 622 more)	⨁⨁◯◯ LOW	CRITICAL
Change in mTSS/SHS: van der Heijde modified Total Sharp Score (0-528) at 24/48 weeks												
2	randomised trials	not serious	very serious [a]	not serious	not serious	none	467	455	-	MD **1.67 lower** (1.71 lower to 1.64 lower)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (follow up: range 12 weeks to 48 weeks)												
10	randomised trials	not serious	not serious	not serious	very serious [b]	none	46/1331 (3.5%)	39/1164 (3.4%)	**RR 1.08** (0.71 to 1.65)	**3 more per 1,000** (from 10 fewer to 22 more)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
c. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures to capture medication effects on other psoriatic disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA.

1.5.2 Benefits and harms

The evidence came from 34 RCTs and the great majority of comparisons were versus placebo. However there were 3 head to head comparisons all versus TNF inhibitors. The evidence has been discussed below through each manifestation of PsA. When the group came to make recommendations they wished to make them based on mode of action rather than specific medications. This acts to future proof the guideline as new medications are developed but clinicians should be cognisant of the data underlying an individual drug that is chosen for treatment.

The group wished to make the guideline accessible and useful to a "coalface" clinician and to present the evidence in a fashion that allows a physician to make choices on treatment given the range of PsA scenarios they can be presented with. For example, this could be choice of medication based on clinical factors such a severity of psoriasis or the presence of IBD. clinic implementation toolkit?

Head to head trials

The group stated that this data did not indicate a strong difference between any of the treatments being compared. They were cautious of the data in the comparison of IL-12/23 inhibitor to TNF inhibitor because the study (ECLIPSA) is very small and unblinded for either patient or assessor. Also the population included were older people with a lot of potentially mechanical issues as well.

Therefore the group agreed that the head to head trials did not support give rise to recommending any medication class over another for MSK disease.

Peripheral arthritis

The medications were all effective for peripheral arthritis symptoms versus placebo and the guideline recommends abatacept, apremilast, IL12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors, JAK inhibitors, or TNF inhibitors.

Enthesitis

There were positive outcomes linked to enthesitis reported for apremilast, IL-12/23 inhibitors, IL-17 inhibitors, JAK inhibitors, and TNF inhibitors. However, in some cases there were a mixed responses within comparisons for enthesitis outcomes. TNF inhibitors indicated a clinically important benefit in terms

enthesitis presence and enthesitis resolution but not always for an improvement in enthesitis score and there is a similar story for JAK inhibitors. However, all the positive enthesitis outcomes reported across all comparisons versus placebo were linked to resolution/presence rather than a change in enthesitis score. Therefore, the group agreed that the evidence for TNF inhibitors and JAK inhibitors was as strong for that for other medications.

Dactylitis

There were positive dactylitis outcomes linked to IL-17 inhibitors, JAK inhibitors, TNF inhibitor, apremilast. 12/23 inhibitors, and IL-23 inhibitors. Apremilast showed a clinically important benefit in dactylitis resolution but not for change in dactylitis count. All other studies reported dactylitis resolution rather than count and as such apremilast was considered to have a clinically important benefit.

Axial disease

There were trials in people with peripheral PsA that looked for improvement in the Bath Ankylosing Spondylitis Disease activity Index (BASDAI) in those with axial manifestations. However, these are small subgroups in most of the trials and this subgroup analysis breaks randomization. The group noted that BASDAI is not specific to the axial disease and is influenced by peripheral disease and other factors, and is therefore of limited use in assessing the benefit for axial symptoms. However, there was a recent studyRCT with a population with PsA who all had physician reported axial manifestations and this found a clinically important benefit of an IL-17 inhibitor versus placebo.

The group also utilized known results from ankylosing spondylitis (AS) and axial spondyloarthritis (aAxSpA) trials to support their recommendations. The group knew of are positive trials for TNF inhibitors, IL-17 inhibitors, and JAK inhibitors. There was a trial for of an IL-12/23 inhibitor that was stopped early and also a negative trial for apremilast and a negative trial for an IL-23 inhibitor.

The group agreed to a practical approach, utilising what is known from AS / AxSpA studies to support the evidence found for small subgroups in the PsA trials and the single trial in PsA where all people had axial manifestations.

The PsA evidence supported TNF inhibitors and, IL17 Inhibitors, and IL-12/23 inhibitors for axial disease. However the group were cautious of IL-12/23 and IL-23 inhibitors due to AS / AxSpA studies. So the group made a strong recommendation for TNF inhibitors and IL-17 inhibitors but did not recommend IL-12/23 and IL-23 inhibitors. The group were also aware of two relevant RCTs evaluating JAK inhibitor but this is currently only published in abstract form. However, it indicates a positive effect for JAK inhibitors and the group made a weak recommendation for this mode of action.

Psoriasis and nail disease

The studies included in this review often reported psoriasis outcomes in people with 3% or more body surface area (BSA) plaque psoriasis. The review found a benefit for apremilast, IL-12/23 inhibitors, IL-17 inhibitors, and TNF inhibitor.

The group spoke about current dermatology care and commented on changes in psoriasis treatment over the past 2 years. IL-23 inhibitors are commonly used now and, in the experience of a dermatologist on the group, this has led to a reduction in use of IL-12/23 inhibitors. It was stated there are profound regional differences and this has led to differences in treatment across the regions.

In current care IL-17 inhibitors and TNF inhibitors are known to be very effective for psoriasis symptoms but some people respond much better to one or the other. This variation in effectiveness in what superficially

appear to be a single population has led the British Association of Dermatologists (BAD) to develop a clinic implementation toolkit that supports clinicians to prescribe the correct medication for each person given their specific symptoms. The toolkit gives the dermatologist a fuller overview of the evidence behind each medication and allows greater personalization of treatment. A dermatologist member stated the great impact of the implementation toolkit, which has been fed back in a number of ways and was the significant enhancement of dermatology updates provided in a critical time in the middle of 2020.

In PsA terms the group agreed that psoriasis tends to be less severe in people than exists in the psoriasis trial populations. Therefore it is unlikely such large disparities will exist when treating psoriasis in the PsA population. Where psoriasis is more severe then the discussion between the multidisciplinary team including rheumatology, dermatology and other members of the team to agree the treatment that is likely to give the largest benefit.

Eligibility for b/tsDMARDs

This group discussed who should have access to b/tsDMARDs. The ACR guideline investigated this and there was evidence for TNF inhibitor therapy first line. However, starting out on b/tsDMARDs prior to using csDMARDs would be a huge leap in treatment policy in PsA. Also, the group know there is data for csDMARDs, particularly for methotrexate therapy, that indicate its effectiveness and people can achieve low disease activityresolve arrive at remission without use of biologics. So iIt makes sense from a cost-effective perspective to begin with this cheaper and occasionally effective therapy.

However, in people with severe active disease and poor prognostic markers, it makes sense to offer b/tsDMARDs earlier than is currently standard UK care. A member of the group stated occasions where people with such severe disease are treated following treat to target strategy but it is plain that they require biologics at an earlier stage than months or years down the line.

The TICOPA treat to target trial was mentioned where combination csDMARD therapy was found to be effective rather than moving to a b/tsDMARD. However, the trial was designed to assess treat to target rather than combination therapy and it was not powered to draw any conclusions on this.

The group agreed that it makes sense to allow an earlier offer of b/tsDMARDs should be considered to people after 1 csDMARD failure. The group agree this is an option rather than a requirement and allows the multidisciplinary to use their expertise to offer b/tsDMARDs to the person. This eligibility criteria matches well with the clinical trials that are happening now and also matches what has been recommended by EULAR and brings the UK in line with Europe.

The group were keen to include people with severe monoarthritis or oligoarthritis for whom a csDMARD has failed in this recommendation. In the previous guideline it mentioned failure of intra-articular therapy but the group felt this therapy was utilised as and when required by physicians and did not need to be included here.

The group discussed two trials relevant to eligibility for b/tsDMARDs. The SEAM-PsA trial compared etanercept to etanercept plus methotrexate combination therapy and methotrexate monotherapy. The results demonstrated superiority of etanercept over methotrexate providing evidence for the superiority of earlier bDMARD intervention. The control trial compared dose escalation of methotrexate to the addition of anti-TNF in people with active PsA despite 15mg methotrexate. The trial demonstrated superiority of adalimumab overt dose escalation with 13% achieved MDA in the dose escalation arm at week 16. The group felt these two recent trials, in addition to other established data (see ACR guidelines refs) provided supportive evidence for earlier use of b/tsDMARDS over csDMARDs after failure of one csDMARD in patients with poor prognostic markers.

1.5.3 Cost effectiveness and resource use

Where multiple drugs/MoAs are equally appropriate for an individual, cost of treatment should be taken into account.

1.5.4 Other factors the committee took into account

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Appendices

Appendix A: Review protocol

Table 14: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020210029
1.	Review title	Initial biologic and targeted synthetic DMARDs treatment for psoriatic arthritis
2.	Review questions	• In people with active peripheral psoriatic arthritis, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo? • In adults with active psoriatic arthritis-related dactylitis, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo? • In adults with active psoriatic arthritis-related enthesitis what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo? • In adults with active psoriatic arthritis-related axial disease that is not responding to NSAIDs, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitor, IL23 inhibitors, IL17 inhibitors, JAK inhibitors, apremilast or abatacept, in comparison to each other or placebo?
3.	Objective	This review seeks to assess the clinical effectiveness of biologic and targeted synthetic disease modifying anti-Rheumatic Drugs (b/tsDMARDS) in the treatment of peripheral psoriatic arthritis and may have related dactylitis, enthesitis, and axial disease. They will be compared to each other or placebo.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews

		The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Inclusion: Adults with active peripheral psoriatic arthritis who are b/tsDMARDS naïve
7.	Intervention/Exposure/Test	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept Apremilast JAK inhibitors
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions or to placebo
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life including SF-36, PsAQoL (continuous) <u>Arthritis</u> American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous)

		• Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) <u>Enthesitis</u> in those with enthesitis at baseline • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 <u>Dactylitis</u> in those with dactylitis at baseline • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> in those with axial disease at baseline • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u> in those with psoriasis at baseline • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score Outcome timepoints are study defined.
13.	Secondary Outcomes	<u>Arthritis</u> • Radiological progression (continuous) <u>Adverse Events</u> • Serious adverse events (dichotomous) **<u>The outcomes below are extracted if studies do not report ACR response.</u>**

		Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous) Outcome timepoints are study defined.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRARADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

17.	Analysis of sub-groups	Number of joint affected: • Polyarthritis (5 or more joints) • oligoarthritis (4 joints or fewer) • Monoarthritis (one joint) Concomitant conventional synthetic (cDMARD) treatment
18.	Anticipated or actual start date	06/06/2020
19.	Anticipated completion date	29/09/2020
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	New review
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 15: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 12 June 2020	Exclusions
Embase (ProQuest)	1974 – 12 June 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12	None

Medline (ProQuest) and Embase (ProQuest) search term

1. .	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2.	EMB.EXACT.EXPLODE("psoriatic arthritis")
3.	TI,AB(Psoriasis or Psoriatic)
4.	TI,AB(arthrosis or *arthritis)
5.	S3 n/3 S4
6.	S1 or S2 or S5
7.	MESH.EXACT("Anecdotes as Topic") OR MESH.EXACT("Letter") OR EMB.EXACT("letter") OR RTYPE(letter) or RTYPE(note) or RTYPE(editorial) OR MESH.EXACT("Editorial") OR MESH.EXACT("News") OR MESH.EXACT("Historical Article") OR MESH.EXACT("Comment") OR MESH.EXACT("Case Report") OR EMB.EXACT("case report") OR EMB.EXACT("case study") OR TI(LETTER) OR TI(COMMENT*)
8.	EMB.EXACT("randomized controlled trial") OR MESH.EXACT("Randomized Controlled Trial") or TI,AB(random*)
9.	S7 NOT S8
10.	MESH.EXACT("Animals") OR EMB.EXACT("animal")
11.	MESH.EXACT("Humans") OR EMB.EXACT("human")
12.	S10 NOT S11
13.	MESH.EXACT.EXPLODE("Animals, Laboratory") OR MESH.EXACT.EXPLODE("Animal Experimentation") OR MESH.EXACT.EXPLODE("Models, Animal") OR MESH.EXACT.EXPLODE("Rodentia") OR EMB.EXACT("nonhuman") OR EMB.EXACT.EXPLODE("animal experiment") OR EMB.EXACT.EXPLODE("experimental animal") OR EMB.EXACT("animal model") OR EMB.EXACT.EXPLODE("rodent") OR TI(RAT) OR TI(RATS) OR TI(MOUSE) OR TI(MICE)
14.	S9 OR S12 OR S13
15.	S6 NOT S14
16.	TI,AB("TNF inhibitor" or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)

17.	TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
18.	TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
19.	TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
20.	TI,AB(Abatacept)
21.	TI,AB(apremilast)
22.	TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
23.	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
24.	TI(trial)
25.	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
26.	TI,AB(doubl* n/1 blind*)
27.	TI,AB(singl* n/1 blind*)
28.	RTYPE(controlled clinical trial)
29.	RTYPE(randomized controlled trial)
30.	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
31.	EMB.EXACT.EXPLODE("crossover procedure")
32.	EMB.EXACT.EXPLODE("single blind procedure")
33.	EMB.EXACT.EXPLODE("randomized controlled trial")
34.	EMB.EXACT.EXPLODE("double blind procedure")
35.	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
36.	S15 and S23 AND S35
37.	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
38.	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
39.	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
40.	TI,AB(before n/2 after n/2 stud*)
41.	TI,AB(longitudinal or retrospective or prospective or cross sectional)
42.	TI,AB(study or studies or review or analys* or cohort* or data)
43.	S41 and S42
44.	S37 OR S38 OR S39 OR S40 OR S43
45.	S15 AND S23 AND S44
46.	S36 OR S45

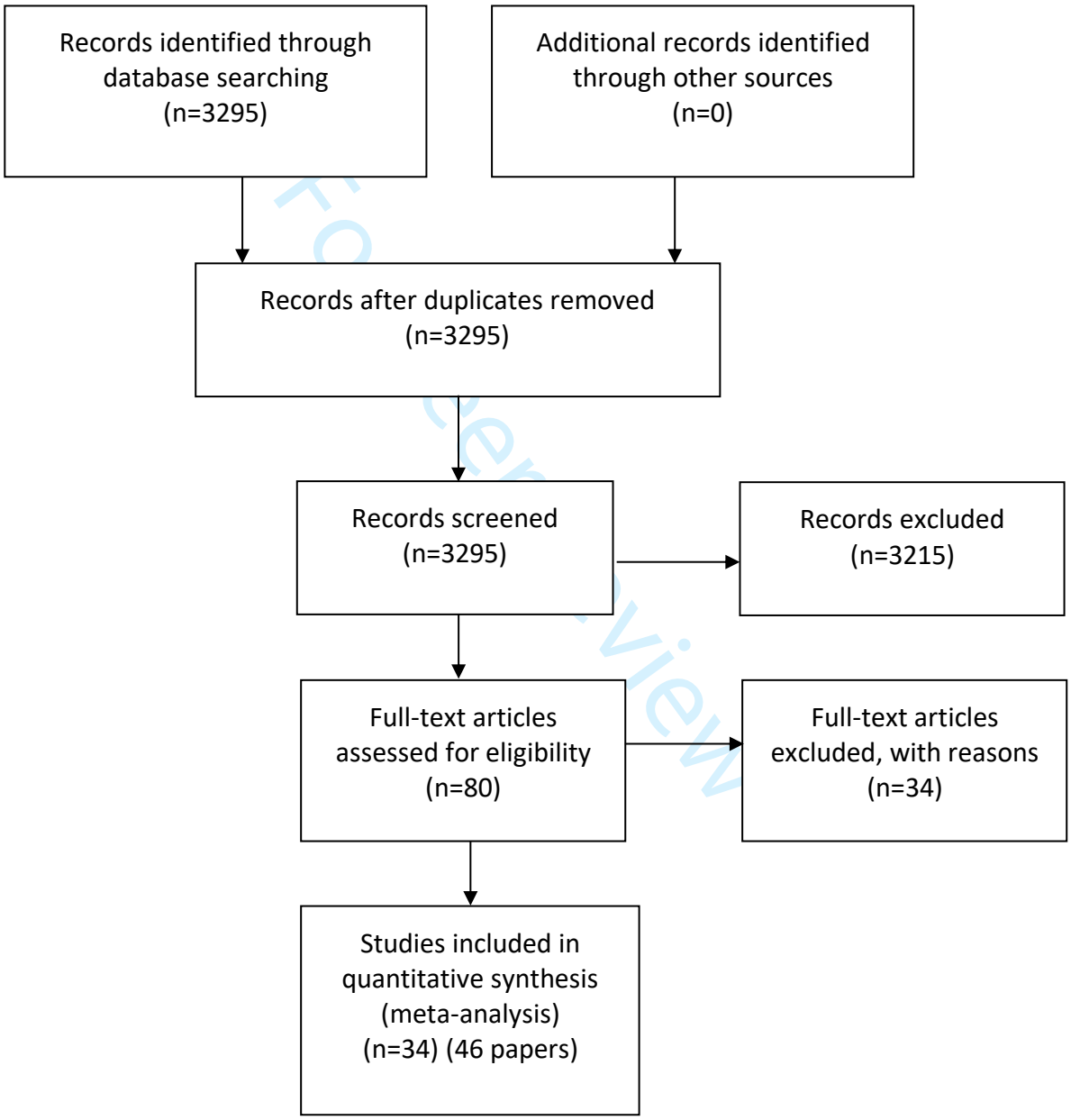
Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] explode all trees

#2	Psoriasis or Psoriatic
#3	arthrosis or *arthritis
#4	#2 and #3
#5	#1 or #4
#6	TNF inhibitor or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab
#7	IL-12/23 inhibitor or IL12/23 inhibitor or Ustekinumab or briankizumab
#8	IL23 inhibitor or IL-23 inhibitor or guselkumab or tildrakizumab or risankizumab or mirikizumab
#9	IL17 inhibitor or IL-17 inhibitor or Ixekizumab or secukinumab or brodalumab or Bimekizumab
#10	Abatacept
#11	apremilast
#12	JAK inhibitors or “Janus kinase inhibitor” or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or tofacitinib
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#5 and #13

Appendix C: **Clinical evidence selection**

Figure 1: Flow chart of clinical study selection



British Society for Rheumatology

Appendix D: **Clinical evidence tables**

Study	ACTIVE Nash 2018(4)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=219
Countries and setting	Conducted in USA, Australia, Canada, Czech Republic, Estonia, Hungary, New Zealand, Romania, Russia, Spain; Setting: 77 sites
Line of therapy	Not applicable
Duration of study	Intervention: Double blind, placebo controlled treatment period of 24 weeks
Method of assessment of guideline condition	CASPAR
Stratum	None
Subgroup analysis within study	None
Inclusion criteria	Adults with active PsA with a documented diagnosis for at least 3 months. They were biologic naïve and discontinued their current csDMARD treatment prior to entering the study.
Exclusion criteria	Prior treatment with more than 1 csDMARD, used prohibited systemic therapies, including cyclosporine or other calcineurin inhibitors, within 4 weeks of randomisation, corticosteroids >10 mg daily (prednisone or equivalent), oral agents such as retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus and tacrolimus; and inflammatory joint disease other than PsA. Also excluded were people with active or incompletely treated tuberculosis, significant infection within 4 weeks of screening and current or history of malignancy (except for treated basal cell or squamous cell skin carcinoma or early forms of cervical carcinoma with no recurrence within 5 years).
Age, gender and ethnicity	Age - Mean (SD): 48 (14) and 51 (12). Gender (M:F): 96/123. Ethnicity: 214 (98%) were white
Further population details	Enthesitis at baseline: 107 (49%)
Indirectness of population	No indirectness
Interventions	(n=110) Intervention 1: Apremilast – 30 mg twice daily. Concurrent medication/care: Stable doses of oral corticosteroids (prednisone ≤10 mg/day or equivalent), non-steroidal anti-inflammatory drugs or opioid analgesics. Indirectness: No indirectness (n=109) Intervention 2: Placebo. Concurrent medication/care: Stable doses of oral corticosteroids (prednisone ≤10 mg/day or equivalent), non-steroidal anti-inflammatory drugs or opioid analgesics. Indirectness: No indirectness Early escape:

	People who did not improve by ≥10% in swollen joint count (SJC) and tender joint count (TJC) at week 16 were eligible for early escape at the investigator's discretion. Early escape patients initially randomised to placebo were switched to apremilast in blinded fashion, with dose titration during the first week of treatment; patients initially randomised to apremilast remained on apremilast.
Funding	Celgene Corporation.

Abatacept versus placebo in subgroup without previous TNF inhibitor use:

- Mortality at 24 weeks. RoB: vh
- ACR20 at 16 weeks. RoB: vh
- ACR50 at 16 weeks. RoB: vh
- ACR70 at 16 weeks. RoB: vh
- Enthesitis resolution in people with enthesitis at baseline. RoB: vh
- Serious adverse events. RoB: vh

Study	ADEPT: MEASE 2005(24), Gladman 2007(25)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=313
Countries and setting	Conducted in Austria, Belgium, Canada, France, Germany, Italy, UK, US; Setting: 50 sites
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks while placebo controlled with possible rescue therapy for people at 12 weeks
Method of assessment of guideline condition	Formal classification criteria not stated.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with moderately to severely active PsA (defined as having at least 3 swollen joints and 3 tender or painful joints), and had either active psoriatic skin lesions or a documented history of psoriasis. People were required to have a history of an inadequate response or intolerance to nonsteroidal antiinflammatory drug therapy for PsA. MTX use was allowed during the study only if it had been taken for at least 3 months previously, with the dosage stable for at least 4 weeks prior to the baseline visit.
Exclusion criteria	Treatment within 4 weeks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids. Topical treatments for psoriasis within 2 weeks of baseline, other than medicated shampoos or low-potency topical steroids. Concurrent treatment with MTX at dosages >30 mg/week and/or corticosteroids in a prednisone-equivalent dosage of >10 mg/day. Anti-TNF therapy at any time. People were not allowed to enter the study if they had a history of neurologic symptoms suggestive of central nervous system demyelinating disease, a history of active

	tuberculosis (TB) or listeriosis, or the presence of a severe infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of study entry.
Age, gender and ethnicity	Age - Mean (SD): 49 (13) and 49 (11). Gender: 56% male. Ethnicity: 95% white
Further population details	BSA ≥3% skin involvement: 140
Indirectness of population	No indirectness
Interventions	(n=151) Intervention 1: TNF inhibitor: Subcutaneous injections of 40 mg adalimumab given every other week. After week 12, people who failed to have at least a 20% decrease in both swollen and tender joint counts on 2 consecutive visits could receive rescue therapy with corticosteroids or DMARDs. Indirectness: No indirectness (n=162) Intervention 2: Placebo. Subcutaneous injections of placebo given every other week. After week 12, people who failed to have at least a 20% decrease in both swollen and tender joint counts on 2 consecutive visits could receive rescue therapy with corticosteroids or DMARDs.
Funding	Janssen Research and Development.

TNF Inhibitors versus placebo

- ACR20 response at week 12. RoB: vh
- ACR50 response at week 12. RoB: vh
- ACR70 response at week 12. RoB: vh
- PASI response: ≥50% improvement at week 12. RoB: vh
- PASI response: ≥75% improvement at week 12. RoB: vh
- PASI response: ≥90% improvement at week 12. RoB: vh
- Serious adverse events at 24 weeks. RoB: vh
- Change in SF-36 physical component at 12 weeks. RoB: vh
- Change in SF-36 mental component at 12 weeks. RoB: vh

Study	ASTRAEA: Mease 2017(1), Strand 2018(2)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=424
Countries and setting	Conducted in USA, Argentina, Brazil, Canada, Chile, Colombia, Czech Republic, France, Germany, Greece, Israel, Italy, Mexico, Peru, Poland, South Africa, Spain; Setting: 82 sites
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks treatment double blind while placebo controlled
Method of assessment of guideline condition	CASPAR

Stratum	None
Subgroup analysis within study	Outcomes in people who were bDMARD naïve were extracted. N=165 (39%)
Inclusion criteria	Adults with active PsA and inadequate response or intolerance to at least one non-biologic DMARD. They were required to active plaque psoriasis.
Exclusion criteria	None detailed
Age, gender and ethnicity	Age - Mean (SD): 51 (11) and 50 (11). Gender (M:F): 224/233. Ethnicity: 93% were white
Further population details	Enthesitis at baseline: 272 (64%) Dactylitis at baseline: 111 (26%) Psoriasis covering ≥3% BSA at baseline: 294 (69%)
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: Abatacept – 125 mg weekly dose administered subcutaneously. Concurrent medication/care: Treatment with cDMARDs, oral corticosteroids, low potency topical corticosteroids was permitted. Indirectness: No indirectness (n=130) Intervention 2: Placebo. At week 16, all patients with less than 20% improvement in both swollen and tender joint counts were eligible for early escape to abatacept treatment. Indirectness: No indirectness.
Funding	Bristol-Myers Squibb.

Abatacept versus placebo in subgroup without previous TNF inhibitor use:

- ACR20 at 24 weeks. RoB: vh
- ACR50 at 24 weeks. RoB: vh
- ACR70 at 24 weeks. RoB: vh
- PASI50 response. RoB: vh
- PASI75 response. RoB vh

Study	DISCOVER 1: Deodhar 2020(11)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=381
Countries and setting	Conducted in Australia, Canada, Czech Republic, Germany, Hungary, Malaysia, Poland, South Korea, Russia, Spain, Taiwan, Ukraine, USA; Setting: 86 sites
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks while placebo controlled
Method of assessment of guideline condition	Formal classification criteria not stated.

Stratum	Overall
Subgroup analysis within study	Data extracted on subgroup of people without previous TNF inhibitor use: N=239. It is possible up to 12 of these people were previously exposed to apremilast.
Inclusion criteria	People with psoriatic arthritis and displaying at least three tender and at least three swollen joints and CRP concentration of 0·3 mg/dL or more. They had a current or documented history of psoriasis and had demonstrated inadequate response to or intolerance of standard treatment, including at least 4 months of apremilast (if discontinued >4 weeks before receiving study treatment), at least 3 months of non-biologic DMARDs (limited to methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day), or at least 4 weeks of NSAIDs for psoriatic arthritis. Background use of stable doses of one selected nonbiologic DMARD, oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), and NSAIDs or other analgesics was permitted. People had to meet criteria for screening laboratory testing and tuberculosis history, testing, and treatment (for latent tuberculosis)
Exclusion criteria	People with other inflammatory diseases and those who had previously received biologics other than TNF inhibitors were excluded.
Age, gender and ethnicity	Age - Mean (SD): 48 (12) and 49 (11). Gender (M:F): 195/186. Ethnicity: 349 were white
Further population details	Enthesitis at baseline: 222 Dactylitis at baseline: 142
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: IL-23 inhibitor – the study contained 2 guselkumab intervention groups administered every 4 weeks or 8 weeks. Guselkumab was administered as a 100-mg subcutaneous injection. At week 16, all patients with less than 5% improvement in both swollen and tender joint counts were eligible for early escape—i.e. they continued with study treatment but the investigator could initiate or increase the dose of NSAIDs or other analgesics (up to the regional marketed dose approved), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), or non-biologic DMARDs (per study inclusion criteria). Indirectness: No indirectness (n=87) Intervention 2: Placebo. At week 16, all patients with less than 5% improvement in both swollen and tender joint counts were eligible for early escape—i.e. they continued with study treatment but the investigator could initiate or increase the dose of NSAIDs or other analgesics (up to the regional marketed dose approved), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), or non-biologic DMARDs (per study inclusion criteria). Indirectness: No indirectness.
Funding	Janssen Research and Development.

IL-23 inhibitor versus placebo in subgroup without previous TNF inhibitor use

- ACR20 at 24 weeks. RoB: low
- ACR50 at 24 weeks. RoB: low

- ACR75 at 24 weeks. RoB: low

Study	ECLIPSA: Araujo 2017(39)
Study type	Open label RCT (Patient randomised; Parallel)
Number of participants	n=51
Countries and setting	Conducted in Germany; Setting: Single hospital (University Hospital Erlangen).
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with a diagnosis of PsA according to CASPAR criteria, presence of active enthesitis defined as ≥1 painful entheses using the Spondyloarthritis Research Consortium of Canada (SPARCC) index and failure of treatment with methotrexate at the highest tolerable dose for at least 3 months.
Exclusion criteria	People who had received or were receiving biologic disease-modifying anti-rheumatic drug (bDMARD) therapy.
Age, gender and ethnicity	Age - Mean (SD): 62 (18) and 58 (21). Gender (M:F): 119/81. Ethnicity: Not detailed
Further population details	Using methotrexate at baseline: 92%
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: IL-12/23 inhibitor – Subcutaneous ustekinumab at weeks 0, 4, 12 and 24 using 45mg in people under 100kg and 90mg in people over 100kg. Concurrent medication/care: Glucocorticoids of less than 5 mg prednisolone/day were allowed during the study. Symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was also allowed, but NSAIDs were stopped at screening. Indirectness: No indirectness (n=24) Intervention 2: TNF inhibitor – specific medication according to a person's preferences related to route and frequency of administration. People were followed for a total of 24 weeks with regular visits at week 0 and weeks 12 and 24. TNF inhibitor used: Adalimumab n=10, Cetolizumab n=6; Etanercept n=5; Infliximab n=3. Concurrent medication/care: Glucocorticoids of less than 5 mg prednisolone/day were allowed during the study. Symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was also allowed, but NSAIDs were stopped at screening.
Funding	No funding (No external funding)

IL-12/23 inhibitor versus TNF inhibitor

- Complete resolution of enthesitis, arthritis and skin at 24 weeks. RoB: h

- Presence or absence of enthesitis via enthesitis resolution (LEI = 0, SPARCC = 0, MASES = 0) at 24 weeks. RoB: h
- BASDAI: Bath Ankylosing Spondylitis Disease Activity Index at 24 weeks. RoB: h
- DAPSA: Disease Activity Index for Psoriatic Arthritis at 24 weeks. RoB: h
- SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 24 weeks. RoB: h
- SF-36 MCS: Short Form-36 Health Survey, Mental Component Summary at 24 weeks. RoB: h
- MDA: Minimal disease activity (7 of 7 criteria) at 24 weeks. RoB: h
- PASI response: 100% improvement at week 24. RoB: h

Study	EQUATOR: Mease 2018(22)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=131
Countries and setting	Conducted in 25 centres in Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine.
Line of therapy	Not applicable
Duration of study	Intervention: 16 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 111 (84%) people in the study who were TNF inhibitor naïve
Inclusion criteria	People with a diagnosis of psoriatic arthritis for at least 12 weeks before screening. They were required to have active moderate-to-severe disease), active or a documented history of plaque psoriasis, and an insufficient response or intolerance to at least one csDMARD.
Exclusion criteria	People exposed to teatment with more than one anti-TNF agent, or any alkylating agent, JAK inhibitor, or other investigational or approved biologic immune-modulator at any time. Also receipt of intramuscular or intravenous corticosteroids or intra-articular injection within 4 weeks before screening, receipt of oral steroids (>10 mg/day prednisone or equivalent), receipt of oral steroids (≤10 mg/day prednisone or equivalent) at a dose that was not stable for at least 4 weeks before baseline, or very poor functional status or inability to perform self-care.
Age, gender and ethnicity	Age - Mean (SD): 49 (12) and 50 (11). Gender (M:F): 65/66. Ethnicity: Not detailed
Further population details	Enthesitis (LEI): 87 (66%) Psoriasis ≥ 3% of BSA at baseline: 82 (63%)
Indirectness of population	No indirectness
Interventions	(n=54) Intervention JAK inhibitor– filgotinib 200 mg orally once daily for 16 weeks. Concurrent medication/care: People continued to take csDMARDs during the study if they had received this treatment for at least 12 weeks before screening and were on a stable dose for at least 4 weeks before baseline. Indirectness: No indirectness

	(n=57) Intervention 2: Placebo - orally once daily for 16 weeks. Concurrent medication/care: People continued to take csDMARDs during the study if they had received this treatment for at least 12 weeks before screening and were on a stable dose for at least 4 weeks before baseline. Indirectness: No indirectness
Funding	Galapagos and Gilead Sciences.

JAK inhibitor versus placebo in people who are bDMARD naïve

- ACR20 response at week 16. RoB: h

Study	EXCEED: McInnes 2020(37)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=853
Countries and setting	Conducted in 168 centres across USA, Australia, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Israel, Italy, Republic of Korea, Latvia, Lithuania, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, UK.
Line of therapy	Not applicable
Duration of study	Intervention: 52 weeks
Method of assessment of guideline condition	Not stated
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults who fulfil the Classification Criteria for Psoriatic Arthritis and have active PsA. People had an inadequate response or intolerance to cDMARDs. cDMARD treatment was stopped prior to inclusion in the trail.
Exclusion criteria	Previous exposure to bDMARDs or opioids, pregnancy, evidence of ongoing infection or malignancy, ongoing use of oral or topical retinoids, photochemotherapy, photoherapy, topical skin treatment.
Age, gender and ethnicity	Age - Mean (SD): 49 (12.4). Gender (M:F): 437/416. Ethnicity: White: 93%, Asian: 4%, Other/unknown: 3%.
Further population details	People with dactylitis at baseline: 267 (31%) People with enthesitis (LEI) at baseline: 498 (58%) People with ≥3% body area involvement with psoriasis: 417 (49%)
Indirectness of population	No indirectness
Funding	Novartis
Interventions	(n=426) Intervention 1: IL17 inhibitor – Secukinumab 300 mg was administered at baseline, weeks 1, 2, 3, and 4, and then every 4 weeks until week 48. Concurrent medication/care: People had to stop any csDMARD, including methotrexate, before randomisation, with a washout period of 4 weeks for all csDMARDs or 8 weeks for leflunomide. People who were receiving concomitant corticosteroids were required to be on a stable dose of 10 mg/day or less of

prednisone or equivalent for at least 2 weeks before randomisation and remain on a stable dose up to week 52. Indirectness: no indirectness.

(n=427) Intervention 2: TNF inhibitors - Adalimumab 40 mg was administered every 2 weeks from baseline until week 50. Concurrent medication/care: People had to stop any csDMARD, including methotrexate, before randomisation, with a washout period of 4 weeks for all csDMARDs or 8 weeks for leflunomide. People who were receiving concomitant corticosteroids were required to be on a stable dose of 10 mg/day or less of prednisone or equivalent for at least 2 weeks before randomisation and remain on a stable dose up to week 52. Indirectness: no indirectness.

IL-17 inhibitors versus TNF inhibitors

- Mortality at 52 weeks. RoB: low
- ACR20 response at 52 weeks. RoB: low
- ACR50 response at 52 weeks. RoB: low
- Minimal disease activity after 52 weeks. RoB: low
- Absence of enthesitis at 52 weeks. RoB: h
- Absence of dactylitis at 52 weeks. RoB: h
- PASI response: ≥90% improvement at week 52
- Serious adverse events at 52 weeks. RoB: low

Study	FUTURE 1: Mease 2015(12)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=606
Countries and setting	Conducted in 109 centres in USA, Argentina, Australia, Belgium, Canada, Brazil, Bulgaria, Czech Republic, Germany, Israel, Italy, Philippines, Poland, Romania, Russia, Singapore, Slovakia, Thailand, UK.
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	People who are TNF inhibitor Naïve: 428 (78%)
Inclusion criteria	People with PsA active disease, defined as ≥ 3 tender and ≥ 3 swollen joints, despite previous treatment with either NSAIDs, cDMARDs, or TNF inhibitors.

Exclusion criteria	Previous therapy with biologic drugs other than anti-TNF agents, treatment with more than three anti-TNF therapies, the presence of active inflammatory diseases other than psoriatic arthritis, and active infection in the 2 weeks before randomization or a history of ongoing, chronic, or recurrent infections..
Age, gender and ethnicity	Age - Mean (SD): 47 (12) and 49 (11). Gender (M:F): 330/276. Ethnicity: White: 481 (79%), Black: 5 (1%), Asian: 19%, Other: 4 (1%)
Further population details	Dactylitis at baseline: 324 (53%) Enthesitisat baseline: 372 (61%) Psoriasis ≥ 3% of BSA: 225 (53%)
Indirectness of population	No indirectness
Interventions	(n=285) Intervention 1: IL-17 inhibitor – People received intravenous secukinumab dose of 10 mg per kilogram of body weight at baseline and weeks 2 and 4, followed by subcutaneous secukinumab at a dose of either 150 mg or 75 mg every 4 weeks thereafter. Concurrent medication/care: The concomitant use of oral glucocorticoids (at a dose of ≤10 mg per day of prednisone or its equivalent) and methotrexate (at a dose of ≤25 mg per week) was permitted, provided that the dose was stable Indirectness: No indirectness (n=143) Intervention 2: Placebo matched the intervention to maintain blinding. Concurrent medication/care: The concomitant use of oral glucocorticoids (at a dose of ≤10 mg per day of prednisone or its equivalent) and methotrexate (at a dose of ≤25 mg per week) was permitted, provided that the dose was stable Indirectness: No indirectness
Funding	Novartis Pharma

IL-17 inhibitor versus placebo in people who are bDMARD naïve

- ACR20 response at 24 weeks. RoB: vh
- ACR50 response at 24 weeks. RoB: vh
- ACR70 response at 24 weeks. RoB: vh
- Change in mTSS/SHS: van der Heijde modified Total Sharp Score (0-528) at 24 weeks. RoB: h

Study	FUTURE 2. McInnes 2015(13), Kavanaugh 2016(14), Coates 2018(15)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=397
Countries and setting	Conducted in 76 centres in USA, Australia, Belgium, Canada, Czech Republic, Germany, Poland, Puerto Rico, Russia, Thailand, UK.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 year study but randomisation was broken after 24 weeks
Method of assessment of guideline condition	CASPAR

Stratum	Overall
Subgroup analysis within study	This is an analysis of 258 people who were TNF inhibitor naïve in the study
Inclusion criteria	People with PsA fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) and active disease, defined as ≥ 3 tender and ≥ 3 swollen joints, despite previous treatment with conventional therapy.
Exclusion criteria	Patients were excluded if they had previously received biologics other than TNF inhibitors, or had received > 3 TNF inhibitors. Where applicable, TNF inhibitors were discontinued for 4–10 weeks before randomization.
Age, gender and ethnicity	Age - Mean (SD): 47 (12) and 49 (12). Gender (M:F): 122/136. Ethnicity: Not detailed
Further population details	Dactylitis: 95 (78 and 17) Enthesitis: 161 (119 and 42) Psoriasis ≥ 3% of BSA: 130 (99 and 31)
Indirectness of population	No indirectness
Interventions	(n=195) Intervention 1: IL-17 inhibitor – People were randomised to either secukinumab 300 mg (n=67), 150 mg (n=63), 75 mg (n=65) at baseline, and weeks 1, 2, 3, and 4, and every 4 weeks thereafter. Concurrent medication/care: Concomitant methotrexate (MTX; ≤ 25 mg per week) was permitted. Indirectness: No indirectness (n=63) Intervention 2: Placebo at baseline, and weeks 1, 2, 3, and 4, and every 4 weeks thereafter. At week 16 they were randomised to either 300 mg or 150 mg secukinumab. Concurrent medication/care: Concomitant methotrexate (MTX; ≤ 25 mg per week) was permitted. Indirectness: No indirectness
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people who are bDMARD naïve

- Enthesitis resolution at 24 weeks. RoB: h
- Dactylitis resolution at 24 weeks. RoB: h
- PASI response: ≥90% improvement at week at 24 weeks. RoB: h
- PASI response: ≥75% improvement at week at 24 weeks. RoB: h
- Mortality at 24 weeks. RoB: h
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 16 weeks. RoB: vh
- ACR20 response at 24 weeks. RoB: h
- ACR50 response at 24 weeks. RoB: h
- ACR70 response at 24 weeks. RoB: h

Study	FUTURE 3: Nash 2018(16)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=414

Countries and setting	Conducted in 77 centres in USA, Australia, Bulgaria, Canada, Czech Republic, Germany, Italy, Netherlands, Puerto Rico, Russia, Spain, Switzerland, UK.
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks double blind, placebo controlled treatment period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 282 (68%) people who were TNF inhibitor naïve at the beginning of the study
Inclusion criteria	Adults with active PsA despite treatment with NSAIDs, cDMARDs or TNF inhibitors.
Exclusion criteria	Previous use of any biological agent other than anti-TNF agents or the use of > 3 anti-TNF agents; active inflammatory diseases other than PsA; active infection in the 2 weeks before randomization, or a history of ongoing, chronic, or recurrent infections, or evidence of tuberculosis infection; history of malignant disease within the past 5 years (excluding basal cell carcinoma or actinic keratosis, in-situ cervical cancer, or noninvasive malignant colon polyps); and pregnancy.
Age, gender and ethnicity	Age - Mean (SD): 49 (13) and 50 (12) and 50 (13). Gender (M:F): 187/227. Ethnicity: White: 392 (95%), Asian: 9 (2%), American Indian or Alaska Native: 2 (0%), Other: 11 (3%)
Further population details	Dactylitis at baseline: 118(29%) Enthesitis at baseline: 281 (68%) Psoriasis ≥ 3% of BSA: 189 (46%)
Indirectness of population	No indirectness
Interventions	(n=189) Intervention 1: IL-17 inhibitor – 2 treatment groups. These were secukinumab 300 mg or secukinumab150 mg. People self-administered via autoinjector at baseline, weeks 1, 2, 3, 4 followed by treatment every 4 weeks from week 4. Concurrent medication/care: Concomitant use of oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and methotrexate (MTX; ≤ 25 mg/week) was allowed if the dose was stable for at least 2 weeks and 4 weeks before randomization, respectively. Indirectness: No indirectness (n=93) Intervention 2: Placebo - People self-administered via autoinjector at baseline, weeks 1, 2, 3, 4 followed by treatment every 4 weeks from week 4. Concurrent medication/care: Concomitant use of oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and methotrexate (MTX; ≤ 25 mg/week) was allowed if the dose was stable for at least 2 weeks and 4 weeks before randomization, respectively. Indirectness: No indirectness Early escape: At week 16, people were classified either as responders (≥ 20% improvement from baseline in both tender joint count (TJC) and swollen joint count (SJC)) or nonresponders. People in the placebo group were re-randomized to receive secukinumab 300 or 150 mg s.c. every 4 weeks at week 16.

Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people who are bDMARD naïve

- ACR20 response at 24 weeks. RoB: vh
- ACR50 response at 24 weeks. RoB: vh

Study	FUTURE 4: Kivitz 2019(17)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=341
Countries and setting	Conducted in 64 centres in USA, Australia, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Italy, Poland, Russia, Sweden, UK.
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks double blind, placebo controlled treatment period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 260 (76%) people who were TNF inhibitor naïve at the beginning of the study
Inclusion criteria	Adults with active PsA despite treatment with NSAIDs or c/bDMARDs.
Exclusion criteria	Previous exposure to secukinumab or any other biologic drug directly targeting the IL-17 or IL17 receptor. Also excluded were patients with active infection in the 2 weeks before randomization or those with a history of ongoing, chronic or recurrent infections, or evidence of tuberculosis infection or with active inflammatory diseases other than psoriatic arthritis. People with a history of malignant disease within the past 5 years (excluding basal cell carcinoma or actinic keratoses, in situ cervical cancer or non-invasive malignant colon polyps) and those having chest X-ray/magnetic resonance imaging (MRI) with evidence of an ongoing infectious or malignant process, obtained within 3 months prior to screening.
Age, gender and ethnicity	Age - Mean (SD): 48 (12) and 50 (12) and 49 (12). Gender (M:F): 143/198. Ethnicity: Not detailed
Further population details	Dactylitis at baseline: 122 (36%) Enthesitis at baseline: 216 (63%) Psoriasis ≥ 3% of BSA: 171 (50%)
Indirectness of population	No indirectness
Interventions	(n=173) Intervention 1: IL-17 inhibitor – 2 treatment groups: loading/no loading. Secukinumab 150 mg load at weeks 0, 1, 2 and 3 followed by dosing every 4 weeks starting at week 4 or secukinumab treatment at baseline followed by secukinumab dosing every 4 weeks from week 4. Concurrent medication/care: People on prescribed NSAIDs were required to be on a stable dose for at least 2 weeks before randomization and were required to remain on a stable

	dose up to week 24. Patients could continue to receive the following medications at a stable dose for at least 2 weeks: prednisone or equivalent (B 10 mg/day); methotrexate (B 25 mg/week). Indirectness: No indirectness (n=87) Intervention 2: Placebo - Concurrent medication/care: People on prescribed NSAIDs were required to be on a stable dose for at least 2 weeks before randomization and were required to remain on a stable dose up to week 24. Patients could continue to receive the following medications at a stable dose for at least 2 weeks: prednisone or equivalent (B 10 mg/day); methotrexate (B 25 mg/week). Indirectness: No indirectness Early escape: At week 16, people were classified either as responders in the placebo group received secukinumab 150 mg every 4 weeks at week 16.
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people who are TNF inhibitor naive

- ACR20 response at 16 weeks. RoB: h
- ACR50 response at 16 weeks. RoB: h

Study	FUTURE 5: Mease 2018(18)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=996
Countries and setting	Conducted in 172 centres in USA, Argentina, Austria, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Guatemala, Hungary, India, Ireland, Israel, Italy, Latvia, Lithuania, Mexico, Netherlands, Philippines, Russia, Spain, Sweden, Thailand, UK, Vietnam.
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks double blind, placebo controlled treatment period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 701 people who were TNF inhibitor naïve at the beginning of the study
Inclusion criteria	People with PsA fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) and active disease, defined as ≥ 3 tender and ≥ 3 swollen joints, despite previous treatment with NSAIDs, cDMARDs, of TNF Inhibitors. .
Exclusion criteria	Patients were excluded if they had previously received biologics other than TNF inhibitors, or had received > 3 TNF inhibitors. Where applicable, TNF inhibitors were discontinued for 4–10 weeks before randomization.
Age, gender and ethnicity	Age - Mean (SD): 49 (12). Gender (M:F): 500/496. Ethnicity: White: 816 (82%), Asian: 113 (11%), American Indian or Alaska Native: 6 (1%), Unknown: 4 (0%), Other: 47 (5%)

	Dactylitis at baseline: 389 (39%)
Further population details	Enthesitis at baseline: 602 (60%)
	Psoriasis ≥ 3% of BSA: 514 (52%)
Indirectness of population	No indirectness
Interventions	(n=469) Intervention 1: IL-17 inhibitor – 3 treatment groups. These were secukinumab 300 mg with loading dose (LD), secukinumab150 mg with LD, secukinumab 150 mg without LD. People self-administered their own treatment using prefilled syringes at baseline, weeks 1, 2 and 3 followed by treatment every 4 weeks from week 4. Patients in the secukinumab 150 mg without LD arm were administered placebo at weeks 1, 2 and 3 to conceal treatment allocation. Concurrent medication/care: Concomitant corticosteroids (≤10 mg/day prednisone or equivalent), NSAIDs and methotrexate (≤25 mg/week) were allowed, provided the dose was stable and remained so for the first 24 weeks of the study. Indirectness: No indirectness (n=234) Intervention 2: Placebo at baseline, and weeks 1, 2, 3, and 4, and every 4 weeks thereafter. People self-administered their own treatment using prefilled syringes at baseline, weeks 1, 2 and 3 followed by treatment every 4 weeks from week 4. At week 16, people with <20% improvement from baseline in tender and swollen joint counts (SJCs) were switched in a double-blind manner to receive secukinumab 300 mg or 150 mg, preassigned at original randomisation. Concurrent medication/care: Concomitant corticosteroids (≤10 mg/day prednisone or equivalent), NSAIDs and methotrexate (≤25 mg/week) were allowed, provided the dose was stable and remained so for the first 24 weeks of the study. Indirectness: No indirectness
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people who are bDMARD naïve

- ACR20 response at 16 weeks. RoB: h
- ACR50 response at 16 weeks. RoB: h
- ACR70 response at 16 weeks. RoB: h

Study	Genovese 2007(26)
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=100
Countries and setting	Conducted in 16 centres in USA and Canada.
Line of therapy	Not applicable
Duration of study	Intervention: 12 week double blind and placebo controlled period.
Method of assessment of guideline condition	Not detailed
Stratum	Overall
Subgroup analysis within study	None

Inclusion criteria	Adults with active PsA and chronic plaque psoriasis or documented history of psoriasis. They were using cDMARDs or had inadequate response to cDMARDs.
Exclusion criteria	Previous anti-TNF therapy; intravenous infusions or intraarticular injections of corticosteroids within 4 weeks of baseline; topical psoriasis therapies (e.g., keratolytics, coal tar, anthralin) within 2 weeks of baseline (although medicated shampoos and lowpotency topical steroid use on the palms, soles of the feet, axilla, and groin area were allowed); ultraviolet A (UVA) phototherapy, including psoralen and UVA, or use of a tanning booth within 2 weeks of the baseline visit; or oral retinoids within 4 weeks of the baseline visit, alefacept or siplizumab within 12 weeks, or any other biologic or investigational therapy within 6 weeks of the baseline visit.
Age, gender and ethnicity	Age – Mean (SD): 48 (11) and 50 (11). Gender (M:F): 54/46. Ethnicity: Caucasian: 96
Further population details	Use of cDMARD at baseline: 66
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: TNF inhibitor –subcutaneous injection of adalimumab 40 mg every 2 weeks. Concurrent medication/care: Oral corticosteroids were allowed during the trial if the dosage did not exceed the equivalent of prednisone 10 mg/day and had been stable during the 4 weeks preceding the baseline visit. Concomitant treatment with MTX or other cDMARD, with the exception of cyclosporine and tacrolimus (oral or topical) received within 4 weeks of the baseline visit, was allowed if the patient had received a minimum of 3 months of therapy and the dosage had been stable during the 4 weeks preceding the baseline visit. Indirectness: No indirectness (n=50) Intervention 2: Placebo administrated every 2 weeks. Concurrent medication/care: Oral corticosteroids were allowed during the trial if the dosage did not exceed the equivalent of prednisone 10 mg/day and had been stable during the 4 weeks preceding the baseline visit. Concomitant treatment with MTX or other cDMARD, with the exception of cyclosporine and tacrolimus (oral or topical) received within 4 weeks of the baseline visit, was allowed if the patient had received a minimum of 3 months of therapy and the dosage had been stable during the 4 weeks preceding the baseline visit. Indirectness: No indirectness
Funding	No funding (No external funding)

TNF inhibitor versus placebo

- ACR20 response at 12 weeks. RoB: low
- ACR50 response at 12 weeks. RoB: low
- ACR70 response at 12 weeks. RoB: low
- People achieving clear/almost clear status at 12/24 weeks in people with psoriasis at baseline. RoB: h
- SF-36 physical component score. RoB: h
- SF-36 mental component score. RoB: h
- Serious adverse events. RoB: low

Study	GO-DACT: Viera-Sousa 2020(27)

Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=397
Countries and setting	Conducted in 11 rheumatology centres in Portugal.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 week double blind and placebo controlled period. After the last golimumab injection, each subject was monitored for safety for 60 days.
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 258 people who were TNF inhibitor naïve in the study
Inclusion criteria	Adults with PsA fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) and active disease, ≥1 digit with tender dactylitis and ≥1 other site of active inflammation (joints, enthesis, spine, skin or nails), naive to MTX and bDMARDs therapy and refractory to at least two NSAIDs at optimal dosage for 3 months.
Exclusion criteria	Contraindications for the use of any TNFi or MTX, and factors that could interfere with trial evaluations or patient safety. A maximum of two previous local corticosteroids injections were allowed, administrated at least 4 weeks prior to screening. NSAIDs dose had to be stable throughout the trial. Cessation of other csDMARDs and corticosteroids, according to their recommended washout periods, was required.
Age, gender and ethnicity	Age – Median (IQR): 46 (20). Gender (M:F): 37/7. Ethnicity: Not detailed
Further population details	Dactylitis at basleine: 44 (100%) Enthesitis at baseline: 23 (52%)
Indirectness of population	No indirectness
Interventions	(n=195) Intervention 1: TNF inhibitor –50 mg golimumab administrated every 4 weeks for 24 weeks. Concurrent medication/care: methotrexate orally, 15 mg/week and increased 5 mg every 4 weeks until a maximum dose of 25 mg/week, as tolerated. Indirectness: No indirectness (n=63) Intervention 2: Placebo administrated every 4 weeks for 24 weeks Concurrent medication/care: methotrexate orally, 15 mg/week and increased 5 mg every 4 weeks until a maximum dose of 25 mg/week, as tolerated. Indirectness: No indirectness
Funding	No funding (No external funding)

IL-17 inhibitor versus placebo in people who are bDMARD naïve

- ACR20 response at 24 weeks. RoB: low
- ACR50 response at 24 weeks. RoB: low
- ACR70 response at 24 weeks. RoB: low
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 24 weeks. RoB: h
- Enthesitis resolution at 24 weeks. RoB: h

- Dactylitis resolution at 24 weeks. RoB: low
- PASI response: ≥50% improvement at week at 24 weeks. RoB: h
- PASI response: ≥90% improvement at week at 24 weeks. RoB: h
- PASI response: ≥75% improvement at week at 24 weeks. RoB: h

Study	GO-REVEAL: Kavanaugh 2009(28)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=405
Countries and setting	Conducted in 52 centres across USA, Belgium, Canada, Poland, Spain, UK.
Line of therapy	Not applicable
Duration of study	Intervention: Double bind period of the study was 24 weeks
Method of assessment of guideline condition	Not stated
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	People with active PsA despite therapy with cDMARD or nonsteroidal antiinflammatory drugs (NSAIDs).
Exclusion criteria	Previous use of anti-TNF agents, rituximab, natalizumab, or cytotoxic agents.
Age, gender and ethnicity	Age - Mean (SD): 47 (11) and 46 (11) and 48 (11). Gender (M:F): 244/161. Ethnicity: Caucasian: 97%
Further population details	Spondylitis with peripheral arthritis: 44 (11%) People with dactylitis at baseline: 137 (34%) People with enthesitis at baseline: 312 (77%) People with ≥3% body area involvement with psoriasis: 303 (75%)
Indirectness of population	No indirectness
Funding	Centocor Research and Development, Inc. and Schering-Plough.
Interventions	(n=292) Intervention 1: TNF inhibitors – subcutaneous injections of either golimumab 50 mg, or golimumab 100 mg a weeks 0, 4, 8, 12, 16, and 20. Concurrent medication/care: care. Stable doses of methotrexate (MTX), NSAIDs, and corticosteroids (prednisone ≤ 10 mg/day) were allowed. Indirectness: no indirectness. (n=113) Intervention 2: Placebo - subcutaneous injections at weeks 0, 4, 8, 12, 16, and 20. Concurrent medication/care: care. Stable doses of methotrexate (MTX), NSAIDs, and corticosteroids (prednisone ≤ 10 mg/day) were allowed. Indirectness: no indirectness.

	Early escape At week 16, patients with <10% improvement from baseline in both the swollen and tender joint counts entered early escape, with dose escalation from placebo to golimumab 50 mg or from golimumab 50 mg to golimumab 100 mg. Patients in the golimumab 100 mg group meeting early escape criteria continued with the 100-mg dose in a blinded manner.

TNF inhibitors versus placebo

- ACR20 response at week 14. RoB: low
- PASI response: ≥75% improvement at week 14 in people with psoriasis at baseline. RoB: h
- Serious adverse events at 24 weeks: RoB: low
- Change in SF-36 mental component score at 14 weeks: RoB: low
- Change in SF-36 physical component score at 12/14/16/24 weeks. RoB: low

Study	GO-VIBRANT: Kavanaugh 2017(29), Kavanaugh 2019(30)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=480
Countries and setting	Conducted in 90 centres across Belarus, Canada, Germany, Hungary, Lithuania, Poland, Romania, Russia, Spain, Ukraine, USA.
Line of therapy	Not applicable
Duration of study	Intervention: Double bind period of the study was 24 weeks
Method of assessment of guideline condition	Classification Criteria for Psoriatic Arthritis
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults with active PsA with a diagnosis for at least 6 months.
Exclusion criteria	Previous biologic therapy for PsA.
Age, gender and ethnicity	Age - Mean (SD): 47 (13) and 46 (11). Gender (M:F): 249/231. Ethnicity: Not detailed
Further population details	People with dactylitis at baseline: 258 People with enthesitis at baseline: 366 People with investigator assessed spondylitis at baseline: 109 People with ≥3% body area involvement with psoriasis: 394
Indirectness of population	No indirectness

Interventions	(n=241Intervention 1: TNF inhibitors – Infusion of 2 mg/kg golimumab at weeks 0 and 4 and every 8 weeks. Concurrent medication/care: care. Concomitant use of methotrexate (MTX) (≤25 mg/week) was permitted for people who had been receiving MTX for ≥3 months before the first golimumab administration; MTX doses had to have remained stable for ≥4 weeks. People could receive concomitant oral corticosteroids if they had been receiving a stable dose (≤10 mg prednisone/day) for ≥2 weeks prior to the first golimumab administration. People were also permitted to receive concomitant NSAIDs at the usual approved marketed doses if they had received stable doses for ≥2 weeks prior to the first golimumab administration. Indirectness: no indirectness. (n=239) Intervention 2: Placebo - Infusions at weeks 0 and 4 and every 8 weeks. Concurrent medication/care: Concomitant use of methotrexate (MTX) (≤25 mg/week) was permitted for people who had been receiving MTX for ≥3 months prior to entry in the study; MTX doses had to have remained stable for ≥4 weeks. People could receive concomitant oral corticosteroids if they had been receiving a stable dose (≤10 mg prednisone/day) for ≥2 weeks prior to entry in the study administration. People were also permitted to receive concomitant NSAIDs at the usual approved marketed doses if they had received stable doses for ≥2 weeks prior to entry in the study. Indirectness: no indirectness. Early escape At week 16, people in either treatment groups with <5% improvement in swollen and tender joint counts entered early escape and were allowed one of the following changes in treatment at the investigator's discretion: an increase in corticosteroid dose (total dose ≤10 mg/day prednisone or equivalent), MTX dose (total dose ≤25 mg/week), or NSAID dose; or initiation of NSAIDs, corticosteroids (≤10 mg/day prednisone or equivalent), MTX (≤25 mg/week), sulfasalazine (≤3 gm/day), hydroxychloroquine (≤400 mg/day), or leflunomide
Funding	Janssen Research & Development LLC

TNF inhibitors versus placebo outcomes:

- Mortality at week 24. RoB: low
- Change in SF-36 mental component score at 14 weeks. RoB: low
- Change in SF-36 physical component score at 14 weeks. RoB: low
- ACR20 response at week 14. RoB: low
- ACR50 response at week 14. RoB: low
- ACR70 response at week 14. RoB: low
- BASDAI20 response at 14 weeks in people with spondylitis and peripheral joint involvement. RoB: h
- LEI: Leeds Enthesitis Index in perople with enthesitis at baseline. RoB: h
- mTSS/SHS: van der Heijde modified Total Sharp Score at 24 weeks. RoB: low.
- PASI response: ≥75% improvement at week 14. RoB: h
- PASI response: ≥90% improvement at week 14. RoB: h

- Serious adverse events at 24 weeks. RoB: h

Study	IMPACT 1: Antoni 2005(31)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=104
Countries and setting	Conducted in 9 centres in Europe, USA and Canada.
Line of therapy	Not applicable
Duration of study	Intervention: Intervention versus placebo for 16 weeks
Method of assessment of guideline condition	Not detailed
Stratum	Overall
Subgroup analysis within study	People with psoriasis at baseline
Inclusion criteria	Adults with an established diagnosis of active PsA of 6 months duration or longer. Active articular disease was defined as five or more swollen joints and five or more tender joints and either C reactive protein (CRP) levels of at least 15 mg/l and/ or morning stiffness lasting 45 minutes or longer. They were required to have previous failure of treatment with at least 1 DMARDs and a negative serum tests for rheumatoid factor and negative results for active or latent tuberculosis.
Exclusion criteria	Not detailed
Age, gender and ethnicity	Age - Mean (SD): 46 (11) and 45 (10). Gender (M:F): 44/60. Ethnicity: Not detailed
Further population details	People with dactylitis: 51 People with enthesopathy: 26 People with PASI ≥2.5: 39
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: TNF inhibitors – Infusions of infliximab 5 mg/kg at weeks 0, 2, 6 and 14. Concurrent medication/care: People were allowed to receive stable concomitant therapy with 1 of the following DMARDs: methotrexate (MTX; dosage of 15 mg/week or more, with folic acid supplementation), leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, penicillamine, or azathioprine. Concomitant therapy with oral corticosteroids (dosage of 10 mg prednisone equivalent/day or less) and nonsteroidal antiinflammatory drugs (NSAIDs) was permitted, provided that dosages had been stable for at least 2 weeks prior to screening. Dosages of corticosteroids and NSAIDs were required to remain stable throughout the study. Use of intramuscular or intravenous corticosteroids, cyclosporine, or tacrolimus was prohibited within 4 weeks of screening and throughout the study. One injection of intraarticular corticosteroids was permitted in phase 2 of the study, and the injected joint would be excluded from subsequent efficacy assessment. Standard topical treatments for psoriatic lesions (e.g., topical

	steroids) were permitted, provided they remained stable throughout the study. Therapy with psoralen ultraviolet A was not permitted. Eligible patients could not have received any investigational drug within 3 months of screening or any previous treatment with a monoclonal antibody or fusion protein. (n=52) Intervention 2: Placebo - Infusions at weeks 0, 2, 6 and 14. Concurrent medication/care: People were allowed to receive stable concomitant therapy with 1 of the following DMARDs: methotrexate (MTX; dosage of 15 mg/week or more, with folic acid supplementation), leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, penicillamine, or azathioprine. Concomitant therapy with oral corticosteroids (dosage of 10 mg prednisone equivalent/day or less) and nonsteroidal antiinflammatory drugs (NSAIDs) was permitted, provided that dosages had been stable for at least 2 weeks prior to screening. Dosages of corticosteroids and NSAIDs were required to remain stable throughout the study. Use of intramuscular or intravenous corticosteroids, cyclosporine, or tacrolimus was prohibited within 4 weeks of screening and throughout the study. One injection of intraarticular corticosteroids was permitted in phase 2 of the study, and the injected joint would be excluded from subsequent efficacy assessment. Standard topical treatments for psoriatic lesions (e.g., topical steroids) were permitted, provided they remained stable throughout the study. Therapy with psoralen ultraviolet A was not permitted. Eligible patients could not have received any investigational drug within 3 months of screening or any previous treatment with a monoclonal antibody or fusion protein T.
Funding	Supported in part by the NIH (grant M01-RR-00827 to the University of California, San Diego), an unrestricted grant from Centocor, Inc., to the University of Erlangen, Erlangen, Germany, and by the Schering-Plough Research Institute.

TNF inhibitors versus placebo outcomes:

TNF inhibitors versus placebo outcomes:

- ACR20 response at week 16. RoB: vh
- ACR50 response at week 16. RoB: vh
- ACR70 response at week 16. RoB: vh
- Dactylitis score over 0 at week 16. RoB: h
- Entesitis at week 16. RoB: h
- PASI response: ≥75% improvement at week 14 PASI response: ≥50% improvement at week 14: RoB: vh
- Serious adverse events at week 16. RoB: h

Study	IMPACT 2: Antoni 2005(32)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=200
Countries and setting	Conducted in 36 centres. 19 in USA, 9 in Europe, 8 in Canada.
Line of therapy	Not applicable

Duration of study	Intervention: 24 weeks
Method of assessment of guideline condition	Not detailed
Stratum	Overall
Subgroup analysis within study	People with psoriasis or dactylitis at baseline
Inclusion criteria	People with active PsA diagnosed at least 6 months before the first study drug infusion. Active articular disease was defined as five or more swollen joints and five or more tender joints and either C reactive protein (CRP) levels of at least 15 mg/l and/ or morning stiffness lasting 45 minutes or longer. People were required to have had an inadequate response to current or previous DMARDs or non-steroidal anti-inflammatory drugs (NSAIDs). In addition, people had to have active plaque psoriasis with at least one qualifying target lesion at least 2 cm in diameter. They were required to have a negative test for rheumatoid factor in their serum.
Exclusion criteria	Evidence of latent or active tuberculosis. Chronic or clinically significant infection, malignancy, or congestive heart failure. Previous use of TNF inhibitor.
Age, gender and ethnicity	Age - Mean (SD): 47 (11) and 47 (13). Gender (M:F): 78/200. Ethnicity: Not detailed
Further population details	Dactylitis at baseline: 81 (41 and 40) In people with ≥3% BSA affected with psoriasis: 170 (83 and 87) Baseline medication MTX: 46% Oral corticosteroids: 13% NSAIDs: 72%
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: TNF inhibitors – Infusions of infliximab 5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing at weeks 14 and 22. Concurrent medication/care: Concomitant methotrexate (MTX) treatment (up to 25 mg/week) was allowed at least 3 months before the first infusion and was maintained at a stable dose for at least 4 weeks before first infusion. Oral corticosteroid use was permitted at a stable dose equivalent to no more than 10 mg prednisone a day. The use of DMARDs (other than MTX) or intra-articular corticosteroids was prohibited within 4 weeks before the first infusion, and DMARD use other than MTX was not allowed during the trial. Concurrent use of topical or systemic drugs/ treatments for psoriasis was not permitted during the study, with the exception of low potency topical corticosteroids on the face or groin. (n=100) Intervention 2: General and regional - Infusions of placebo at weeks 0, 2, 6, 14 and 22. People with <10% improvement from baseline in both swollen and tender joint counts were entered into “early escape” to receive infliximab 5 mg/kg at weeks 16, 18, and 22.

Concurrent medication/care: Concomitant methotrexate (MTX) treatment (up to 25 mg/week) was allowed at least 3 months before the first infusion and was maintained at a stable dose for at least 4 weeks before first infusion. Oral corticosteroid use was permitted at a stable dose equivalent to no more than 10 mg prednisone a day. The use of DMARDs (other than MTX) or intra-articular corticosteroids was prohibited within 4 weeks before the first infusion, and DMARD use other than MTX was not allowed during the trial. Concurrent use of topical or systemic drugs/ treatments for psoriasis was not permitted during the study, with the exception of low potency topical corticosteroids on the face or groin.

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Funding: The IMPACT 2 study was funded by Centocor, Inc, in Malvern, Pennsylvania, USA and Schering-Plough in Kenilworth, NJ, USA.

TNF inhibitors versus placebo outcomes:

- Quality of life: Change in SF-36 physical component at week 14. RoB: h
- Quality of life: Change in SF-36 mental component at week 14. RoB: h
- ACR20 response at week 14. RoB: h
- ACR50 response at week 14. RoB: h
- ACR70 response at week 14. RoB: h
- ≥1 dactylitis digits at week 14. RoB: vh
- Enthesopathy at week 14. RoB: vh
- PASI response: ≥50% improvement at week 14 RoB: h

Adverse events reported until 16 weeks for placebo and 24 weeks for intervention and were not extracted.

Study	Mease 2000(33)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=60
Countries and setting	Unclear though appears to be a single centre in USA
Line of therapy	Not applicable
Duration of study	Intervention: Randomised treatment for 12 weeks
Method of assessment of guideline condition	Active psoriatic arthritis (defined as ≥3 swollen joints and ≥3 tender or painful joints)
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults up to 70 years of age with active psoriatic arthritis who had an inadequate response to NSAIDs.

	People were allowed to use methotrexate though other DMARDs were discontinued. Corticosteroids were allowed if the dose was less than or equal to 10 mg/day of prednisone, stable for at least 2 weeks before the first dose of study drug, and maintained at a constant dose throughout the study. Topical therapies and oral retinoids for psoriasis were discontinued at least 2 weeks before the baseline evaluation and phototherapy was discontinued at least 4 weeks before treatment. All patients were required to have hepatic transaminase concentrations no greater than twice the upper limit of normal, haemoglobin 85 g/L or higher, platelet count 125000 per mL or more, and serum creatinine 152·4 mmol/L or below.
Exclusion criteria	People with evidence of skin conditions other than psoriasis (such as eczema).
Age, gender and ethnicity	Age - Median (range): 44 (24-63) and 46 (30-70). Gender (M:F): 34/26. Ethnicity: White: 87%
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 38 (63%)
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: TNF inhibitor – etanercept at a dose of 25 mg twice weekly by subcutaneous administration. Concurrent medication/care: People with prior use of methotrexate were allowed to continue. No indirectness (n=30) Intervention 2: Placebo. Concurrent medication/care: People with prior use of methotrexate were allowed to continue. Indirectness: No indirectness
Funding	Grant support from the Immunex Corporation.

TNF inhibitor versus placebo

- ACR20 response at week 12. RoB: h
- ACR50 response at week 12. RoB: h
- ACR70 response at week 12. RoB: h
- PASI response: ≥75% improvement at week 12. RoB: vh
- Serious adverse events at 12 weeks. RoB: h

Study	NCT00534313: Mease 2011(3)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=170
Countries and setting	Conducted in 44 centres in USA, Argentina, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Norway, South Africa, and Spain.
Line of therapy	Not applicable
Duration of study	Intervention: Double blind, placebo controlled treatment for 24 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	Outcomes were extracted where reported for people without prior exposure to TNF inhibitors: N=125 (74%)

Inclusion criteria	Adults with active PsA, active plaque psoriasis, and a disease duration of at least 3 months. They were required to have prior inadequate response to DMARDs.
Exclusion criteria	Use of any investigational drug within 28 days before randomization, any prior treatment with abatacept, evidence of latent or active tuberculosis, or evidence of chronic or clinically significant infection or malignancy. Women who were pregnant or lactating were also excluded.
Age, gender and ethnicity	Age – Mean (SD): 52 (10) and 51 (11) and 50 (10) and 53 (12). Gender (M:F): 91/79. Ethnicity: Caucasian: 98%
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 83 (49%%) Concomitant medications: 88%
Indirectness of population	No indirectness
Interventions	(n=95) Intervention 1: Abatacept – 3 treatment groups. Treatments were administered as 30-minute intravenous infusions on days 1, 15, and 29, and every 28 days thereafter. The 3 dosing regimens were 3 mg/kg (calculated based on body weight at screening); 10 mg/kg (currently approved weight-tiered dosing for RA is 500 mg for patients weighing <60 kg, 750 mg for those weighing 60–100 kg, and 1,000 mg for those weighing >100 kg); and 30/10 mg/kg dose (30 mg/kg [calculated based on body weight at screening] given on days 1 and 15, followed by the weight tiered dose of 10 mg/kg). Concurrent medication/care: Aside from MTX, no DMARD was continued during the 6-month double-blind treatment period. MTX was continued at a stable dosage only if it had been taken at a stable dosage for >3 months prior to screening. A decrease in the MTX dosage was allowed in cases of toxicity. The dosage of nonsteroidal antiinflammatory drug (NSAID) remained unchanged throughout the study unless a decrease in dosage was required because of toxicity. Concomitant corticosteroid treatment was allowed if the dosage (no more than 10 mg of prednisone or its equivalent) had been stable for >28 days.. No indirectness (n=30) Intervention 2: Placebo. Concurrent medication/care: Aside from MTX, no DMARD was continued during the 6-month double-blind treatment period. MTX was continued at a stable dosage only if it had been taken at a stable dosage for >3 months prior to screening. A decrease in the MTX dosage was allowed in cases of toxicity. The dosage of nonsteroidal antiinflammatory drug (NSAID) remained unchanged throughout the study unless a decrease in dosage was required because of toxicity. Concomitant corticosteroid treatment was allowed if the dosage (no more than 10 mg of prednisone or its equivalent) had been stable for >28 days. Indirectness: No indirectness
Funding	Bristol-Myers Squibb

Abatacept versus placebo in people not previously exposed to TNF inhibitors

- ACR20 response at week 24. RoB: vh

Study	NCT01516957: Mease 2014(19)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=168
Countries and setting	Conducted in 29 centres in USA and Canada.

Line of therapy	Not applicable
Duration of study	Intervention: Double blind, placebo controlled treatment for 12 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	Outcomes were extracted where reported for people without prior exposure to biologics: N= 92 (55%)
Inclusion criteria	People 18-75 years old with active PsA. They must be on a stable dose of cDMARDs or NSAIDs. A washout period was required for people using TNF inhibitors or IL-12/23 inhibitors
Exclusion criteria	People who had used rituximab or IL-17 therapy. Recent infection (active infection within 28 days or serious infection within 8 weeks), recurrent infections, major chronic inflammatory or connective-tissue disease, clinically significant systemic disease, or a history of cancer (other than in situ cervical cancer, in situ breast ductal cancer, or successfully treated nonmelanoma skin cancers) within the past 5 years.
Age, gender and ethnicity	Age – Mean (SD):53 (13) and 52 (11). Gender (M:F): 61/107. Ethnicity: white: 157 (93%)
Further population details	Enthesitis at baseline: 118 (70%) Dactylitis at baseline: 104 (62%)
Indirectness of population	No indirectness
Interventions	(n=52) Intervention **1**: IL17 inhibitor – 2 groups using brodalumab at 140 mg or 280 mg by subcutaneous injection on day 1 and at weeks 1, 2, 4, 6, 8, and 10. Concurrent medication/care: NSAIDs could be used to treat flares. It was unclear whether previous cDMARDs were continued. No indirectness (n=40) Intervention 2: Placebo. by subcutaneous injection on day 1 and at weeks 1, 2, 4, 6, 8, and 10. Concurrent medication/care: NSAIDs could be used to treat flares. It was unclear whether previous cDMARDs were continued. No indirectness
Funding	Amgen

IL17 inhibitor versus placebo in people not previously exposed to biologics

- ACR20 response at week 12. RoB: vh
- ACR50 response at week 12. RoB: vh
- ACR70 response at week 12. RoB: vh

Study	NCT01871649: van Mens 2019(34)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=51
Countries and setting	Conducted in the Netherlands; Setting: 3 centres..
Line of therapy	Not applicable

Duration of study	Intervention: Double blind, randomised treatment until week 22
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	People 18-70 years old with active PsA.
Exclusion criteria	Previous treatment with methotrexate or bDMARDs. Previous experience of anti-TNF inhibitors. Presence of latent or active tuberculosis, malignancy in the past 5 years (other than basal cell carcinoma of the skin), Recent severe infections or other severe diseases that may affect patient's participation to the study in the opinion of the investigator.
Age, gender and ethnicity	Age - Mean (SD): 48 (12) and 46 (11). Gender (M:F): 38/13. Ethnicity: Not detailed
Further population details	Enthesitis at baseline: 11 (22%) Dactylitis at baseline: 17 (33%)
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: TNF inhibitor –golimumab (50 mg subcutaneous monthly). Concurrent medication/care: MTX was started at 15 mg/week orally and increased to 25 mg/week over 8 weeks. Indirectness: No indirectness (n=25) Intervention 2: Placebo – matching intervention for blinding. Concurrent medication/care: MTX was started at 15 mg/week orally and increased to 25 mg/week over 8 weeks. Indirectness: No indirectness
Funding	Grant from MSD

TNF inhibitor versus placebo

- ACR20 response at 22 weeks. RoB: h
- ACR50 response at 22 weeks. RoB: h
- ACR70 response at 22 weeks. RoB: h
- MDA: Minimal disease activity at 22 weeks. RoB: h
- Median (IQR) BASDAI: Bath Ankylosing Spondylitis Disease Activity Index at 22 weeks. RoB:h
- Serious adverse events. RoB: h

Study	NCT02319759: Deodhar 2018(21)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=149

Countries and setting	Conducted in Canada, Germany, Poland, Romania, Russia, Spain, USA. USA; Setting: 34 rheumatology and dermatology practices.
Line of therapy	Not applicable
Duration of study	Intervention: Randomised treatment until week 24 with ongoing treatment for 52 weeks
Method of assessment of guideline condition	Diagnosed for at least 6 months who met Classification Criteria for Psoriatic Arthritis
Stratum	Overall
Subgroup analysis within study	Outcomes in subgroup of people (n=135) who were TNF inhibitor naïve were extracted
Inclusion criteria	Adults with psoriatic arthritis with three or more of 66 tender joints and three or more of 68 swollen joints at screening and baseline. Also they had C-reactive protein (CRP) concentration of at least 0·3 mg/dL, with at least 3% body surface area affected by plaque psoriasis, and an inadequate response to, or intolerance of, standard therapies (≥3 months of non-biologic disease-modifying antirheumatic drugs [DMARDs] or ≥4 weeks of oral corticosteroids or nonsteroidal anti-inflammatory drugs [NSAIDs]). People exposed to one previous anti-TNF-α drug were permitted, but limited to 20% of participants, following 8–12 weeks of washout from any previous anti-TNF-α treatment. Stable doses of concomitant methotrexate (≤25 mg per week), oral corticosteroids (≤10 mg per day of prednisone or equivalent), and NSAIDs during the first 24 weeks of the study were permitted.
Exclusion criteria	People with other inflammatory diseases, those who had previously been treated with guselkumab or ustekinumab, and people receiving other DMARDs and biologics.
Age, gender and ethnicity	Age - Mean (SD): 47 (13) and 44 (12). Gender (M:F): 76/73. Ethnicity: Not detailed
Further population details	Previous experience of anti-TNF inhibitors: 13 Enthesitis at baseline: 97 Dactylitis at baseline: 81
Indirectness of population	No indirectness
Interventions	(n=91) Intervention 1: IL23 inhibitor –100 mg guselkumab subcutaneously injected at week 0, week 4, and then every 8 weeks. Indirectness: No indirectness (n=44) Intervention 2: Placebo - placebo subcutaneously injected at week 0, week 4, and then every 8 weeks. Indirectness: No indirectness. Early escape All people with less than 5% improvement in swollen and tender joint counts at week 16 were eligible for early escape to open-label ustekinumab.
Funding	Janssen Research & Development.
IL23 inhibitor versus placebo	

- Mortality at 24 weeks. RoB: h
- ACR20 response at 24 weeks. RoB: h

Study	OPAL Broaden: Mease 2017(23)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=422
Countries and setting	Conducted in USA, Australia, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Mexico, Poland, Russia, Slovakia, Spain, Taiwan, UK; Setting: 123 centres.
Line of therapy	Not applicable
Duration of study	Intervention: Randomised treatment for 12 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults who had received a diagnosis of psoriatic arthritis at least 6 months previously and had previously had an inadequate response to at least one conventional synthetic DMARD.
Exclusion criteria	Previous exposure to TNF inhibitor treatment.
Age, gender and ethnicity	Age - Mean (SD): 47 (13) and 44 (12). Gender (M:F): 76/73. Ethnicity: Not detailed
Further population details	Previous exposure of anti-TNF inhibitors: 13 Enthesitis (LEI) at baseline: 280 (66%) Dactylitis at baseline: 237 (56%) Psoriasis involvement of body surface area ≥ 3% at baseline: 172 (41%)
Indirectness of population	11 (3%) were previously exposed to b/tsDMARDs.
Interventions	(n=211) Intervention 1: JAK inhibitor – Two tofacitinib groups where people either used a dose of 5 mg or 10 mg taken orally twice daily. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide Indirectness: No indirectness (n=104) Intervention 2: TNF inhibitor - 40 mg adalimumab administered subcutaneously once every 2 weeks Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide. Indirectness: No indirectness (n=104) Intervention 3: Placebo - placebo subcutaneously injected at week 0, week 4, and then every 8 weeks. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide. Indirectness: No indirectness

Funding Pfizer

JAK inhibitor versus TNF inhibitor

- ACR20 response at week 12
- ACR50 response at week 12
- ACR70 response at week 12
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks
- Enthesitis absence at 12 weeks in people with enthesitis at baseline
- Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline.
- PASI response: ≥75% improvement at week 12
- Serious adverse events at 12 weeks
- LEI: Leeds Enthesitis Index in at 12 weeks in people with enthesitis at baseline

JAK inhibitor versus placebo

- ACR20 response at week 12
- ACR50 response at week 12
- ACR70 response at week 12
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks
- Enthesitis absence at 12 weeks in people with enthesitis at baseline
- Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline.
- PASI response: ≥75% improvement at week 12
- Serious adverse events at 12 weeks
- LEI: Leeds Enthesitis Index in at 12 weeks in people with enthesitis at baseline

TNF inhibitor versus placebo

- ACR20 response at week 12
- ACR50 response at week 12
- ACR70 response at week 12
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks
- Enthesitis absence at 12 weeks in people with enthesitis at baseline
- Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline.
- PASI response: ≥75% improvement at week 12
- Serious adverse events at 12 weeks
- LEI: Leeds Enthesitis Index in at 12 weeks in people with enthesitis at baseline

Study	PALACE 1: Kavanaugh 2014(5)

Study type	RCT (Patient randomised; Parallel)
Number of participants	n=504
Countries and setting	Conducted in USA, Australia, Austria, Canada, France, Germany, Hungary, New Zealand, Poland, Russia, South Africa, Spain, UK. Setting: 92 centres
Line of therapy	Not applicable
Duration of study	Intervention: placebo controlled for 24 weeks with “early escape” at 16 weeks.
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Outcomes in the subgroup of bDMARD naïve people were extracted. This was 373 (74%) of the people in the study.
Inclusion criteria	Adults with a documented diagnosis of active PsA with duration ≥ 6 months. They were required to have had previous treatment with cDMARDs and/or bDMARDs. People using cDMARDs must have been on a stable dose for 16 weeks prior to entering the study.
Exclusion criteria	Failure of more than three agents for PsA (DMARDs or biologics) or >1 TNF inhibitor. People were also excluded if they had a history of or current (1) inflammatory, rheumatic or autoimmune joint disease other than PsA; (2) erythrodermic, guttate or generalised pustular psoriasis; (3) were functional class IV, defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis; (4) had used phototherapy or DMARDs other than methotrexate, leflunomide or sulfasalazine within 4 weeks of randomisation; (5) had used adalimumab, etanercept, golimumab, infliximab, certolizumab pegol or tocilizumab within 12 weeks of randomisation or alefacept or ustekinumab within 24 weeks of randomisation; or (6) had prior treatment with apremilast. Topical therapy for psoriasis within 2 weeks of randomisation was not permitted. Patients with active tuberculosis or a history of incompletely treated tuberculosis could not participate.
Age, gender and ethnicity	Age - Mean (SD): 51 (12) and 48 (11) and 51 (120). Gender (M:F): 249/255. Ethnicity: Not detailed
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 227 (45%) Baseline cDMARD use: 327 (65%) Enthesitis at baseline: 315 (62%) Dactylitis at baseline: 197 (39%)
Indirectness of population	No indirectness
Interventions	(n=336, of whom 253 were bDMARD naïve) Intervention 1: Apremilast – people were randomised to either 20 mg BID or 30 mg BID. Dose titrated over first week until target does reached. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. Indirectness: No indirectness

	(n=168, of whom 120 were bDMARD naïve) Intervention 2: Placebo – Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. Indirectness: No indirectness Early escape: People whose swollen and tender joint counts had not improved by ≥20% were considered non-responders at week 16 and were required to enter the protocol defined early escape. People receiving placebo were re-randomised (1:1) to apremilast 20 mg BID or 30 mg BID, while those on apremilast remained on their initial apremilast dose.
Funding	Study sponsored by Celgene Corp.

Apremilast versus placebo in people who were bDMARD naive

- ACR20 response at week 16. RoB: vh

Study	PALACE 2: Cutolo 2016(6)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=484
Countries and setting	Conducted in USA, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Hungary, Italy, Poland, Russia, South Africa, Spain, Taiwan. UK.
Line of therapy	Not applicable
Duration of study	Intervention: placebo controlled for 24 weeks with “early escape” at 16 weeks.
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Outcomes in the subgroup of bDMARD naïve people were extracted
Inclusion criteria	Adults with a documented diagnosis of PsA with duration ≥ 6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR). They had to have ≥ 3 swollen and ≥ 3 tender joints despite prior treatment with csDMARD and/or bDMARD or concurrent treatment with csDMARD.
Exclusion criteria	People with prior therapeutic failure of > 3 agents for PsA (csDMARD or bDMARD) or > 1 TNF inhibitor were ineligible. People could not have used phototherapy within 4 weeks, bDMARD (including adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab) within 12 weeks, or alefacept and ustekinumab within 24 weeks of randomization. Other exclusions were prior apremilast treatment, active tuberculosis (TB), history of incompletely

	treated TB, or significant infection within 4 weeks of screening, erythrodermic, guttate, or generalized pustular psoriasis.
Age, gender and ethnicity	Age - Mean (SD): 51 (11) and 51 (12). Gender (M:F): 309/275. Ethnicity: Not detailed
Further population details	Baseline cDMARD use: 70% Baseline enthesitis: 312 Baseline dactylitis: 216
Indirectness of population	No indirectness
Interventions	(n=325, of whom 269 were bDMARD naïve) Intervention 1: Apremilast – people were randomised to either 20 mg BID or 30 mg BID. Dose titrated over first week until target does reached. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. These were permitted as background therapy, except ≤ 24 h before each study visit: low-potency topical glucocorticoids for treatment of face, axillae, and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions, and nonmedicated emollient for body lesions. Topical therapies for psoriasis, except those permitted for background therapy, were not allowed, including topical glucocorticoids, topical retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin; immunosuppressive systemic therapy, including cyclosporine, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, and fumaric acid esters; and phototherapy (ultraviolet B, psoralen + ultraviolet A). Indirectness: No indirectness (n=359, of whom 135 were bDMARD naïve) Intervention 2: Placebo – no details of blinding. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. These were permitted as background therapy, except ≤ 24 h before each study visit: low-potency topical glucocorticoids for treatment of face, axillae, and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions, and nonmedicated emollient for body lesions. Topical therapies for psoriasis, except those permitted for background therapy, were not allowed, including topical glucocorticoids, topical retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin; immunosuppressive systemic therapy, including cyclosporine, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, and fumaric acid esters; and phototherapy (ultraviolet B, psoralen + ultraviolet A). Indirectness: No indirectness
Funding	Study sponsored by Celgene Corp.

Apremilast versus placebo in people who were bDMARD naive

- Mortality at week 16. RoB: vh
- ACR20 response at week 16. RoB: vh

Study	PALACE 3: Edwards 2016(7)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=505
Countries and setting	Conducted in USA, Australia, Canada, Finland, Germany, Italy, France, Korea, Lithuania, Poland. Romania, Russia, Slovakia, Spain, Switzerland, UK. Study conducted across 91 centres.
Line of therapy	Not applicable
Duration of study	Intervention: placebo controlled for 24 weeks with “early escape” at 16 weeks.
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Outcomes in the subgroup of bDMARD naïve people were extracted. N=363.
Inclusion criteria	Adults with a documented diagnosis of PsA with duration ≥ 6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR). They had to have ≥ 3 swollen and ≥ 3 tender joints despite prior treatment with csDMARD and/or bDMARD or concurrent treatment with csDMARD.
Exclusion criteria	People with prior therapeutic failure of > 3 agents for PsA (csDMARD or bDMARD) or > 1 TNF inhibitor were ineligible. People could not have used phototherapy within 4 weeks, bDMARD (including adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab) within 12 weeks, or alefacept and ustekinumab within 24 weeks of randomization. Other exclusions were prior apremilast treatment, active tuberculosis (TB), history of incompletely treated TB, or significant infection within 4 weeks of screening, erythrodermic, guttate, or generalized pustular psoriasis.
Age, gender and ethnicity	Age - Mean (SD): 50 (12) and 50 (12). Gender (M:F): 236/269. Ethnicity: 481 white, 15, Asian, 2 black, 6 other.
Further population details	Baseline cDMARD use: 306 Baseline enthesitis: 318 Baseline dactylitis: 222
Indirectness of population	No indirectness
Interventions	(n=336, of whom 242 were bDMARD naïve) Intervention 1: Apremilast – people were randomised to either 20 mg BID or 30 mg BID. Dose titrated over first week until target does reached. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. These were permitted as background therapy, except ≤ 24 h before each study visit: low-potency topical glucocorticoids for treatment of face, axillae, and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions, and nonmedicated emollient for body lesions.Topical

	therapies for psoriasis, except those permitted for background therapy, were not allowed, including topical glucocorticoids, topical retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin; immunosuppressive systemic therapy, including cyclosporine, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, and fumaric acid esters; and phototherapy (ultraviolet B, psoralen + ultraviolet A). Indirectness: No indirectness (n=169, of whom 121 were bDMARD naïve) Intervention 2: Placebo – no details of blinding. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. These were permitted as background therapy, except ≤ 24 h before each study visit: low-potency topical glucocorticoids for treatment of face, axillae, and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions, and nonmedicated emollient for body lesions. Topical therapies for psoriasis, except those permitted for background therapy, were not allowed, including topical glucocorticoids, topical retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin; immunosuppressive systemic therapy, including cyclosporine, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, and fumaric acid esters; and phototherapy (ultraviolet B, psoralen + ultraviolet A). Indirectness: No indirectness
Funding	Study sponsored by Celgene Corp.

Apremilast versus placebo in people who were bDMARD naïve.

- ACR20 response at 16 weeks: RoB: vh
- Mortality at 16 weeks. RoB: vh

Study	PALACE 4: Wells 2018(8)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=527
Countries and setting	Conducted in USA, Australia, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Hungary, Italy, Republic of Korea, Lithuania, New Zealand, Poland, Romania, Russia, Taiwan, UK; setting: 118 centres.
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind, placebo controlled period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with active psoriatic arthritis who have not previously received treatment with csDMARDs or bDMARDs.

Exclusion criteria	Erythrodermic, guttate or generalized pustular psoriasis; inflammatory joint disease or rheumatic disease other than PsA; ACR Classification of Functional Status in Rheumatoid Arthritis class IV status; other clinically significant disease (as determined by the investigator) or other major uncontrolled disease; active tuberculosis, a history of incompletely treated tuberculosis (no purified protein derivative or QuantiFERON screening for latent tuberculosis was required) or significant infection within 4 weeks of screening; or malignancy (except treated basal cell or squamous cell skin carcinoma or early forms of cervical carcinoma with no recurrence in 5 years).
Age, gender and ethnicity	Age – Mean (SD): 51 (12) and 49 (12) and 48 (13). Gender (M:F): 250/277. Ethnicity: White: 520, Asian: 3, Black: 0, Other: 4.
Further population details	People with psoriasis at baseline: 306 (58%) Enthesitis at baseline: 343 (65%) Dactylitis at baseline: 263 (50%)
Indirectness of population	No indirectness
Interventions	(n=409) Intervention 1:Apremillast– : 2 treatment groups receiving either 20 mg or 40 mg twice per day. Concomitant medication: Stable doses of oral corticosteroids (prednisone 410 mg/day or equivalent for 51 month) and NSAIDs (2 weeks) before study entry were permitted. Background therapy with low-potency topical corticosteroid for face, axillae and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions and non-medicated emollient for body lesions was permitted, except within 24 h before each study visit. Indirectness: No indirectness (n=108) Intervention 2: Placebo– : Concomitant medication: Stable doses of oral corticosteroids (prednisone 410 mg/day or equivalent for 51 month) and NSAIDs (2 weeks) before study entry were permitted. Background therapy with low-potency topical corticosteroid for face, axillae and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions and non-medicated emollient for body lesions was permitted, except within 24 h before each study visit. Indirectness: No indirectness Early escape: At week 16, patients not achieving ≥20% improvement in swollen and tender joint counts (SJC and TJC) were considered nonresponders and were required to enter early escape; patients initially randomized to placebo were rerandomized (1:1) to apremilast 20 mg BID or 30 mg BID; apremilast patients continued with their initial apremilast dose.
Funding	Celgene Corporation.

Apremilast versus placebo

- Mortality at 24 weeks. RoB: vh
- SF36 physical component score at 16 weeks. RoB: vh
- SF36 mental component score at 16 weeks. RoB: vh
- ACR20 response at 24 weeks. RoB: vh
- ACR50 response at 24 weeks. RoB: vh

- ACR70 response at 24 weeks. RoB: low
- Dactylitis presence at 24 weeks. RoB: vh
- Change in dactylitis count at 16 weeks in people with dactylitis at baseline. RoB: vh
- Enthesitis presence at 24 weeks. RoB: vh
- PASI response: ≥55% improvement at week 24. RoB: vh
- PASI response: ≥75% improvement at week 24. RoB: vh
- Serious adverse events at 24 weeks. RoB: vh

Study	PSUMMIT 1: McInnes 2013(9)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=615
Countries and setting	Conducted in USA, Australia, Austria, Canada, Finland, Germany, Hungary, Latvia, Lithuania, New Zealand, Poland, Russia, Spain, UK; Setting: 105 centres
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind period of treatment
Method of assessment of guideline condition	Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with active psoriatic arthritis for 6 months or longer despite 3 months or more of treatment with disease-modifying antirheumatic drugs or 4 weeks or more of treatment with nonsteroidal anti-inflammatory drugs, or both, or with intolerance to these treatments.
Exclusion criteria	None detailed
Age, gender and ethnicity	Age – Median (range): 48 (18-81). Gender (M:F): 330/285. Ethnicity: not detailed
Further population details	People with psoriasis at baseline: 440 (72%) Methotrexate use at baseline: 296 (48%) Enthesitis at baseline: 441 (72%) Dactylitis at baseline: 296 (48%)
Indirectness of population	No indirectness
Interventions	(n=409) Intervention 1: IL-12/23 inhibitor – : 2 treatment groups receiving either 90 mg or 45 mg ustekinumab subcutaneously at week 4, and every 12 weeks thereafter. People were eligible for early escape at week 16. Indirectness: No indirectness

	(n=206) Intervention 2: Placebo– : Administered via subcutaneous injection at week 4, and every 12 weeks thereafter. Indirectness: No indirectness Early escape possible from any group at week 16.
Funding	Janssen Research & Development

IL-12/23 inhibitor versus placebo

- Mortality at 24 weeks. RoB: low
- ACR20 response at 24 weeks. RoB: low
- ACR50 response at 24 weeks. RoB: low
- ACR70 response at 24 weeks. RoB: low
- Dactylitis presence at 24 weeks. RoB: h
- Enthesitis presence at 24 weeks. RoB: h
- PASI response: ≥75% improvement at week 24. RoB: h
- BASDAI20 response at 24 weeks. RoB: h
- Serious adverse events at 24 weeks. RoB: low.

Study	PSUMMIT 2: Richlin 2014(10)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=312
Countries and setting	Conducted in USA, Austria, Canada, France, Germany, Hungary, Poland, Russia, Sweden, UK; Setting: 92 centres
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind, placebo controlled period
Method of assessment of guideline condition	Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with active psoriatic arthritis for 6 months or longer despite 3 months or more of treatment with disease-modifying antirheumatic drugs or 4 weeks or more of treatment with nonsteroidal anti-inflammatory drugs, or both, or with intolerance to these treatments.
Exclusion criteria	History of active tuberculosis (TB)
Age, gender and ethnicity	Age – Median (IQR): 48 (39-56) and 49 (40-56) and 48 (41-57). Gender (M:F): 148/164. Ethnicity: not detailed
Further population details	People with ≥ 3% BSA involved with psoriasis at baseline: 241 (77%) Enthesitis at baseline: 221 (71%)

	Dactylitis at baseline: 127 (41%)
	People with spondylitis/peripheral joint involvement: 70 (22%)
Indirectness of population	No indirectness
Interventions	(n=208) Intervention 1: IL-12/23 inhibitor – : 2 treatment groups receiving either 90 mg or 45 mg ustekinumab subcutaneously at week0, 4, and every 12 weeks thereafter. Concurrent medication/care: Concomitant methotrexate (MTX) was permitted if started ≥ 3 months prior to study start and at a stable dose (≤ 25 mg/week) for ≥ 4 weeks. Concomitant NSAIDs and oral corticosteroids (≤ 10 mg prednisone/day) were permitted if stable for ≥ 2 weeks. Indirectness: No indirectness (n=104) Intervention 2: Placebo– : Administered via subcutaneous injection at week 0, 4, and every 12 weeks thereafter. Concurrent medication/care: Concomitant methotrexate (MTX) was permitted if started ≥ 3 months prior to study start and at a stable dose (≤ 25 mg/week) for ≥ 4 weeks. Concomitant NSAIDs and oral corticosteroids (≤ 10 mg prednisone/day) were permitted if stable for ≥ 2 weeks. Indirectness: No indirectness Early escape At week 16, people with <5% improvement in tender and swollen joints entered blinded early escape (EE); those receiving placebo switched to ustekinumab 45 mg, those receiving ustekinumab 45 mg increased to 90 mg and people receiving ustekinumab 90 mg continued with blinded 90 mg dosing.
Funding	Janssen Research & Development

IL-12/23 inhibitor versus placebo

- ACR20 response at 24 weeks. RoB: h
- PASI response: ≥75% improvement at week 24. RoB: h

Study	RAPID-PsA: Mease 2014(35)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=409
Countries and setting	Conducted in USA, Argentina, Belgium, Brazil, Canada, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Poland, Spain, UK; Setting: 92 centres
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind, placebo controlled period of treatment
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	People who were TNF inhibitor naïve n=329.

Inclusion criteria	Adults with adult-onset, active psoriatic arthritis for 6 months or longer. They had active psoriatic skin lesions or a documented history of psoriasis.
Exclusion criteria	Evidence of latent or active tuberculosis (TB) (PPD>5 mm) were excluded unless prophylactic treatment of latent TB had begun ≥4 weeks prior to baseline. Evidence of: chronic or clinically significant infections, malignancy, or demyelinating disease of the central nervous system; previous exposure to >2 biologics or >1 TNF inhibitor for the treatment of PsA or psoriasis, or primary failure of a prior TNF inhibitor.
Age, gender and ethnicity	Age – Mean(SD): 47 (11) and 48 (12) and 47 (11). Gender: 55% female, 45 % male. Ethnicity: 98% white
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 61% Methotrexate use at baseline: 64% Enthesitis at baseline: 64% Dactylitis at baseline: 26%
Indirectness of population	No indirectness
Interventions	(n=219) Intervention 1:TNF inhibitor – 2 treatment groups of 400 mg CZP at week 0, 2 and 4 followed by either 200 mg certolizumab every 2 weeks or 400 mg certolizumab every 4 weeks, administered subcutaneously. Concurrent medication/care: The use of DMARDs other than MTX, SSZ, LEF, or intra-articular corticosteroids, was prohibited during the trial. Use of combinations of MTX, SSZ and LEF was not permitted. Concurrent use of topical, systemic, or phototherapy treatments was not permitted. Indirectness: No indirectness (n=110) Intervention 2: Placebo– Patients were randomised 1:1:1 to placebo (0.9% saline). People who failed to achieve a 10% improvement from baseline in both swollen and tender joints at weeks 14 and 16 underwent mandatory escape to active treatment. This was randomised to either dose of certolizumab. Concurrent medication/care: The use of DMARDs other than MTX, SSZ, LEF, or intra-articular corticosteroids, was prohibited during the trial. Use of combinations of MTX, SSZ and LEF was not permitted. Concurrent use of topical, systemic, or phototherapy treatments was not permitted.. Indirectness: No indirectness
Funding	UCB Pharma

TNF inhibitor versus placebo in people with no prior TNF exposure

- ACR20 response at 24 weeks. RoB: h
- ACR50 response at 24 weeks. RoB: h
- ACR70 response at 24 weeks. RoB: h

Study	SEAM-PsA: Mease 2019(36)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=851

Countries and setting	Conducted in USA, Argentina, Bulgaria, Canada, Chile, Czech Republic, France, Greece, Hungary, Latvia, Mexico, Poland, Portugal, Puerto Rico, Russia, South Africa, Spain, UK; Setting: 92 hospital centres
Line of therapy	Not applicable
Duration of study	Intervention plus follow-up: 48 weeks week of treatment and 30 days follow-up
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults who active PsA who were naïve to bDMARDs and no prior use of methotrexate for PsA. People receiving nonsteroidal antiinflammatory drugs (NSAIDs), the dose had to be stable ≥2 weeks prior to initiation of the study. People receiving oral corticosteroids, the dose had to be stable (not to exceed the equivalent of 10 mg prednisone per day) ≥4 weeks prior to initiation of the study.
Exclusion criteria	People had to test negative for hepatitis B surface antigen and hepatitis B core antibody, test negative for hepatitis C antibody, have no known history of active tuberculosis, and test negative for tuberculosis during screening. Women had to test negative for pregnancy if not at least 2 years postmenopausal. People were excluded if they had a known history of alcoholic hepatitis, nonalcoholic steatohepatitis, or immunodeficiency syndromes.
Age, gender and ethnicity	Age – Mean (SD): 49 (13) and 49 (14) and 48 (13). Gender (M:F): 419/432. Ethnicity: 90% white
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 548 (64%) Enthesitis at baseline: 576 (68%) Dactylitis at baseline: 284 (33%)
Indirectness of population	No indirectness
Interventions	(n=284) Intervention 1:TNF inhibitor – Etanercept was administered at a dosage of 50 mg/week by subcutaneous injection. Concurrent medication/care: Methotrexate, supplied as 2.5-mg tablets in capsules, and was initiated at a dosage of 10 mg/week and titrated up to 20 mg/week over a 4-week period. Folic acid was administered at 5–7 mg/week. People entering the study taking oral corticosteroids had to remain on a stable dose up to week 24. Those taking acetaminophen, narcotic analgesics, or NSAIDs had to remain on a stable dose up to week 24 and could not take these agents within 12 hours (24 hours for oxycontin) before a scheduled study visit. Indirectness: No indirectness (n=284) Intervention 2: Placebo– placebo administered to support blinding. Concurrent medication/care: Concurrent medication/care: Methotrexate, supplied as 2.5-mg tablets in capsules, and was initiated at a dosage of 10 mg/week and titrated up to 20 mg/week over a 4-week period. Folic acid was administered at 5–7 mg/week. People entering the study taking oral corticosteroids had to remain on a stable dose up to week 24. Those taking acetaminophen, narcotic analgesics, or NSAIDs had to remain on a stable dose up to week 24 and could not take these agents within 12 hours (24 hours for oxycontin) before a scheduled study visit. Indirectness: No indirectness

Funding	Amgen

TNF inhibitor versus placebo

- Mortality at 48 weeks. RoB: low
- SF36 physical component score at 24 weeks. RoB: low
- SF36 mental component score at 24 weeks. RoB: low
- ACR20 response at 24 weeks. RoB: low
- ACR50 response at 24 weeks. RoB: low
- ACR70 response at 24 weeks. RoB: low
- Minimal disease activity at 24 wees. RoB: low
- Dactylitis resolution at 24 weeks. RoB: h
- Enthesitis resolution at 24 weeks. RoB: h
- People achieving clear/almost clear on sPGA-psoriasis at 24 weeks. RoB: h
- Seious adverse events at 48 weeks. RoB: low
- Radiological progression at 48 weeks. RoB: low
- SPARCC Enthesitis Index at 24 weeks. BoB: low

Study	SPIRIT-P1: Mease 2017(20)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=417
Countries and setting	Conducted in USA, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Japan, Mexico, Netherlands, Poland, Russia, Spain, Ukraine, UK; Setting: 116 centres
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind period of treatment
Method of assessment of guideline condition	Fulfilled the Classification Criteria for Psoriatic Arthritis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with a diagnosis of PsA for at least 6 months who were naïve to biologic DMARD treatment. They had ≥3 of 68 tender and ≥3 of 66 swollen joint counts and had either ≥1 PsA-related hand or foot joint erosion on centrally read X-rays or CRP > 6 mg/l at baseline.
Exclusion criteria	None detailed
Age, gender and ethnicity	Age - Mean (SD): 50 (12). Gender (M:F): 192/225. Ethnicity: American Indian/Alaska native: 9, Asian: 15, White: 392, Multiple: 1.
Further population details	People with psoriasis at baseline: 394 (95%)

	Methotrexate use at baseline: 226 (54%) Enthesitis at baseline: 242 (58%) Dactylitis at baseline: 157 (38%)
Indirectness of population	No indirectness
Interventions	(n=210) Intervention 1: IL-17 inhibitor – : 2 treatment groups of either ixekizumab 80 mg every 2 weeks or every 4 weeks. Administered via subcutaneous injection. People were administered a starting dose of 160 mg given as two injections at week 0. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness (n=101) Intervention 2: TNF inhibitor – : Adalimumab at 40 mg every 2 weeks. Administered via subcutaneous injection. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness (n=101) Intervention 3: Placebo– : Administered via subcutaneous injection. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness
Funding	Funded and sponsored by Eli Lilly and Company.

IL-17 inhibitor versus TNF inhibitor

- ACR20 response at 12 weeks. RoB: low
- ACR50 response at 12 weeks. RoB: low
- ACR70 response at 12 weeks. RoB: low
- Dactylitis resolution (LDI-B = 0) at 12 weeks. RoB: h
- Enthesitis absence (LEI=0) at 12 weeks. RoB: h
- PASI response: ≥75% improvement at week 12. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks. RoB: h
- Serious adverse events at 24 weeks. RoB: low

IL-17 inhibitor versus placebo

- ACR20 response at 12 weeks. RoB: low
- ACR50 response at 12 weeks. RoB: low
- ACR70 response at 12 weeks. RoB: low
- Dactylitis resolution (LDI-B = 0) at 12 weeks. RoB: h

- Enthesitis absence (LEI=0) at 12 weeks. RoB: h
- PASI response: ≥75% improvement at week 12. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks. RoB: h
- Serious adverse events at 24 weeks. RoB: low

TNF inhibitor versus placebo

- ACR20 response at 12 weeks. RoB: low
- ACR50 response at 12 weeks. RoB: low
- ACR70 response at 12 weeks. RoB: low
- Dactylitis resolution (LDI-B = 0) at 12 weeks. RoB: h
- Enthesitis absence (LEI=0) at 12 weeks. RoB: h
- PASI response: ≥75% improvement at week 12. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks. RoB: h
- Serious adverse events at 24 weeks. RoB: low

Study	SPIRIT-H2H: Mease 2020(38)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=566
Countries and setting	Conducted in Argentina, Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Hungary, India, Israel, Italy, Mexico, Netherlands, Poland, South Africa, Spain, Sweden, Switzerland, Ukraine, UK; Setting: 131 centres
Line of therapy	Not applicable
Duration of study	Intervention: 52 week period of treatment (open-label)
Method of assessment of guideline condition	Fulfilled the Classification Criteria for Psoriatic Arthritis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with an established diagnosis of PsA for at least 6 months, fulfilled the Classification for Psoriatic Arthritis criteria with at least 3/66 swollen and 3/68 tender joints, had previous inadequate response to ≥1 csDMARD, had active plaque psoriasis affecting ≥3% of body surface area (BSA) and had not previously received bDMARD or Janus kinase inhibitor therapy. Patients on csDMARDs at screening were allowed to continue a stable dose of csDMARD therapy.
Exclusion criteria	None detailed

Age, gender and ethnicity	Age - Mean (SD):48 (12). Gender (M:F): 312/254. Ethnicity: White: 76%, Asian: 11%
Further population details	Concomitant csDMARD use: 392 (69%) Enthesitis at baseline: 360 (64%) Dactylitis at baseline: 100 (18%)
Indirectness of population	No indirectness
Interventions	(n=283) Intervention 1: IL-17 inhibitor – 2 injections of ixekizumab 80 mg at week 0. Then 80 mg every 4 weeks. If they met the criteria for moderate-sever psoriasis then they received 80 mg every 2 week from weeks 2-12. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness (n=283) Intervention 2: TNF inhibitor – : Adalimumab at 40 mg every 2 weeks. Administered via subcutaneous injection. If they met the criteria for moderate-sever psoriasis then they received 80 mg at week 0. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness
Funding	Funded and sponsored by Eli Lilly and Company.

IL-17 inhibitor versus TNF inhibitor

- Mortality at 24 weeks. RoB: h
- ACR20 response at 24 weeks. RoB: vh
- ACR50 response at 24 weeks. RoB: vh
- ACR70 response at 24 weeks. RoB: vh
- PASI response: ≥75% improvement at week 24. RoB: vh
- Minimal disease activity at 12 weeks. RoB: vh
- Dactylitis resolution at 24 weeks in people with dactylitis at baseline. RoB: vh
- Enthesitis resolution at week 24 in people with enthesitis at baseline. RoB: vh
- Serious adverse events at 24 weeks. RoB: h

British Society for Rheumatology

Appendix E: **Forest plots**

E.1 Head to head comparisons

E.1.1 IL-17 inhibitors versus TNF inhibitors

Figure 2: Mortality at 16 weeks

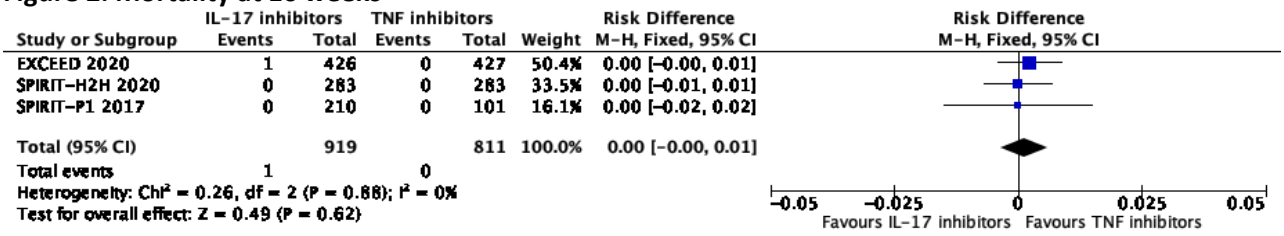


Figure 3: Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks

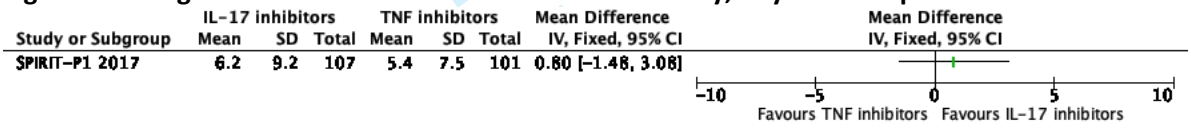


Figure 4: Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks

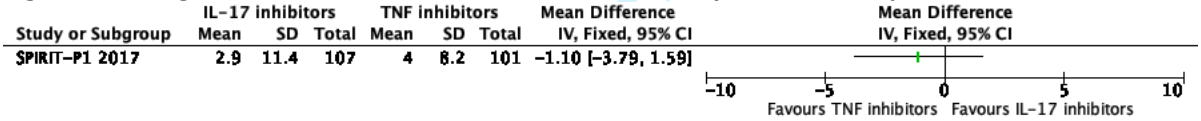


Figure 5: ACR20 response at week 12/52

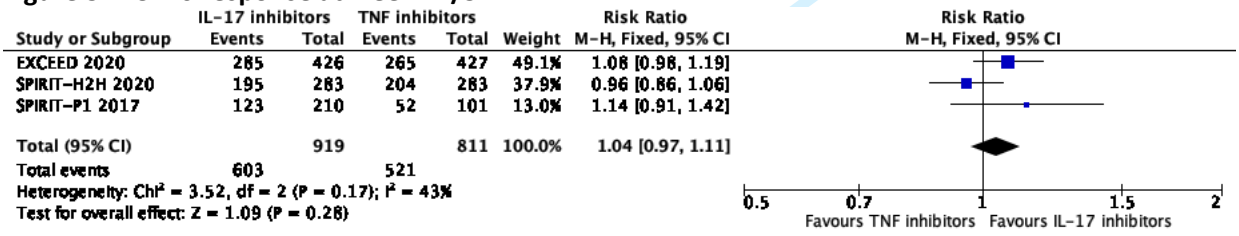


Figure 6: ACR50 response at week 12/52

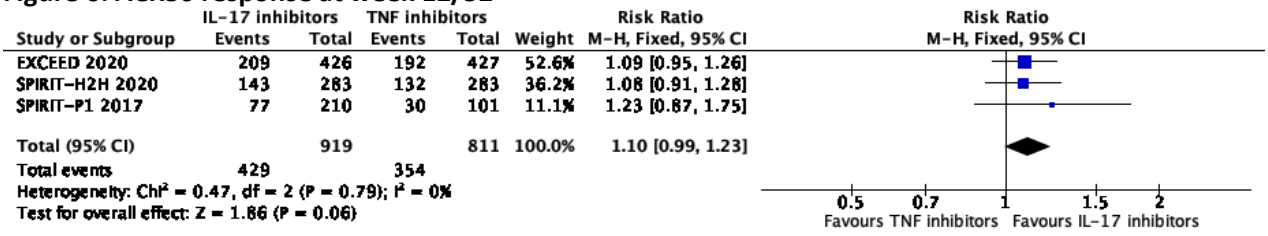


Figure 7: ACR70 response at 12 weeks

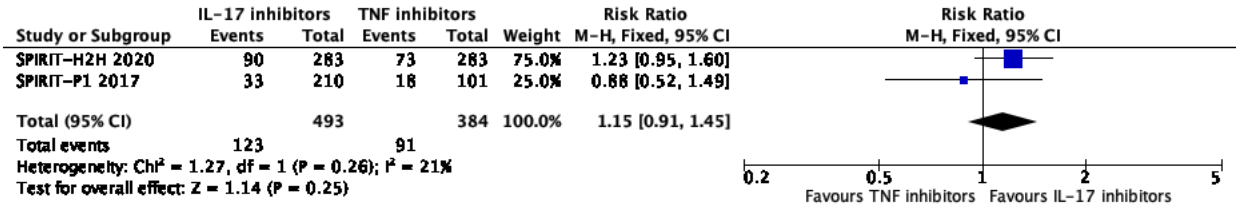


Figure 8: Minimal disease activity (78/76 joints) at 12/52 weeks

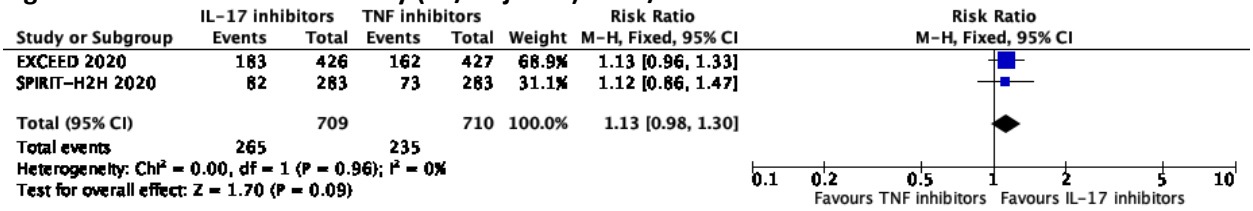


Figure 9: Dactylitis resolution at 12/24/52 weeks in people with dactylitis at baseline

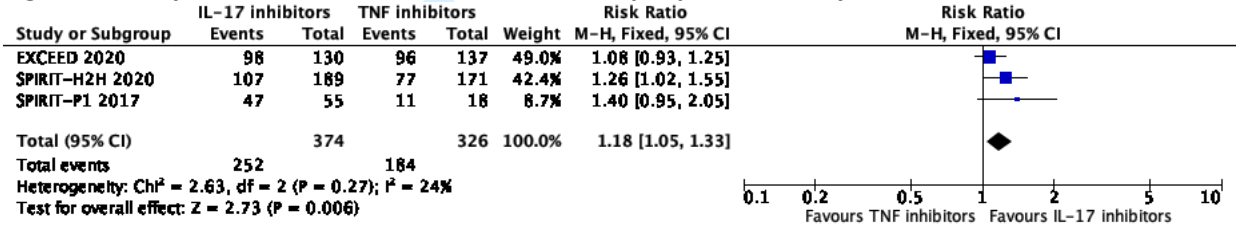


Figure 10: Enthesitis resolution at week 16/24/52 in people with enthesitis at baseline

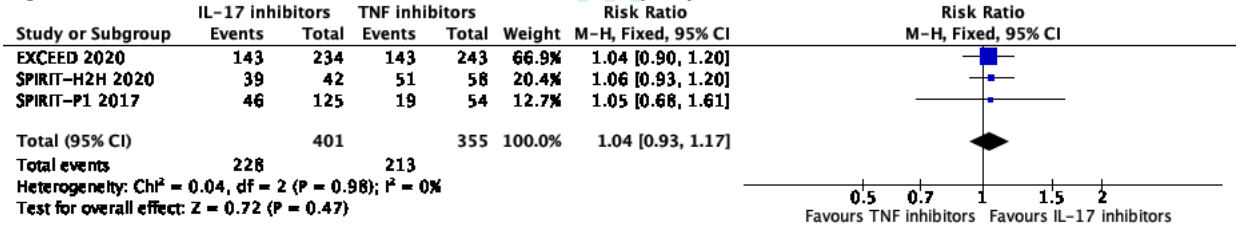


Figure 11: PASI response: ≥75% improvement at week 12/24. In people with ≥3% BSA affected with psoriasis

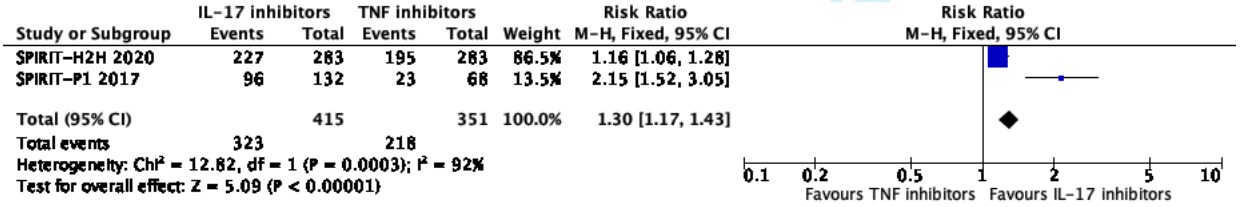


Figure 12: PASI response: ≥100% improvement at week 12/52. In people with ≥3% BSA affected with psoriasis

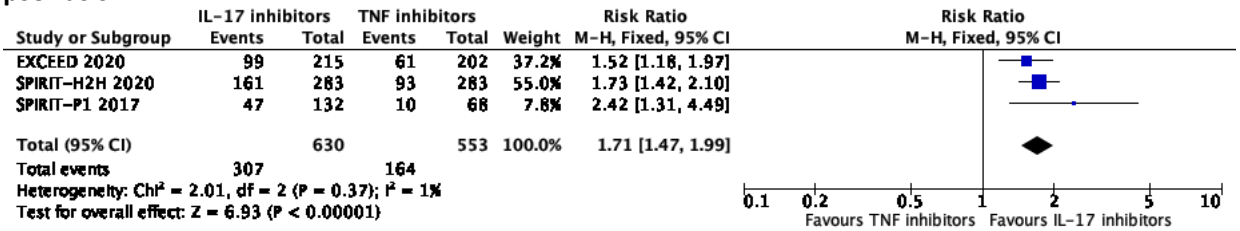
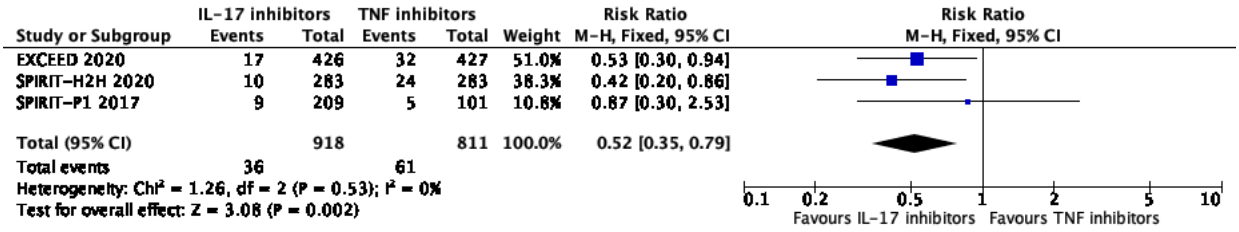


Figure 13: Serious adverse events at 24/52 weeks



E.1.2 IL-12/23 inhibitors versus TNF inhibitors

Figure 14: Complete resolution of enthesitis, arthritis and skin [PASI100] (%) at 24 weeks

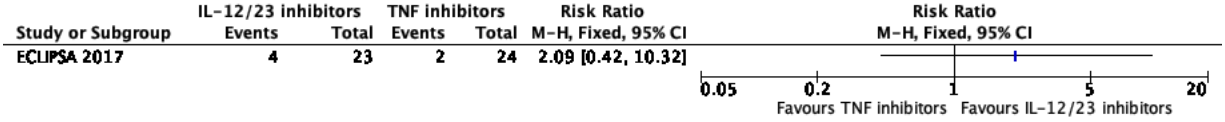


Figure 15: MDA: Minimal disease activity (7 of 7 criteria) at 24 weeks

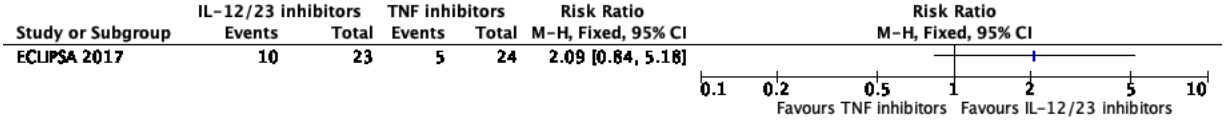


Figure 16: Enthesitis resolution (LEI = 0, SPARCC = 0, MASES = 0) at 24 weeks

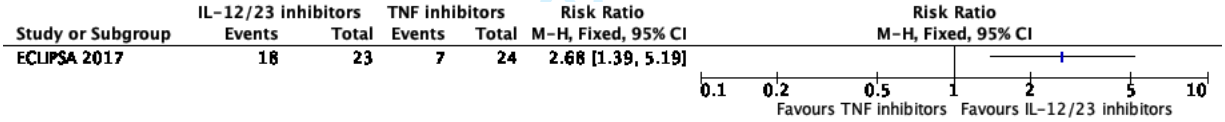
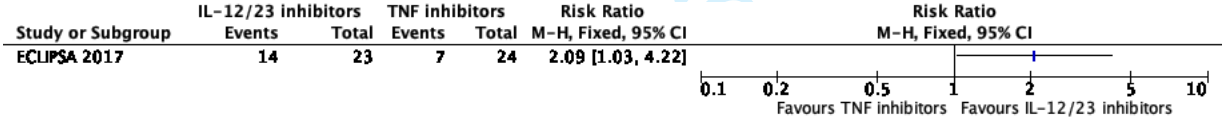


Figure 17: PASI response: 100% improvement at week 24



E.1.3 JAK inhibitors versus TNF inhibitors

Figure 18: ACR20 response at week 12

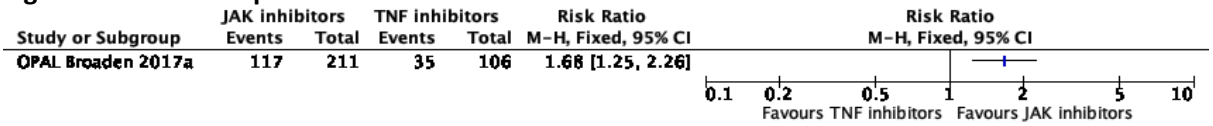


Figure 19: ACR50 response at week 12

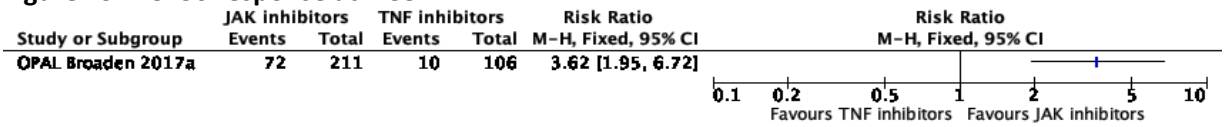


Figure 20: ACR70 response at week 12

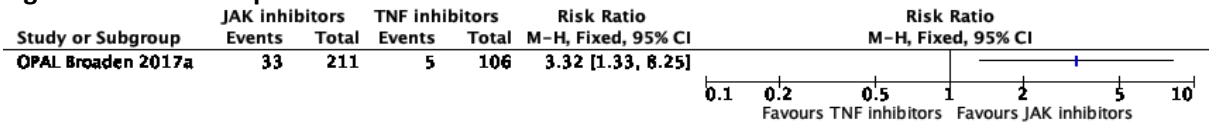


Figure 21: MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks

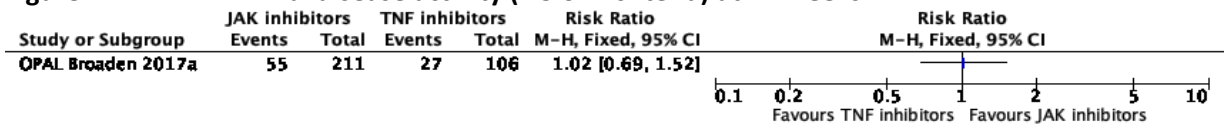


Figure 22: Enthesitis absence at week 12 in people with enthesitis at baseline

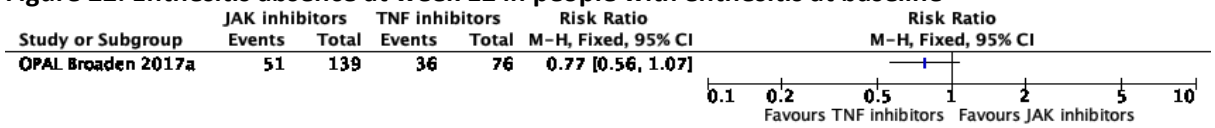


Figure 23: LEI: Leeds Enthesitis Index in perople with enthesitis at baseline

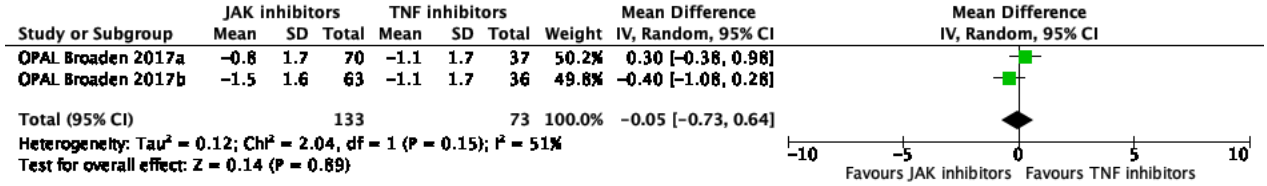


Figure 24: Dactylitis Severity Score at 12 weeks in people with dactylitis at baseline

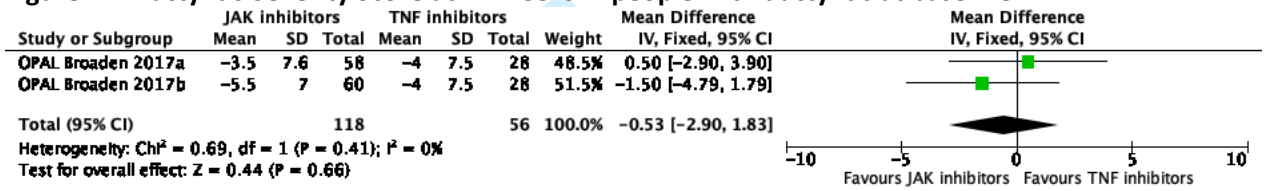


Figure 25: Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline.

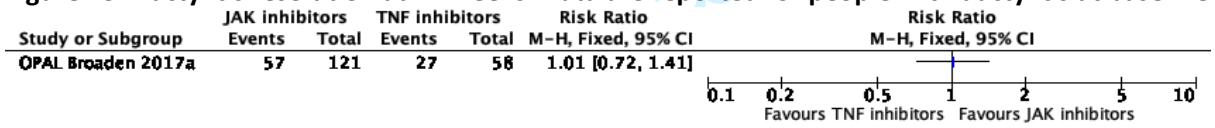


Figure 26: PASI response: ≥75% improvement at week 12

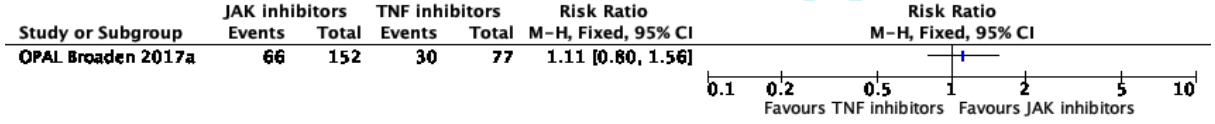
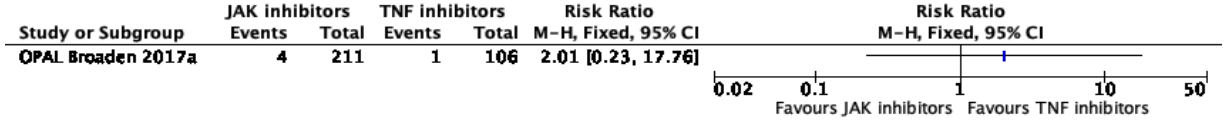


Figure 27: Serious adverse events at 12 weeks



E.2 Comparisons versus placebo

E.2.1 Abatacept versus placebo

Figure 28: ACR20 response at week 16/24

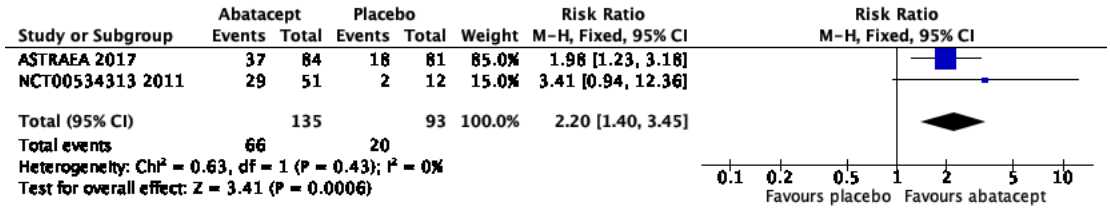


Figure 29: ACR50 response at week 16

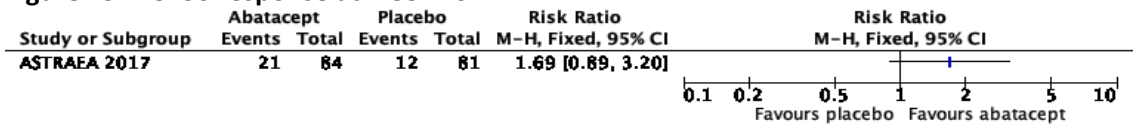


Figure 30: ACR70 response at week 16

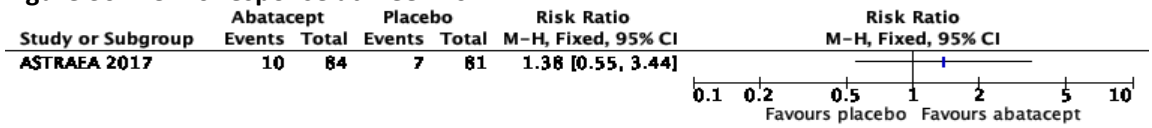


Figure 31: PASI50 response at week 24

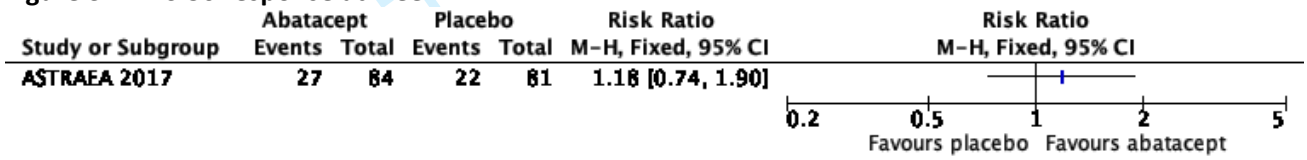
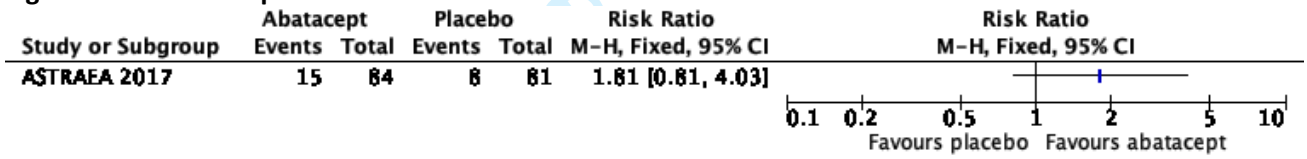


Figure 32: PASI75 response at week 24



E.2.2 Apremilast versus placebo

Figure 33: Mortality at 16/24 weeks

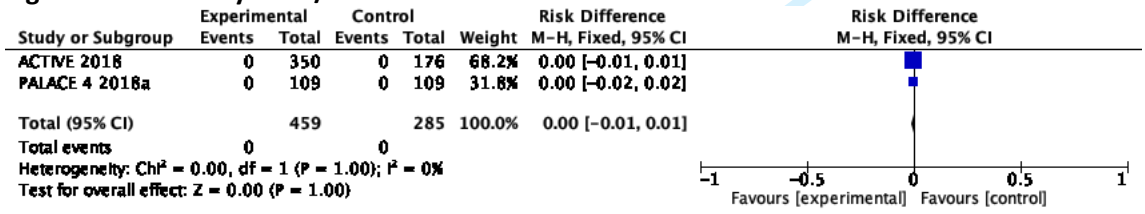


Figure 34: Change in SF36 physical component score at 16 weeks

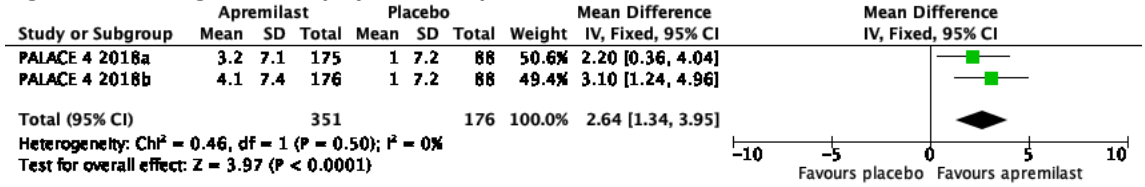


Figure 35: ACR20 response at 16 weeks

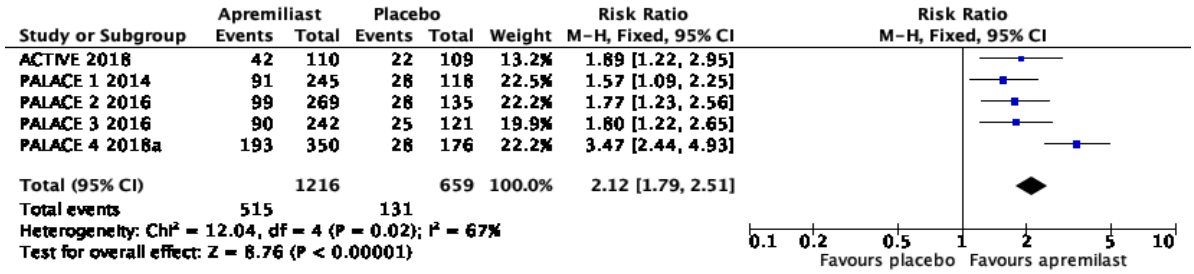


Figure 36: ACR50 response at 16 weeks

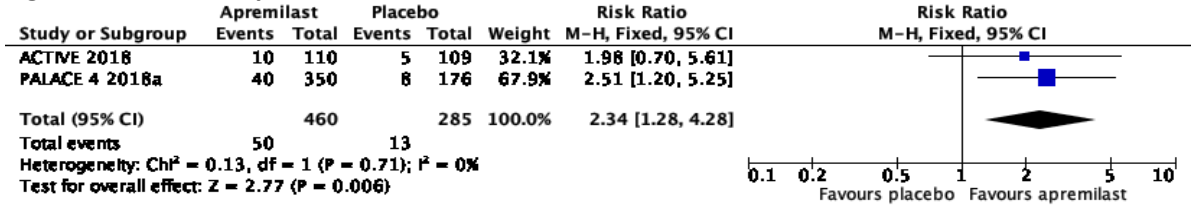


Figure 37: ACR70 response at 16 weeks

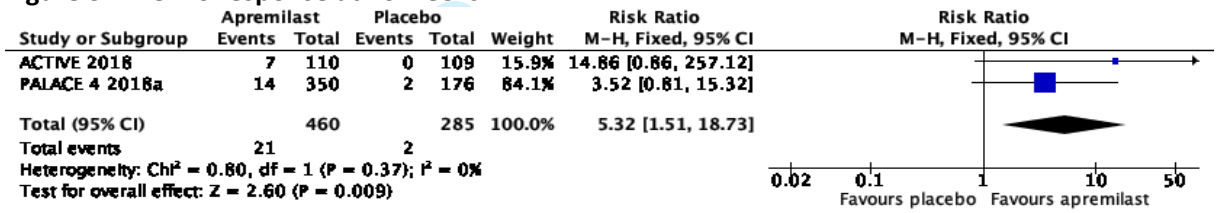


Figure 38: Enthesitis resolution at 16 weeks in people with enthesitis at baseline

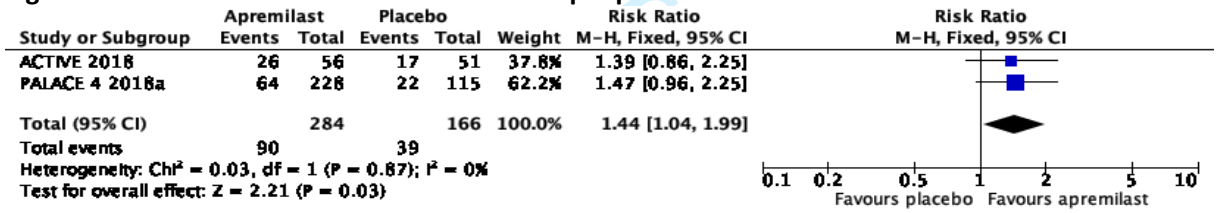


Figure 39: Dactylitis resolution at 16 weeks in people with dactylitis at baseline

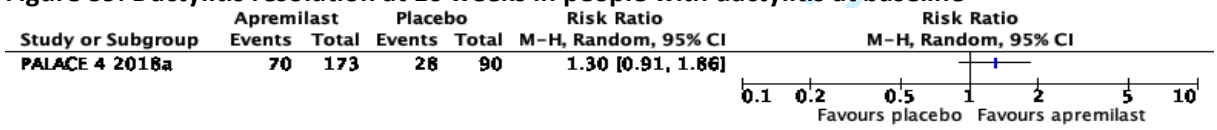


Figure 40: Change in dactylitis count at 16 weeks in people with dactylitis at baseline

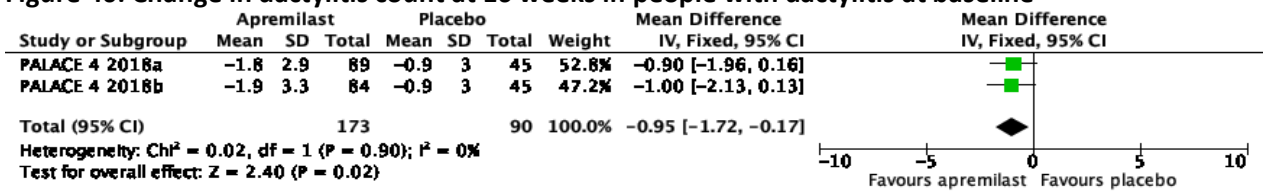


Figure 41: PASI50 response at 16 weeks in people with psoriasis at baseline

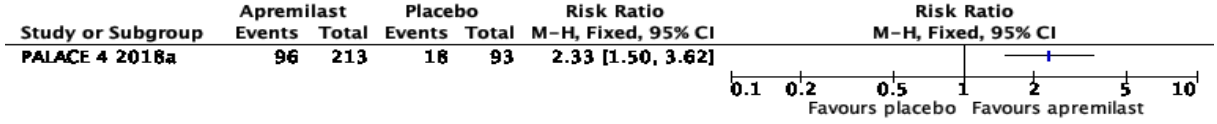


Figure 42: PASI75 response at 16 weeks in people with psoriasis at baseline

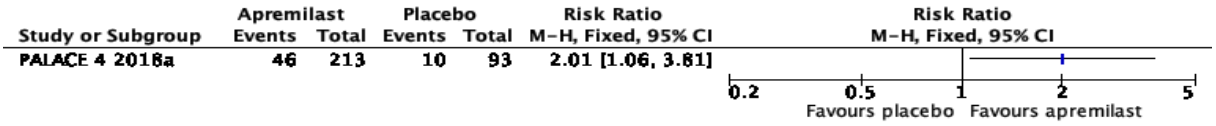
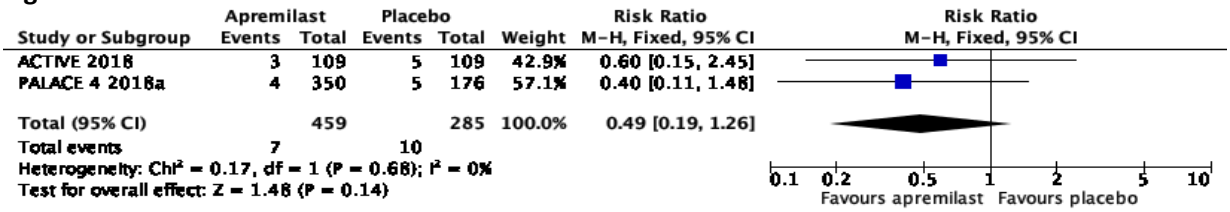


Figure 43: Serious adverse events at 24 weeks



E.2.3 IL-12/23 inhibitors versus placebo

Figure 44: Mortality at 24 weeks

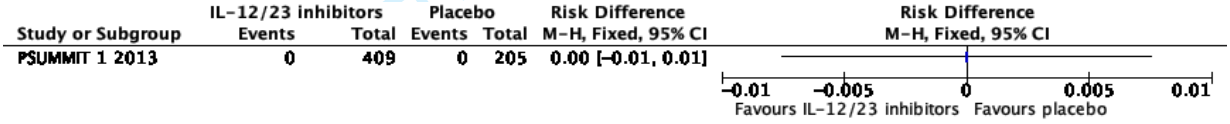


Figure 45: ACR20 response at 24 weeks

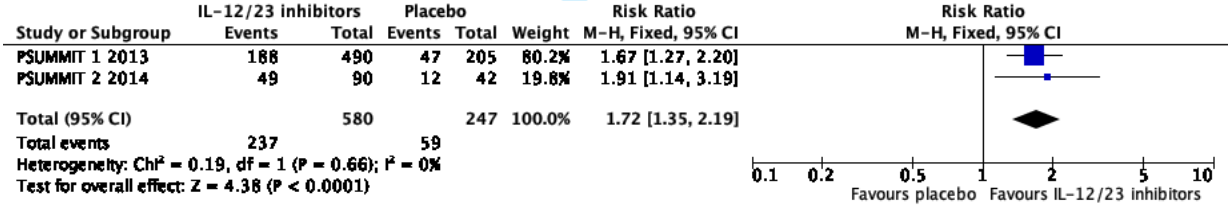


Figure 46: ACR50 response at week 24

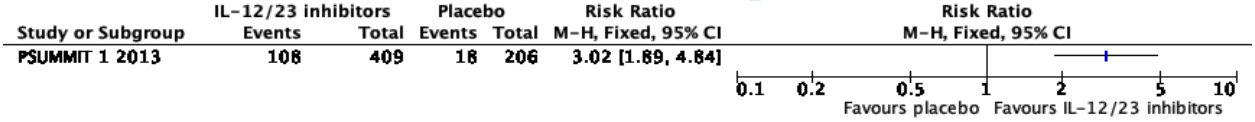


Figure 47: ACR70 response at 24 weeks

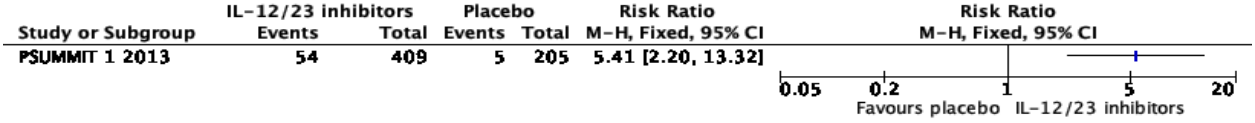


Figure 48: Enthesitis presence at 24 weeks in people with enthesitis at baseline

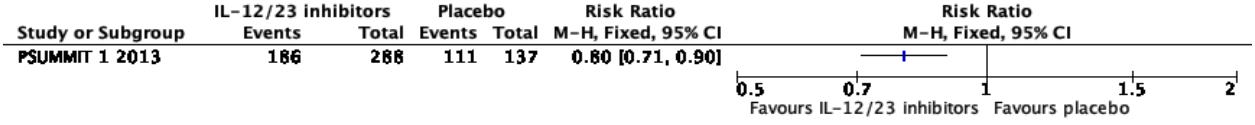


Figure 49: PASI response: ≥75% improvement at week 12/24 In people with ≥3% BSA affected with psoriasis

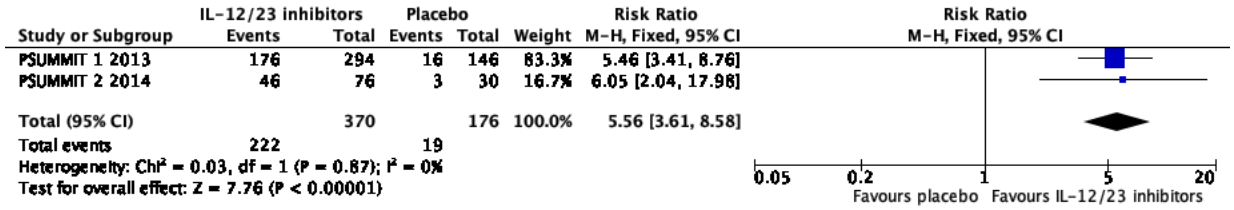


Figure 50: BASDAI20 response at 24 weeks in people with spondylitis at baseline

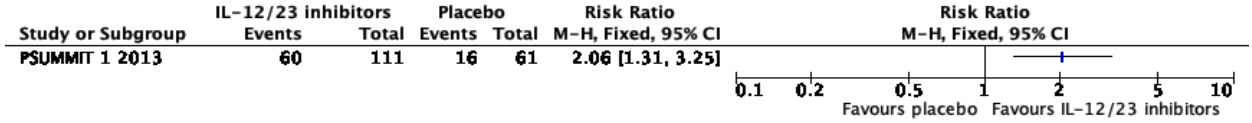
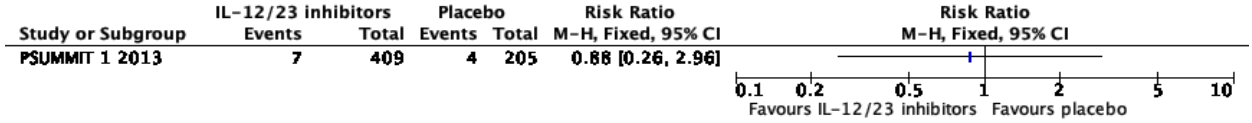


Figure 51: Serious adverse events at 16 weeks



E.2.4 IL-17 inhibitors versus placebo

Figure 52: Mortality at 24 weeks

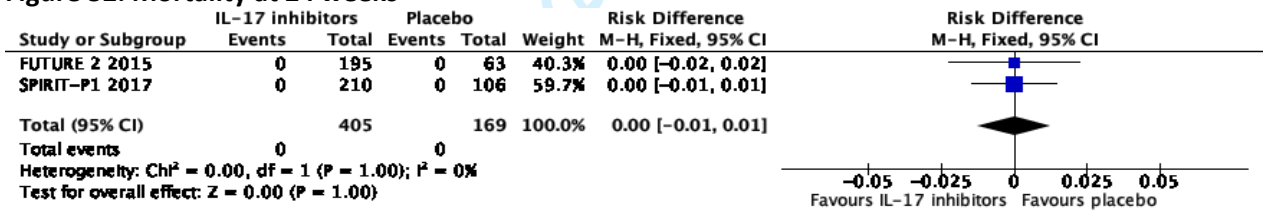


Figure 53: Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks

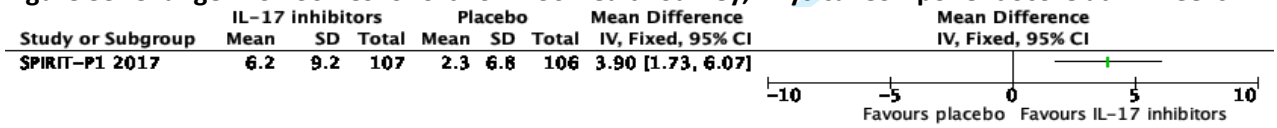


Figure 54: Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks

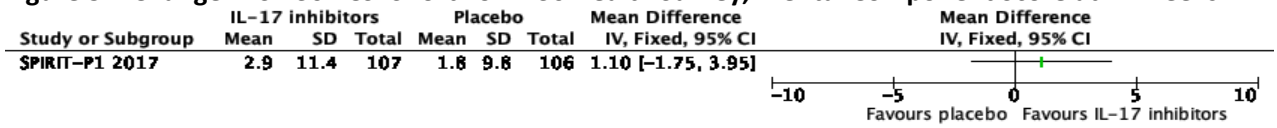


Figure 55: MDA: Minimal disease activity (≥ 5 of 7 criteria) at week 16

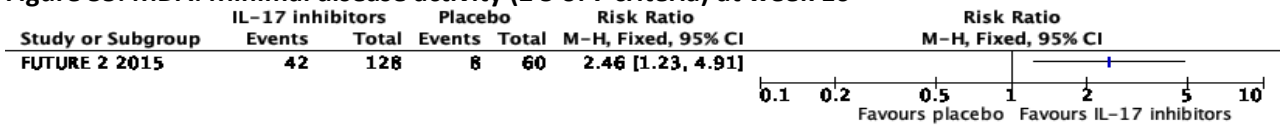


Figure 56: ACR20 response at 12/16/24 weeks

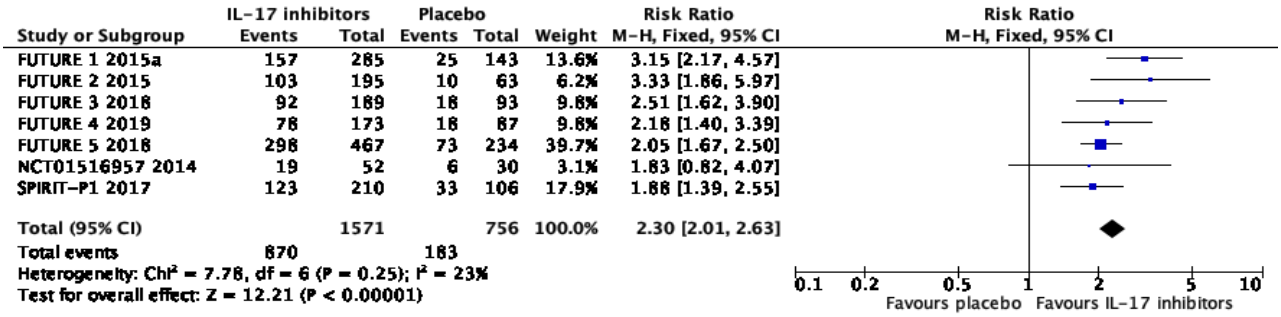


Figure 57: ACR50 response at week 12/16/24

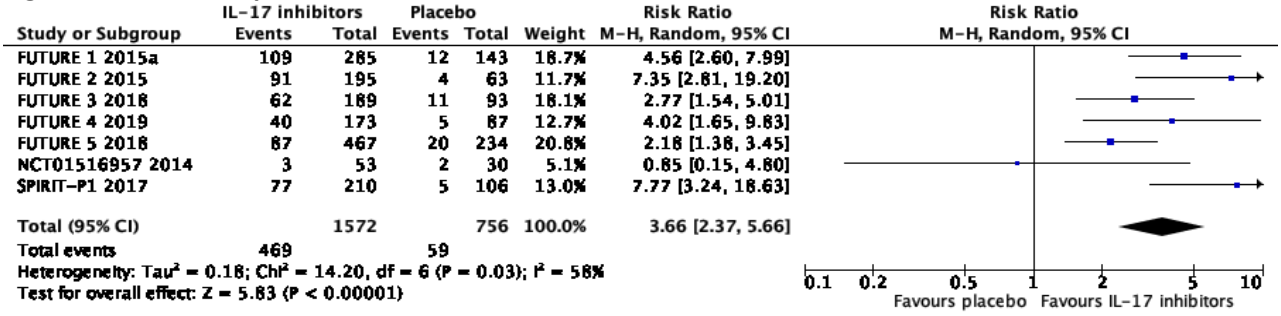


Figure 58: ACR70 response at week 12/24

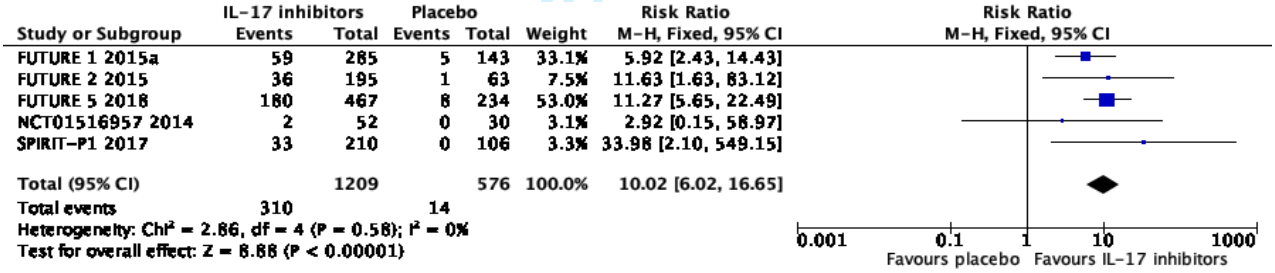


Figure 59: Dactylitis resolution at 12/24 weeks. Data are reported for people with dactylitis at baseline.

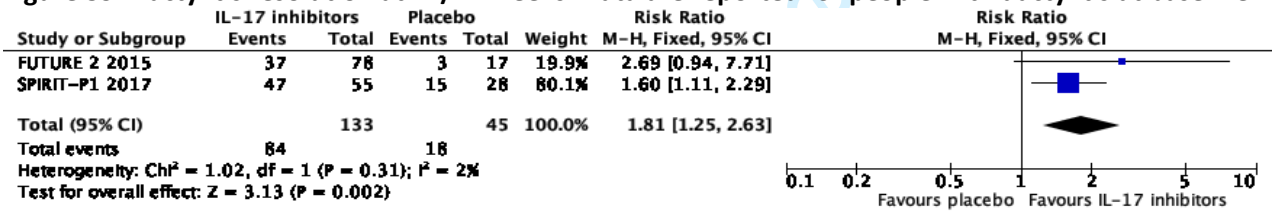


Figure 60: Enthesitis absence/resolution at 12/24 weeks in people with enthesitis at baseline

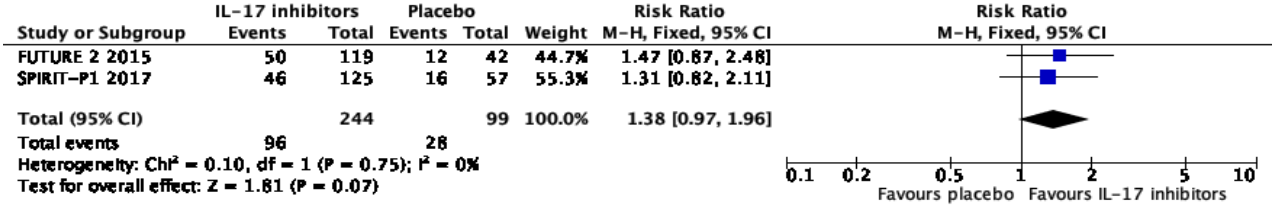


Figure 61: PASI response: ≥75% improvement at week 12/24

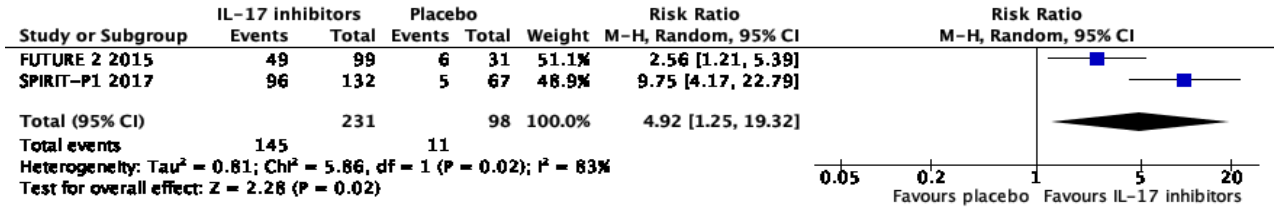


Figure 62: mTSS/SHS: van der Heijde modified Total Sharp Score (0-528) at 24 weeks

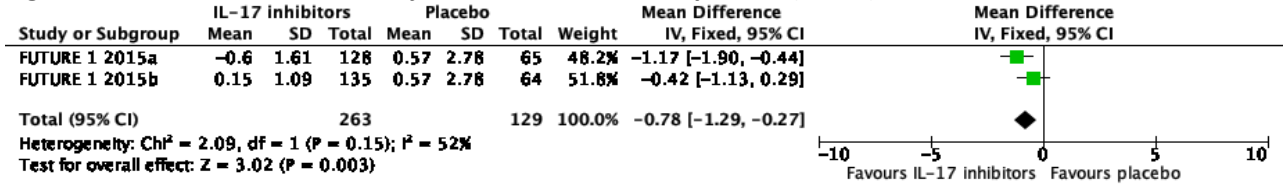
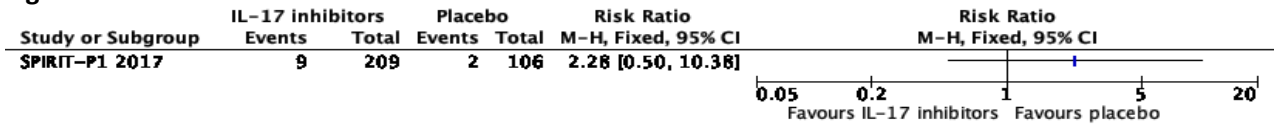


Figure 63: Serious adverse events at 24 weeks



E.2.5 IL-23 inhibitors versus placebo

Figure 64: Mortality at 24 weeks

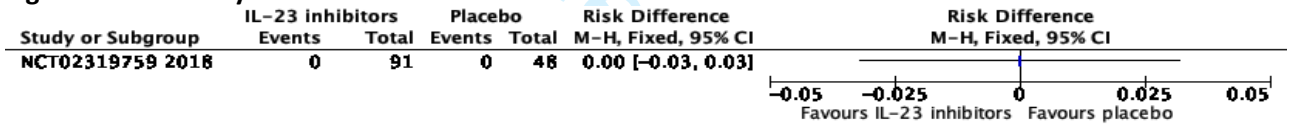


Figure 65: ACR20 response at week 24

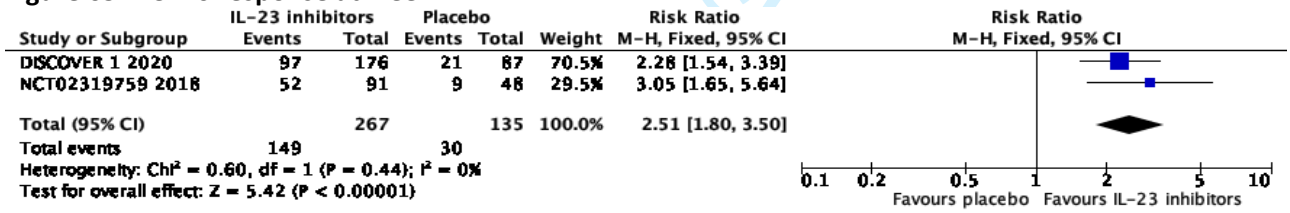


Figure 66: ACR50 response at week 24

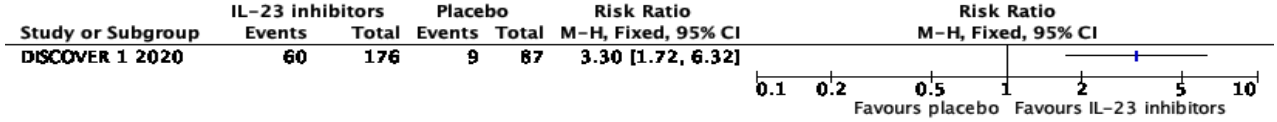
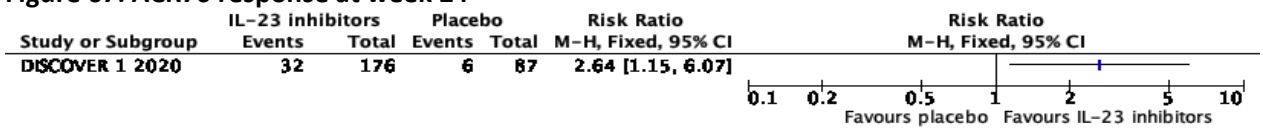


Figure 67: ACR70 response at week 24



E.2.6 JAK inhibitors versus placebo

Figure 68: ACR20 response at week 12

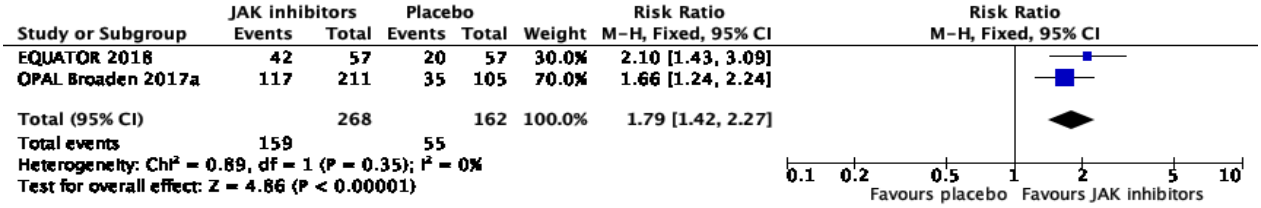


Figure 69: ACR50 response at week 12

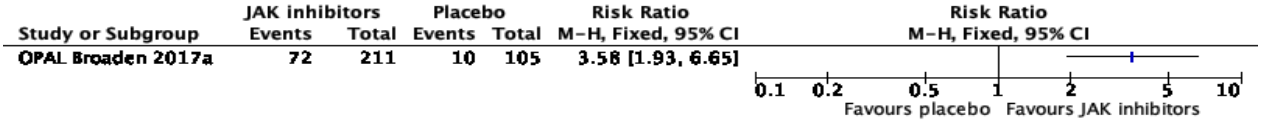


Figure 70: ACR70 response at week 12

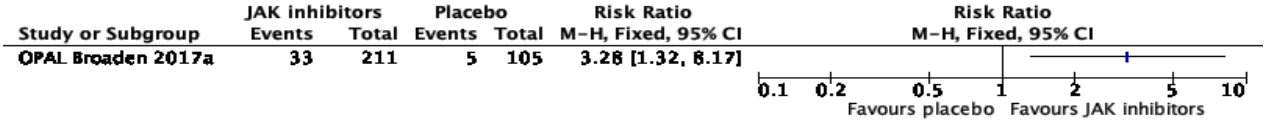


Figure 71: MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks

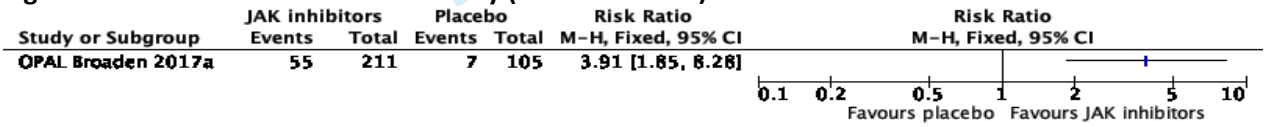


Figure 72: Enthesitis absence at 12 weeks in people with enthesitis at baseline

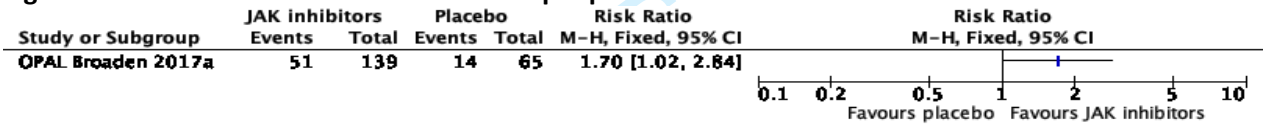


Figure 73: LEI: Leeds Enthesitis Index at 12/14 weeks in people with enthesitis at baseline

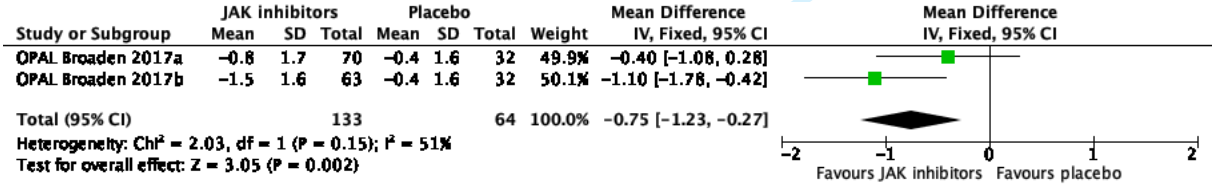


Figure 74: Dactylitis Severity Score at 12/14 weeks in people with dactylitis at baseline

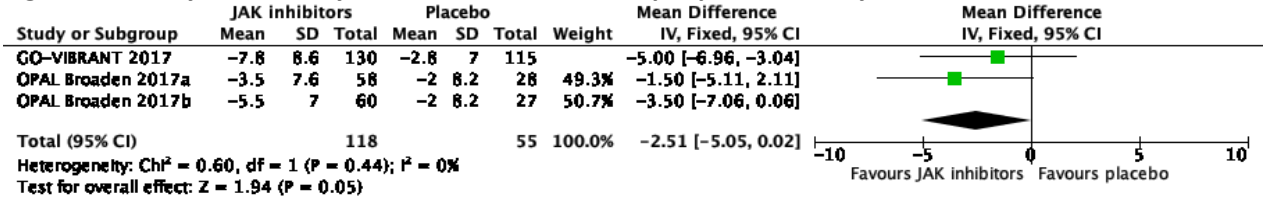


Figure 75: Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline

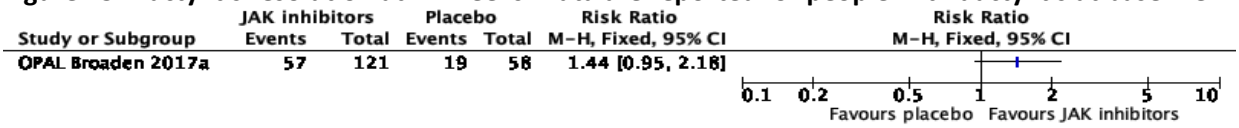


Figure 76: PASI response: ≥75% improvement at week 12 In people with ≥3% BSA affected with psoriasis

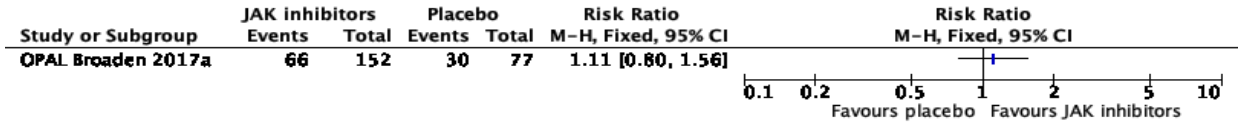
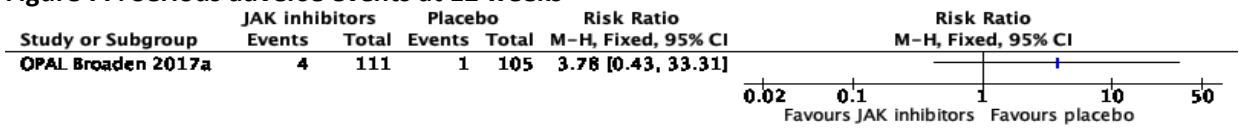


Figure 77: Serious adverse events at 12 weeks



E.2.7 TNF inhibitors versus placebo

Figure 78: Mortality at 16/24 weeks

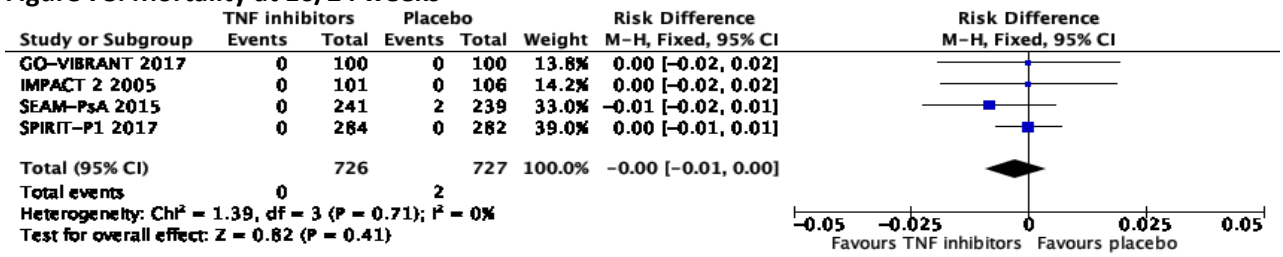


Figure 79: Change in SF-36 mental component score at 12/14/16/24 weeks

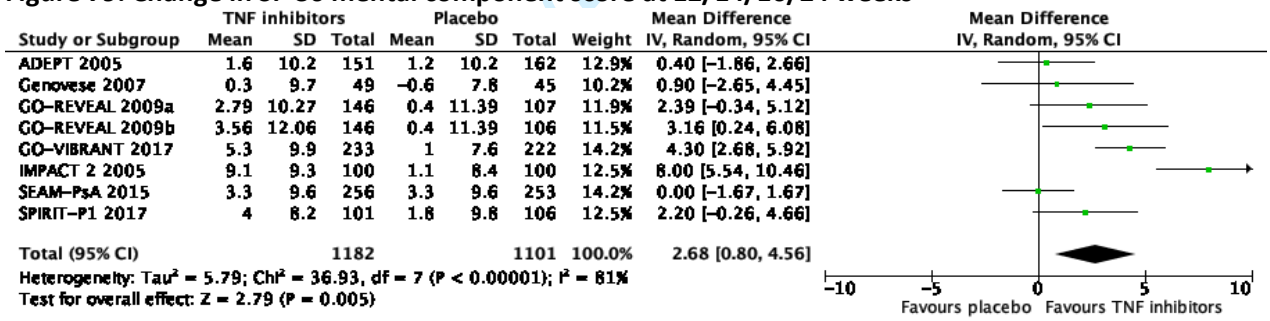


Figure 80: Change in SF-36 physical component score at 12/14/16/24 weeks

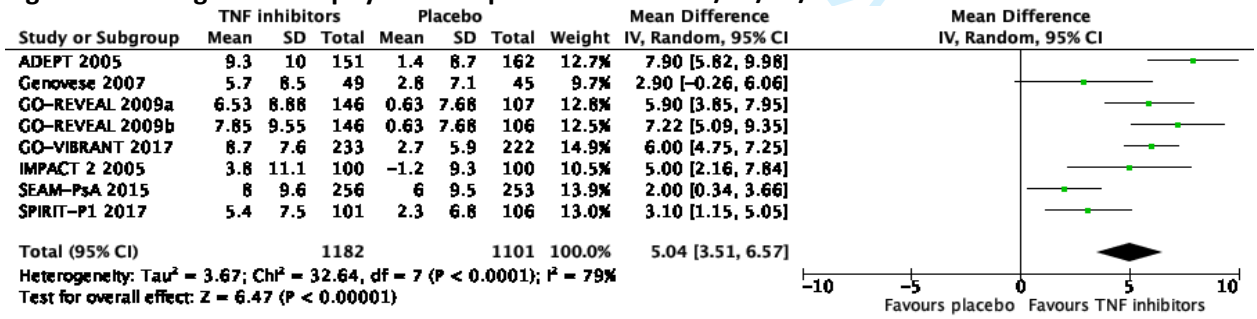


Figure 81: ACR20 response at week 12/14/22/24

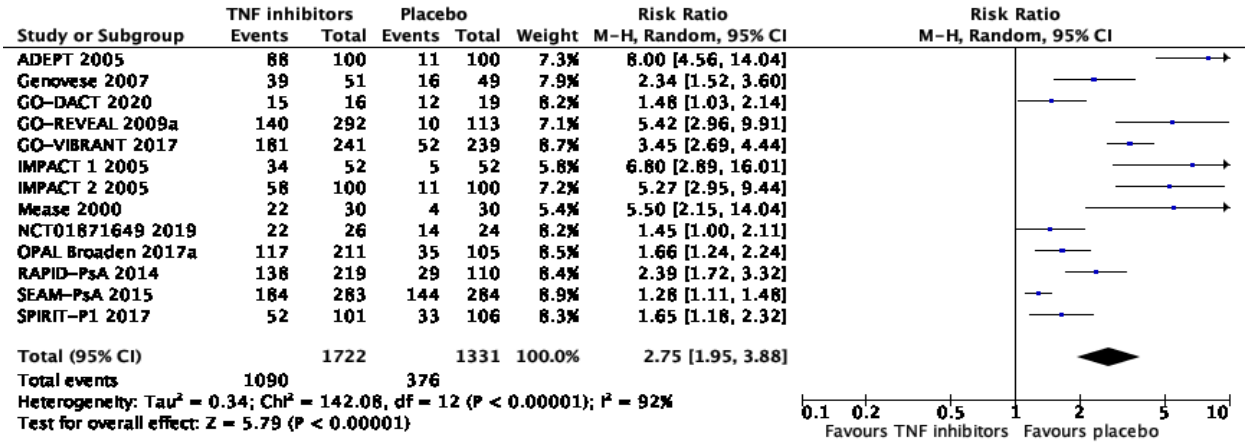


Figure 82: ACR50 response at week 12/14/22/24

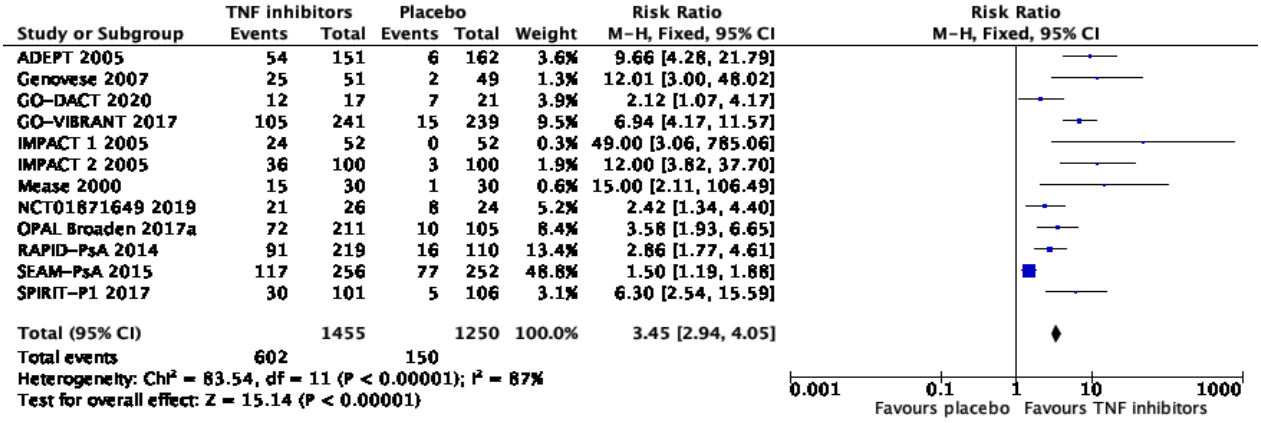


Figure 83: ACR70 response at week 12/14/22/24

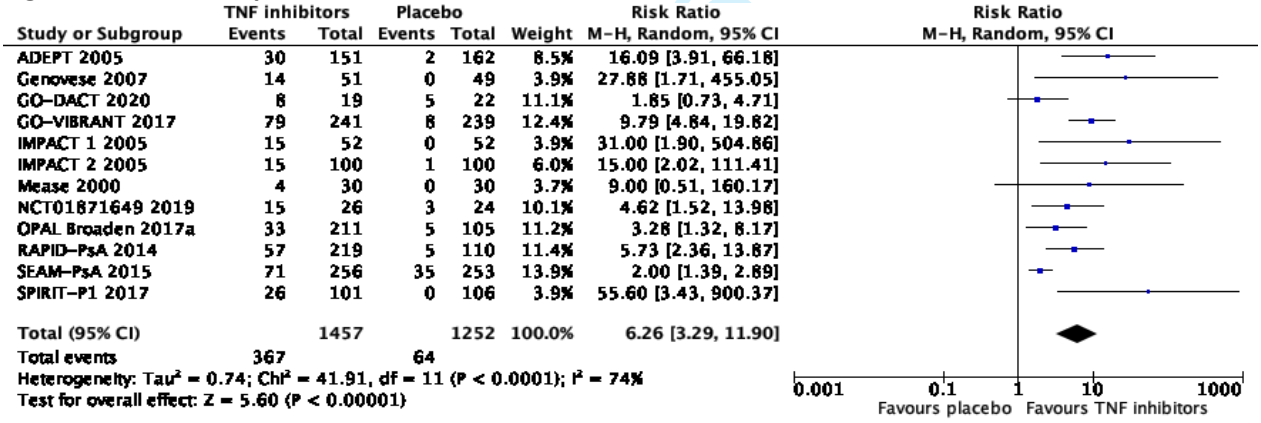


Figure 84: MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12/22/24 weeks

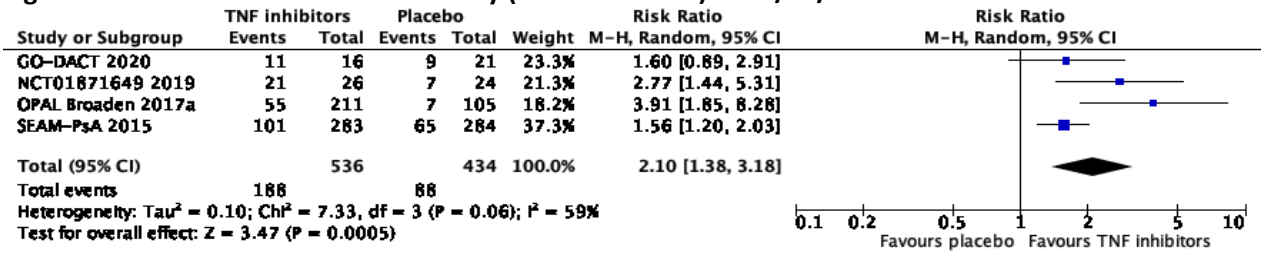


Figure 85: ≥1 dactylitis digits/dactylitis score over 0 at week 14/16

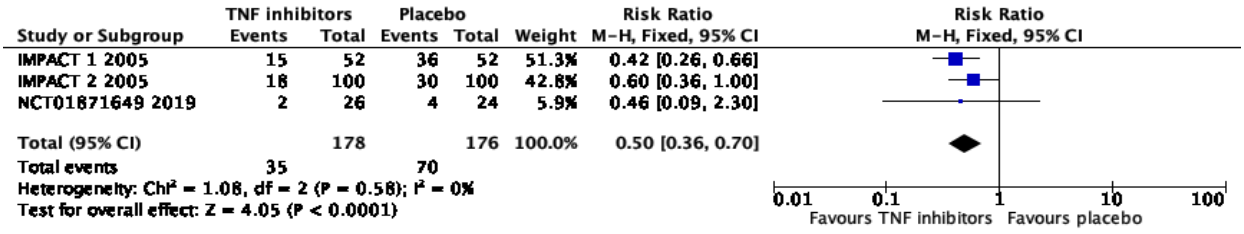


Figure 86: Dactylitis Severity Score at 12/14 weeks in people with dactylitis at baseline

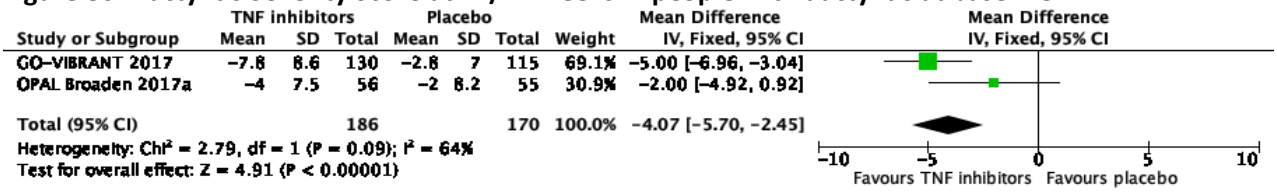


Figure 87: Dactylitis resolution at 12/24 weeks. Data are reported for people with dactylitis at baseline

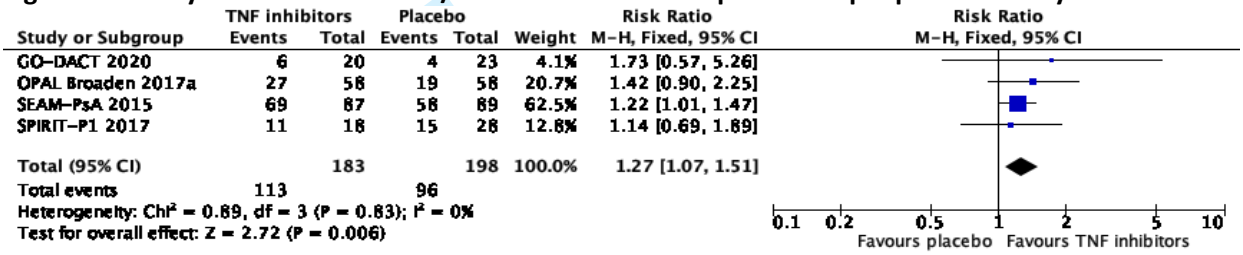


Figure 88: LEI / SPAECC Enthesitis index at week 12/14/24 in people with enthesitis at baseline

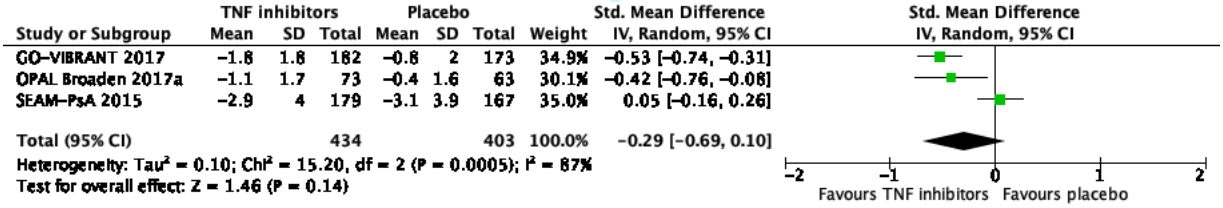


Figure 89: Enthesopathy/enthesitis at week 14/16

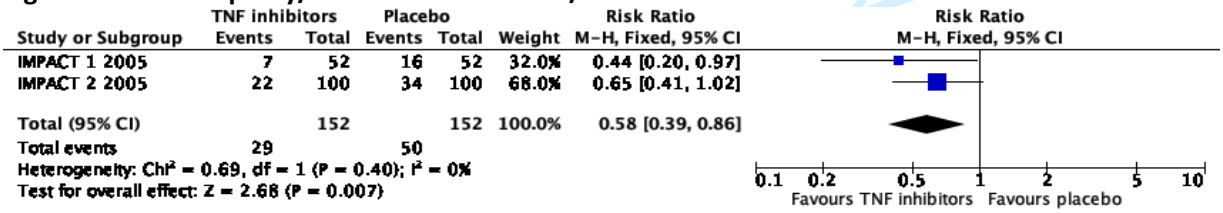


Figure 90: Enthesitis resolution at week 16/24 in people with enthesitis at baseline

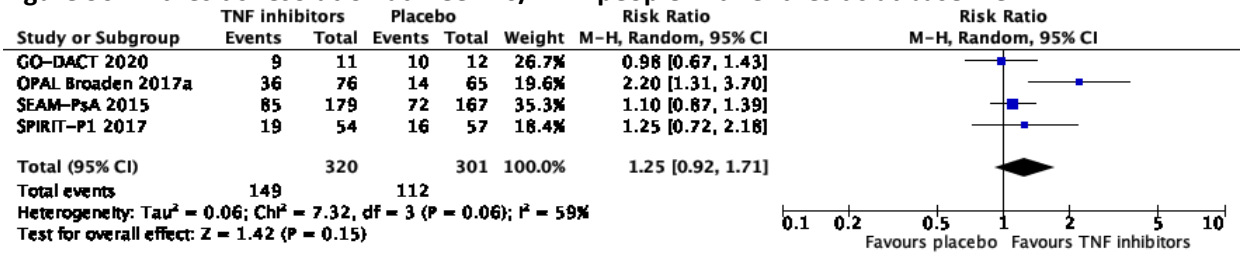


Figure 91: BASDAI20 response at 14 weeks in people with spondylitis and peripheral joint involvement

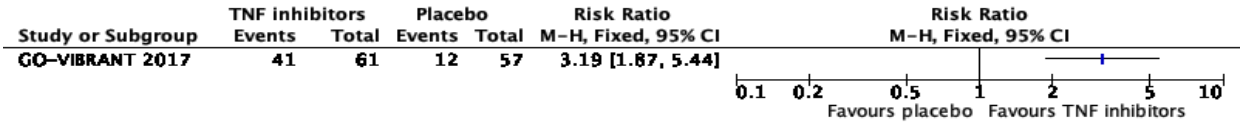


Figure 92: PASI response: ≥50% improvement at week 12/14

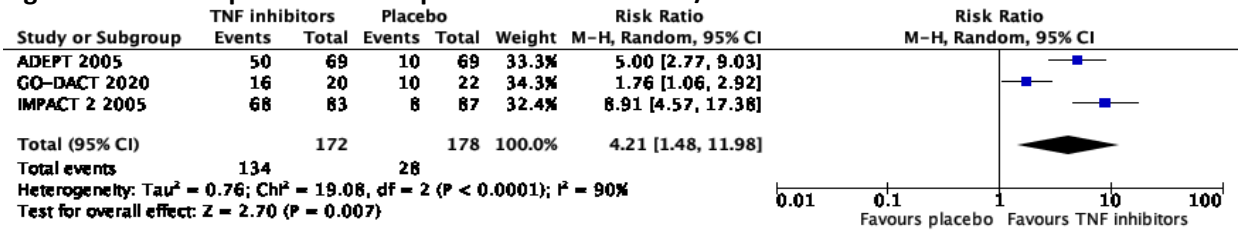


Figure 93: PASI response: ≥75% improvement at week 12/14

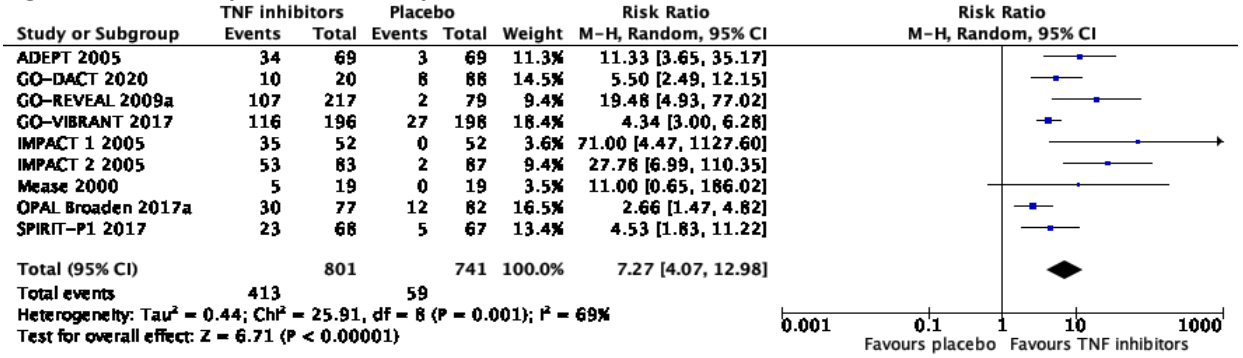


Figure 94: Change in mTSS/SHS: van der Heijde modified Total Sharp Score (0-528) at 24/48 weeks

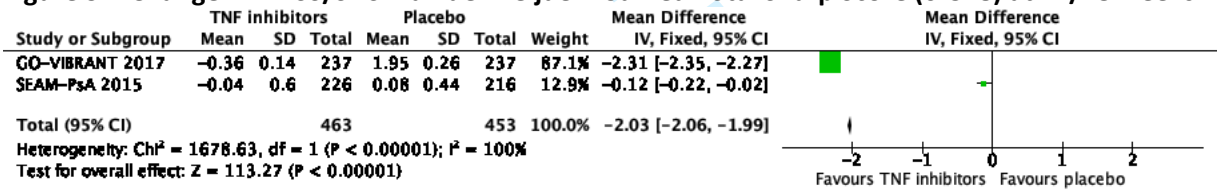
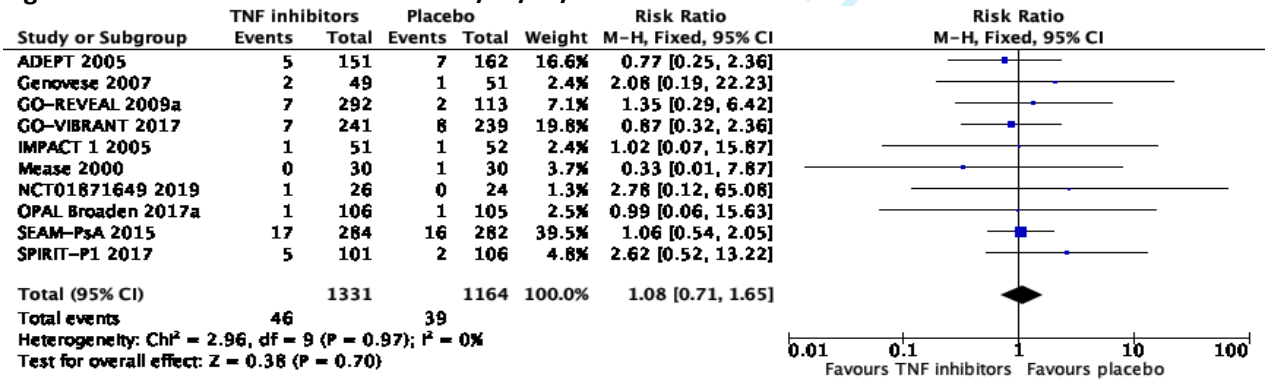


Figure 95: Serious adverse events at 12/14/24/48 weeks



Excluded studies

Table 16: studies excluded from the evidence review

Study	Exclusion reason
Abdulrahim 2019(55)	Unable to obtain
Atteno 2010(54)	Comparison of TNF inhibitors
Baranauskaite 2012(70)	No placebo use in comparator group
Bilal 2018(56)	Unable to obtain
Blegvad 2019(57)	Unable to obtain
Carron 2017(75)	Incorrect population
Caso 2020(58)	Unable to obtain
Craig 2020(59)	Unable to obtain
De Marco 2017(40)	Trial protocol
Dressler 2019(60)	Systematic review with different inclusion criteria however included studies were checked for this review
Garcia-Montoya 2018(71)	Literature review
Glatt 2018(73)	No outcomes reported in the b/tsDMARD naive subgroup
Gottlieb 2009(41)	Included people using bDMARDs / tsDMARDs without subgroup analysis
Gottlieb 2015(42)	Unable to obtain
Griffiths 2015(43)	Unclear if the people are bDMARDs / tsDMARDs naive
Kavanaugh 2006(44)	Outcomes of a trial after placebo group is moved to active treatment
Kavanaugh 2014(45)	Includes a mix of people who were exposed to bDMARDs and people who are bDMARD naive
Kerschbaumer 2020(61)	Systematic review with different inclusion criteria however included studies were checked for this review
Lu 2019(62)	Systematic review with different inclusion criteria however included studies were checked for this review
McInnes 2018(46)	Systematic review with different inclusion criteria however included studies were checked for this review
Mease 2004(72)	Unclear if the population is naive to b/tsDMARD treatment
Ogdie 2020(48)	Systematic review with different inclusion criteria however included studies were checked for this review
Ohtsuki 2019(47)	A subgroup of the population had psoriatic arthritis and they may or may not have been bDMARD or tsDMARD naive
Orbai 2019(49)	Population included people who were bDMARD naive but seperate analysis not provided in this paper
Ruyssen-Witrand 2020(63)	Systematic review with different inclusion criteria however included studies were checked for this review
Schett 2012(50)	Population included people who were bDMARD and tsDMARD naive but seperate analysis not provided in this paper
Simons 2020(64)	Systematic review with different inclusion criteria however included studies were checked for this review
Song 2018(65)	Systematic review with different inclusion criteria however included studies were checked for this review

Study	Exclusion reason
Song 2019(66)	Systematic review with different inclusion criteria however included studies were checked for this review
Strand 2013(74)	No outcomes reported in the b/tsDMARD naive subgroup
Strand 2018(51)	Unable to obtain
Strand 2018(67)	Systematic review with different inclusion criteria however included studies were checked for this review
Strand 2019(68)	Systematic review with different inclusion criteria however included studies were checked for this review
Thaçi 2017(52)	Population were people with severe plaque psoriasis
Torii 2010(53)	Population included people with plaque psoriasis, a number of whom had psoriatic arthritis. Prior bDMARD and tsDMARD treatment unclear.
Wu 2018(69)	Systematic review with different inclusion criteria however included studies were checked for this review

British Society for Rheumatology

Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on b/tsDMARD treatment of people with psoriatic arthritis and uveitis

BSR Guideline

Intervention evidence review

October 2020

Contents

1 b/tsDMARD treatment for people with psoriatic arthritis and uveitis

1.1 In adults with active psoriatic arthritis and uveitis, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo

1.2 INTRODUCTION

Uveitis is more common in people with psoriatic arthritis. This review seeks to establish what b/tsDMARD treatment is most effective in addressing both psoriatic arthritis symptoms and also uveitis symptoms.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with active psoriatic arthritis with uveitis who are b/tsDMARDS naïve
Intervention	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors abatacept apremilast JAK inhibitors
Comparison	Comparison of interventions or to placebo
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life including SF-36, PsAQoL (continuous) Arthritis • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) Psoriasis (in those with psoriasis at baseline) • Psoriasis score (PASI / IGA / BSA) (continuous) **Important** Arthritis • Radiological progression (continuous) Adverse Events

	• Serious adverse events (dichotomous) **The outcomes below are extracted if studies do not report ACR response.** • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous), • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted to find RCTs or observational studies comparing b/tsDMARDs to each other or placebo in people with psoriatic arthritis and uveitis. Zero studies were included in this review.

1.4.2 Excluded studies

The Excluded studies table can be found in the appendix.

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The outcomes were assigned to cover peripheral psoriatic arthritis and also uveisits. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. The uveitis outcomes were designed to cover the effects of uveitis on people with PsA and highight how treatment can ameliorate them alongside peripheral arthritis symptoms.

Benefits and harms

No studies were included in this review and the group spoke about their experiences and their understanding of research in the area.

Uveitis is an umbrella term that accounts for over 35 conditions. However wtihin an anatomical taxonomy (SUN reference) over 50% of uveitic conditions are related to systemic disease. The most common systemic associations include (although recognising global variations): seronegative and seropositive spondyloarthropathies such as psoriatic arthritis, and multiple sclerosis andsarcoidosis. There is a challenge to finding effective treatments for uveitis, separated by each of the underlying conditions. Therefore to date, trials for uveitis have mostly incorporated collective uveitic conditions. This means that no trials were found that answered the PICO for this clinical question.

The group were aware of a number of trials and the overall outcomes of those trials. The trials that led to licensing were in adalimumab, and they are called the "VISUAL" studies. There were 3 trials and were in a wider uveitis population that included a number of people with psoriatic arthritis. The outcome of these studies was agreement that adalimumab is effective for active / sight threatening uveitis. People rarely have adalimumab alone and usually there is a backbone of methotrexate or sometimes we use mycophenolate depending on the disease.

3 further significant studies were run on secukinumab and were terminated and showed that the endpoints of the trials were not met. However further analysis did show a beneficial effect of reducing the concomitant immunomodulatory therapy and therefore further discussion on dose and route of administration to assess IL-17 neutralisation is continuing.

Evidence in people specifically with spondyloarthropathy comes from nested trials within larger trials. They have looked mainly at people using adalimumab and whether it reduces relapse rates. They were not powered to show any effect in this subgroup but the signal was that adalimumab was effective. Also this has been supported in prospective open label studies.

There are trials currently or about to commence again on IL17 and IL12/23 blockade for uveitis. , and JAK inhibitors in children. However none of these trials are only in people with psoriatic arthritis.

The group agreed there is registry data linked to TNF inhibition in PSA patients with uveitis. Also there is low level evidence for the effectiveness of ixekizumab in this population from cohort studies.

The group spoke about how care works for people with psoriatic arthritis and uveitis works in the NHS. The ophthalmology and rheumatology care teams agree a treatment strategy and that is put in place.

Treatment of minor uveitis begins with topical steroids. This could be followed by local therapy, which is now also considering depo steroid therapy. This might be effective and there is no need for further treatment escalation linked to uveitis.

Anterior uveitis over time has a lifetime incidence of sight threatening disease of about 12% over lifetime. So any relapses can be justifiably treated by topical treatment without escalation, if there's a concern that it's at all sight threatening is when it is escalated.

Therefore people with moderate to severe disease may be escalated and this is likely to involve TNF inhibitors. This is primarily adalimumab as that is where the evidence sits but ixekizumab could also be prescribed. The biggest caveat there is that the TNF inhibitor not be right for peripheral arthritis symptoms and this is where the multi-disciplinary decision-making comes to the fore.

Length of treatment with adalimumab is very condition dependent. Median length of time is two years and then review. However there are people with certain diseases where it is a lifetime treatment.

The group spoke specifically about etanercept which has been thought to increase the chance of a person developing uveitis. However it was agreed that this evidence is weak but also that fusion proteins, such as etanercept, have shown no benefit in the outcomes of uveitis.

Aside from the treatment of relapsing uveitis, the group spoke about the decision to change systemic treatment in people who have a psoriatic arthritis flare but whose uveitis is stable. A situation could arise where a psoriatic arthritis flare indicates a change of treatment away from a TNF inhibitor that was effective at making a person uveitis stable. The group agreed this is a risk for their uveitis stability and their treatment should be discussed among the person's multi-disciplinary team and the person themselves to agree a way forward.

Cost effectiveness and resource use

Other factors the committee took into account

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British Society for Rheumatology Appendices

Appendix A: **Review protocols**

Table 2: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020215861
1.	Review title	Biologic and targeted synthetic DMARDs for PsA with uveitis
2.	Review question	In adults with active psoriatic arthritis and uveitis, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo?
3.	Objective	This review seeks to assess the clinical effectiveness of biologic and targeted synthetic disease modifying anti-Rheumatic Drugs (b/tsDMARDS) in the treatment of psoriatic arthritis with uveitis in comparison with placebo or each other.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.

5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with active psoriatic arthritis with uveitis who are b/tsDMARDS naïve
7.	Intervention/Exposure/Test	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept apremilast JAK inhibitors
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions or to placebo
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous)

		• Quality of life (continuous) <u>Arthritis</u>: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	

		Adverse Events • Serious adverse events (dichotomous) **These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous) Outcome timepoints are study defined.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies.

		Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Anatomical subgroup: Anterior Intermediate Pan uveitis Posterior uveitis.
18.	Anticipated or actual start date	12/10/20
19.	Anticipated completion date	30/10/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.

21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.

For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 16 October 2020	RCTs or observational studies filters
Embase (ProQuest)	1974 – 16 October 2020	RCTs or observational studies filters
The Cochrane Library (Wiley)	Cochrane Reviews to issue 10 of 12, October 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2	EMB.EXACT.EXPLODE("psoriatic arthritis")
3	TI,AB(Psoriasis or Psoriatic)
4	TI,AB(arthrosis or *arthritis)
5	S3 n/3 S4
6	S1 or S2 or S5
7	TI,AB(Uveiti*)
8	TI,AB(Eye* n/5 inflam*)
9	MESH.EXACT.EXPLODE("Uveitis") OR EMB.EXACT.EXPLODE("uveitis")
10	S7 or S8 or S9
11	TI,AB("TNF inhibitor" or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
12	TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
13	TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
14	TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
15	TI,AB(Abatacept)
16	TI,AB(apremilast)
17	TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
18	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

19	TI(trial)
20	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
21	TI,AB(doubl* n/1 blind*)
22	TI,AB(singl* n/1 blind*)
23	RTYPE(controlled clinical trial)
24	RTYPE(randomized controlled trial)
25	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
26	EMB.EXACT.EXPLODE("crossover procedure")
27	EMB.EXACT.EXPLODE("single blind procedure")
28	EMB.EXACT.EXPLODE("randomized controlled trial")
29	EMB.EXACT.EXPLODE("double blind procedure")
30	S19 OR S20 OR S21 OR S22 OR S23 OR 24 OR S25 OR S26 OR S27 OR S28 OR S29
31	S6 and S10 and S18 AND S30
32	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
33	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
34	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
35	TI,AB(before n/2 after n/2 stud*)
36	TI,AB(longitudinal or retrospective or prospective or cross sectional)
37	TI,AB(study or studies or review or analys* or cohort* or data)
38	S36 and S37
39	S32 OR S33 OR S34 OR S38
40	S6 AND S10 AND S18 AND S39
41	S31 OR S40

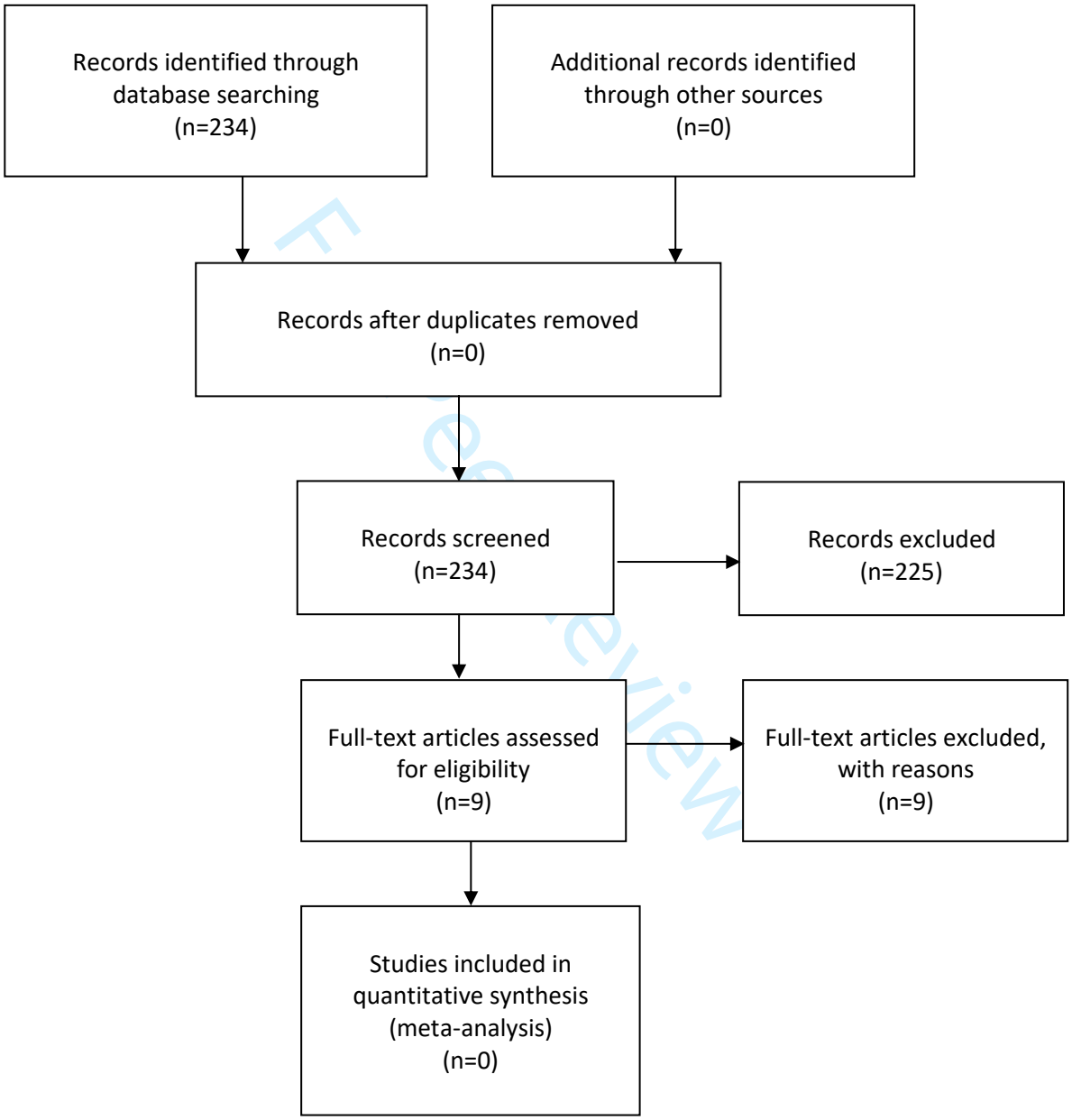
Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2	arthrosis or *arthritis
#3	Psoriasis or Psoriatic
#4	#2 and #3
#5	#1 or #4
#6	Uveiti*

#7	Eye* and inflam*
#8	MeSH descriptor: [Uveitis] explode all trees
#9	#6 or #7 or #8
#10	#5 and #9

Appendix C: **Clinical evidence selection**

Figure 1: Flow chart of clinical study selection



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Appendix D: **Excluded studies**

Table 4: studies excluded from the evidence review

Study	Exclusion reason
Arepalli 2019(1)	Review of biologics in people with uveitis associated with spondylarthritis
Borrás-Blasco 2015(2)	Review of case series where uveitis was treated with TNF inhibitors
Braun 2005(3)	Review of reporting anterior uveitis flares of in trials of TNF inhibitors in people with ankylosing spondylitis
Díaz-Llopis 2012(4)	Case series of people with refractory uveitis
Guignard 2006(5)	Study comparing TNF inhibitors in an ankylosing spondylitis population
Mitulescu 2018(6)	Review of treatment of uveitis in people with spondylarthritis
Rudwaleit 2009(7)	Non-comparative study of TNF inhibitors in people with ankylosing spondylitis and uveitis
Sharma 2017(8)	Paper detailing the manifestation of uveitis in spondylarthrosis and possible treatments
Silvestri 2020(9)	Not a comparison of treatments for uveitis

Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on b/tsDMARD treatment of people with psoriatic arthritis and inflammatory bowel disease

BSR Guideline

Intervention evidence review

October 2020

Contents

1b/tsDMARD treatment for people with psoriatic arthritis and inflammatory bowel disease

1.1 In adults with active psoriatic arthritis and inflammatory bowel disease, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo?

1.2 INTRODUCTION

IBD is more common in people with psoriatic arthritis. This review seeks to establish the most effective b/tsDMARD treatment for psoriatic arthritis symptoms and also IBD symptoms.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with active psoriatic arthritis with inflammatory bowel disease who are b/tsDMARDS naïve
Intervention	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept apremilast JAK inhibitors
Comparison	Comparison of interventions or to placebo
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life including SF-36, PsAQoL (continuous) Arthritis • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Psoriasis in those with psoriasis at baseline • Psoriasis score (PASI / IGA / BSA) (continuous) **Important** Arthritis • Radiological progression (continuous) Adverse Events

	• Serious adverse events (dichotomous) **The outcomes below are extracted if studies do not report ACR response.** • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • PsARC score • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	Randomised Controlled Trials (RCT's)- inclusion and exclusion criteria as stated above If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted to find RCTs or observational studies comparing b/tsDMARDs to each other or placebo in people with psoriatic arthritis and inflammatory bowel disease. Zero studies were included in this review.

1.4.2 Excluded studies

See the Excluded studies table in appendix D

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The outcomes were assigned to cover peripheral psoriatic arthritis and also uveisits. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. The uveitis outcomes were designed to cover the effects of uveitis on people with PsA and highight how treatment can ameliorate them alongside peripheral arthritis symptoms.

Benefits and harms

No studies were found that met the inclusion criteria for this question. Therefore the group concluded there are no good quality comparative trials for b/tsDMADs in people with PsA and IBD.

However there are many studies in relevant b/tsDMARDs in the IBD population who may or may not have co-occurring PsA. Well constructed guidelines such as those of the British Society of Gastroenterology (BSG) and those of the European Crohn's and Colitis Organisation (ECCO) have been written and are well regarded. The BSG guideline {Lamb, 2019 #576} was created utilising a UK perspective while the ECCO guideline {Torres, 2019 #577} gives a wider European perspective.

The purpose of this guideline is not to challenge or recrate what they have produced but to provide practical and useful recommendations that can be applied to people who have both PsA and either ulcerative colitis (UC) or Crohn's disease (CD).

The group decided that given the lack of direct evidence in people with co-occurring PsA and IBD, the guideline could offer summations of the relevant medications in people who have either PsA or IBD. Thus clinicians could offer treatment to people based specifically on their manifestations of PsA and their IBD co-morbidity, such as UC. The group agreed it would be useful to distinguish between UC and CD trial results and to make recommendations specific to each.

A group member stated that purely from an IBD perspective the relevant b/tsDMARD medications can be divided into 4 distinct groups. One is a group where there is high quality evidence supporting their use in IBD, either UC and/or CD. Promising medications where they have promising phase 2 trials and phase 3 trials have yet to be completed. These medications are not licensed for IBD but may be prescribed in certain situations. Next there are medications for which no studies have been completed and their safety and effectiveness is uncertain. A fourth group consists of medications that have shown no benefit after well conducted trials, a relevant example of this would be tofacitinib. Finally a fifth group would be where medications have adversely effected the IBD symptoms and this in this case this is primarily linked to IL-17 inhibitors, such as secukinumab or ixekizumab.

There are complexities to this approach as certain medications have not been assessed or have shown uncertain efficacy or safety making them difficult to assign. The group spoke specifically about IL-17 inhibitors as they did not want to completely rule out their use in people with IBD. There are people with well-controlled IBD and no other therapeutic alternatives for whom IL-17 may be the best option. This again, should be a decision made in the multispecialty team.

In terms of syncing up PsA and IBD treatment the group spoke about dose differentials. Doses utilised in IBD have a higher threshold than PsA and can be given more often. The group agreed it makes sense to utilise the higher dose where there is a differential and this will more often be the

dose indicated for IBD. The potential of dose de-escalation was also discussed. The group was clear that the key to this being a good process for the patient is good communication between the multidisciplinary and multispecialty teams.

Another matter of syncing treatments is the use of vedolizumab for IBD. It is not known to be effective for arthritis so further medication may be required. It can be combined with b/tsDMARDs but commissioners may resist funding 2 separate drugs when a single different drug could be used. Also, from a person perspective, it may be preferable to utilise a single medication rather than 2. This should be a discussion amongst the treating physicians to find out what can be offered to the person.

The group understood there are gastroenterology specific treatments for mild flares such as enemas, suppositories or topical therapies that do not involve a change of systemic treatment. It is appropriate to alert the gastroenterology team to a possible flare to allow these treatments to be deployed. Linked to the above, if a calprotectin stool (faecal) test is used to detect inflammation in the intestine, the result of this test should similarly be reported to the gastroenterology team.

The gastroenterologist on the group indicated that the use of NSAIDs is more common than is generally thought. The data that they cause IBD flares is based on case series data from the 1980s. However this is not upheld by population level data that has been available since then. More recent analysis of COX-II inhibitors also does not support this and the modern thinking is to prescribe NSAIDs where required. Ideally they would use selective COX-II inhibitors at the lowest effective dose for the shortest possible time.

“There have been two systematic literature reviews assessing the effect of non-selective NSAIDs and selective COX2i on IBD exacerbation. The first, was a Cochrane systematic review {Miao, 2014 #578} that found an RCT of celecoxib (up to 14 days use) {Sandborn, 2006 #579} and an RCT of etoricoxib (up to 3 months use) {El Miedany, 2006 #580}, and concluded that there is no evidence that COX2i increases IBD exacerbation. The second, and more recent SLR included 18 somewhat heterogenous trials of COX2i and non-selective NSAIDs, and found no association between their use and exacerbation of IBD in the short term (<3 months of use) {Moninuola, 2018 #581}.

According to two recent Cochrane Database Systematic Reviews, whilst methotrexate is effective in maintaining clinical remission in CD, it is ineffective at inducing remission {Patel, 2014 #582} and methotrexate is ineffective for the management of UC {Wang, 2015 #583}. Sulfasalazine is metabolised in the colon to mesalazine, which at moderate to high doses has shown some efficacy in inducing {Wang, 2016 #584} and maintaining {Wang, 2016 #585} remission in mild-to-moderate UC according to two recent Cochrane Database Systematic Reviews. Leflunomide has not shown efficacy for IBD {Di Jiang, 2020 #586}.”

The group spoke about people who have a first degree relative with IBD. This increases the likelihood the person will develop IBD and limits whether they should be prescribed medications known to adversely effect IBD symptoms such as IL-17 inhibitors. Also, there are people with persistent lower body GI symptoms that have not been assessed by the gastroenterology team who and not be treated with IL-17 inhibitors until IBD is ruled out. For both groups, there should be a low threshold for opening discussions with the gastroenterology team.

Cost effectiveness and resource use

Other factors the committee took into account

1
2

References

1. Guidi L, Pugliese D, Armuzzi A. Update on the management of inflammatory bowel disease: Specific role of adalimumab. Clinical and Experimental Gastroenterology. 2011;4(1):163-72.
2. Kavanaugh A, Singh AG. Rheumatologic complications of inflammatory bowel diseases. Practical Gastroenterology. 2017;41(5):36-9.
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4. Whitlock SM, Enos CW, Armstrong AW, Gottlieb A, Langley RG, Lebwohl M, et al. Management of psoriasis in patients with inflammatory bowel disease: From the Medical Board of the National Psoriasis Foundation. Journal of the American Academy of Dermatology. 2018;78(2):383-94.

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Appendices

Appendix A: Review protocols

Table 2: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020215852
1.	Review title	Biologic and targeted synthetic DMARDs for PsA with inflammatory bowel disease
2.	Review question	In adults with active psoriatic arthritis and IBD, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, abatacept, apremilast or JAK inhibitors, in comparison to each other or placebo?
3.	Objective	This review seeks to assess the clinical effectiveness of biologic and targeted synthetic disease modifying anti-Rheumatic Drugs (b/tsDMARDS) in the treatment of psoriatic arthritis with IBD in comparison with placebo or each other.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with active psoriatic arthritis with inflammatory bowel disease who are b/tsDMARDS naïve
7.	Intervention/Exposure/Test	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept apremilast JAK inhibitors

8.	Comparator/Reference standard/Confounding factors	Comparison of interventions or to placebo
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (e.g. age…) • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	Adverse Events • Serious adverse events (dichotomous)

		These outcomes are extracted if studies do not report ACR response criteria. Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous) Outcome timepoints are study defined.
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16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	None
18.	Anticipated or actual start date	15/10/20

19.	Anticipated completion date	25/10/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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The Cochrane Library (Wiley)	Cochrane Reviews to issue 10 of 12, October 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2	EMB.EXACT.EXPLODE("psoriatic arthritis")
3	TI,AB(Psoriasis or Psoriatic)
4	TI,AB(arthrosis or *arthritis)
5	S3 n/3 S4
6	S1 or S2 or S5
7	TI,AB("ulcerative colitis" OR crohn* OR IBD OR “Inflammatory bowel disease”)
8	EMB.EXACT.EXPLODE("inflammatory bowel disease")
9	MESH.EXACT.EXPLODE("Inflammatory Bowel Diseases")
10	S7 or S8 or S9
11	TI,AB(“TNF inhibitor” or “Tumor necrosis factor inhibitor” or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
12	TI,AB(“IL-12/23 inhibitor” or “IL12/23 inhibitor” or Ustekinumab or briankizumab)
13	TI,AB(“IL23 inhibitor” or “IL-23 inhibitor” or guselkumab or tildrakizumab or risankizumab or mirikizumab)
14	TI,AB(“IL17 inhibitor” or “IL-17 inhibitor” or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
15	TI,AB(Abatacept)
16	TI,AB(apremilast)
17	TI,AB(“JAK inhibitors” or “Janus kinase inhibitor” or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)

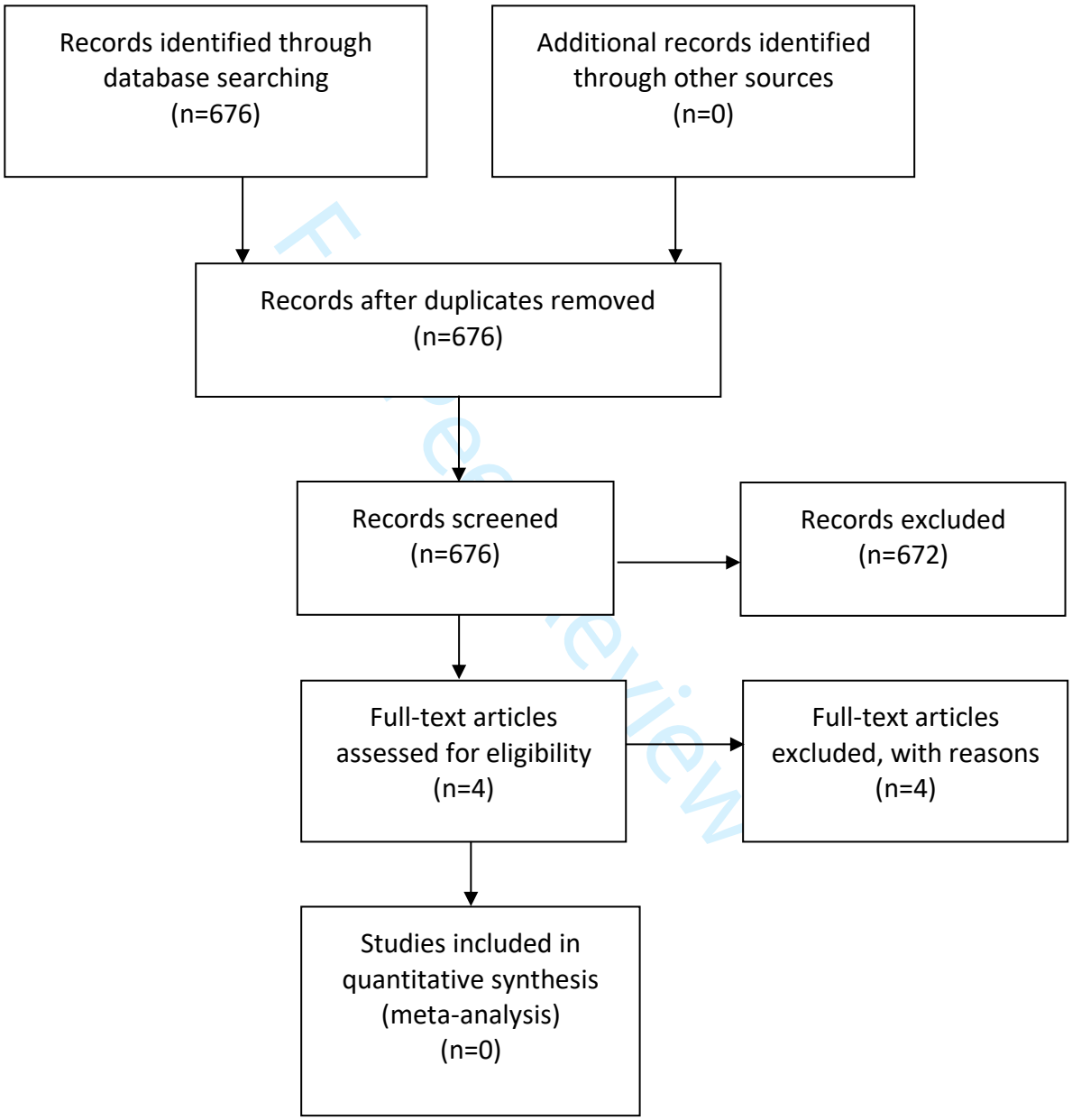
18	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
19	TI(trial)
20	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
21	TI,AB(doubl* n/1 blind*)
22	TI,AB(singl* n/1 blind*)
23	RTYPE(controlled clinical trial)
24	RTYPE(randomized controlled trial)
25	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
26	EMB.EXACT.EXPLODE("crossover procedure")
27	EMB.EXACT.EXPLODE("single blind procedure")
28	EMB.EXACT.EXPLODE("randomized controlled trial")
29	EMB.EXACT.EXPLODE("double blind procedure")
30	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
31	S6 and S10 and S18 AND S30
32	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
33	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
34	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
35	TI,AB(before n/2 after n/2 stud*)
36	TI,AB(longitudinal or retrospective or prospective or cross sectional)
37	TI,AB(study or studies or review or analys* or cohort* or data)
38	S36 and S37
39	S32 OR S33 OR S34 OR S38
40	S6 AND S10 AND S18 AND S39
41	S31 OR S40

Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2	arthrosis or *arthritis
#3	Psoriasis or Psoriatic
#4	#2 and #3
#5	#1 or #4
#6	ulcerative colitis OR crohn* OR IBD OR “Inflammatory bowel disease”
#7	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#8	#6 or #7
#9	#5 and #8

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D: **Excluded studies**

Table 4: studies excluded from the evidence review

Study	Exclusion reason
Guidi 2011(1)	Review of treatment papers for inflammatory bowel disease without direct reference to treatment with co-occurring PsA
Kavanaugh 2017(2)	Review paper on IBD with rheumatologic manifestations
Pugliese 2019(3)	Non-comparative study looking at people with IDB and either psoriatic arthritis or psoriasis
Whitlock 2018(4)	Review of trials of relevant medication in either IBD populations or psoriatic arthritis populations.

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Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on treat to target

BSR Guideline

Intervention evidence review

July 2020

Contents

1Treat to target

1.1 In adults with active psoriatic arthritis, what is the clinical effectiveness of a treat to target strategy compared with usual care?

1.2 INTRODUCTION

Treat to target is a treatment strategy that involves setting a specific testing goal that signals either remission or a low disease state. There is a regular testing program to monitor progress and people's medication regimen is switched promptly if progress isn't made. This review seeks to assess whether this treatment strategy is superior to usual care.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults commencing b/tsDMARDS for the treatment of active psoriatic arthritis
Intervention	Treat to target
Comparison	Usual care
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: • American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Minimal disease activity (MDA) (dichotomous) • Radiological progression (continuous) Enthesitis: • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS 20/40/50/70 response (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Uveitis • VRQol (continuous) • Visual acuity (continuous)

	• SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous)
Study design	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search we conducted to find RCTs or observational studies comparing a treat to target strategy to usual care in people with active psoriatic arthritis.

One RCT was included in the review.(1) This study did not begin when a person starts b/tsDMARDs but in fact with recent onset of the condition and had not previously received any DMARD treatment. This was not considered indirect evidence as either strategy can, and in some bases did, lead to treatment with b/tsDMARDS.

1.4.2 Excluded studies

See the Excluded studies table in

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
TICOPA trial (Coates 2014)(1)	Treat to target versus usual care For 48 weeks	Adults with recent onset (<24 months symptom duration) psoriatic arthritis who had never previously received treatment with DMARDs	• Mortality • Quality of life • ACR20/50/70 • Radiological progression • Enthesitis score • BASDAI score • Dactylitis score • Psoriasis via PASI75 • Serious adverse events	Multicentre UK study Funded by Arthritis Research UK and Pfizer.

1.4.4 Quality assessment of clinical studies included in the evidence review

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	0/101 (0.0%)	0/105 (0.0%)	not estimable	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (follow up: mean 48 weeks; assessed with: mean QALYs via EQ-5D)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	101	205	-	MD **0.04 higher** (0.01 higher to 0.06 higher)	⊕⊕◯◯ LOW	CRITICAL
ACR20 (follow up: mean 48 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	55/89 (61.8%)	37/84 (44.0%)	**OR 1.91** (1.03 to 3.55)	**160 more per 1,000** (from 7 more to 296 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 (follow up: mean 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	44/86 (51.2%)	27/81 (33.3%)	**OR 2.36** (1.25 to 4.47)	**208 more per 1,000** (from 51 more to 358 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR70 (follow up: mean 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	33/87 (37.9%)	15/86 (17.4%)	**OR 2.64** (1.32 to 5.26)	**184 more per 1,000** (from 44 more to 352 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Radiological progression (follow up: mean 48 weeks; assessed with: presence of erosive disease)												
1	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	29/89 (32.6%)	25/87 (28.7%)	**RR 1.13** (0.73 to 1.77)	**37 more per 1,000** (from 78 fewer to 221 more)	⊕◯◯◯ VERY LOW	CRITICAL
Enthesitis score in those with enthesitis at baseline (follow up: mean 48 weeks; assessed with: Lower score is better.)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [d]	none	Treat to target (n=73): median improvement (IQR) was 2 (0 to 4). Usual care (n=72): median improvement (IQR) was 1 (-1 to 4). Score at baseline was 4 for both groups. Unclear what score was used but could include Maastricht ankylosing spondylitis enthesitis index, the Leeds Enthesitis Index, and tenderness at the plantar fascia.				⊕⊕◯◯ LOW	CRITICAL

Change in Bath Ankylosing Spondylitis Disease activity Index (BASDAI) in people with axial disease at baseline (follow up: mean 48 weeks; assessed with: 0-10 where lower is better)

1	randomised trials	not serious	not serious	not serious	serious [d]	none	Treat to target (n=18): median change (IQR) was -3.9 (0.3 to -5.8). Usual care (n=21): median change (IQR) was -0.9 (0.1 to -3).				⊕⊕⊕◯ MODERATE	CRITICAL

Change in dactylitis score for those with dactylitis at baseline. (follow up: mean 48 weeks; assessed with: Lower is better. Leeds Dactylitis Index.)

1	randomised trials	serious [b]	not serious	not serious	serious [d]	none	Treat to target (n=31): median improvement (IQR) was 38 (20 to 70). Usual care (n=22): median improvement (IQR) was 58.5 (30 to 112). Median score of 39 at baseline.				⊕⊕◯◯ LOW	CRITICAL

Psoriasis (follow up: mean 48 weeks; assessed with: PASI75)

1	randomised trials	not serious	not serious	not serious	not serious	none	44/75 (58.7%)	27/81 (33.3%)	**OR 2.92** (1.56 to 5.65)	**260 more per 1,000** (from 105 more to 405 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Serious adverse events (follow up: mean 48 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [c]	none	14/101 (13.9%)	8/105 (7.6%)	**RR 1.82** (0.80 to 4.15)	**62 more per 1,000** (from 15 fewer to 240 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Unable to assess imprecision due to 0 events with either group
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
c. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
d. Unable to assess the median and IQR imprecision

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1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and arthritis disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures capable of capturing medication effects on other disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA, are available.

1.5.2 Benefits and harms

One RCT was included in this evidence review. The senior authors were both on the group and were limited to answering factual questions on the study and had no role in formulating the recommendation.

The RCT provided indirect evidence, in that it included people who did not have b/tsDMARD treatment during the course of the trial. However, many were treated with biological drugs. It compared treat to target to usual care and found clinically important benefits for treat to target for most outcomes, including all ACR response criteria (20/50/70), enthesitis score, BASDAI, and dactylitis score. One outcome, serious adverse events favoured usual care. No benefit was found for either strategy in terms of mmortality, quality of life, and radiological progression.

A lay member indicated that some people are very worried about escalating therapy due to adverse events. However, treat to target is seen positively by patients in his opinion. He indicated it is important to discuss all aspects with the patient especially what they could expect to get out of it and jointly deciding what the target should be for them. It was also agreed that some people with PsA will concentrate on joints symptoms and others on the skin/nail disease. Therefore, setting targets should be individualised and one size does not fit all. A member of the group said that goalsetting would be a way of future-proofing the guideline.

The group spoke more generally about the target setting and how this was undertaken in the TICOPA trial. The target in the trial was MDA and so the only evidence presented for this question was a trial utilising MDA as a target and the evidence indicated it has benefits across a range of domains. Given that this was the target utilised in the trial, the group agreed it was significant.
However, the group also considered whether they should recommend a multidimensional target rather than a unidimensional one. The group felt that utilising a single measurement of disease activity as a target can lead to people being switched too often in search of MDA without addressing the bigger picture of a person's symptoms. The group agreed the totality of the disease should be assessed when applying a treat to target strategy including all domains.

It was mentioned that other guidelines have addressed treat to target. ACR recommend treat to target approach in all patients with active PsA and EULAR recommendations 'treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy'. The group were keen to provide a practical guideline that supports routine clinical implementation.

The group understand the guideline will be utilized by physicians who are not experts in PsA and therefore must be usable by a wider audience.

1.5.3 Cost effectiveness and resource use

A treat to target strategy in TICOPA was more costly, partly due to the more frequent visits, and partly due to the more frequent use of biologics. Sensitivity analysis suggests likely cost effectiveness with reduction in drug cost (as available now) and review every 3 months, instead of monthly.

1.5.4 Other factors the committee took into account

References

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4. Dures E, Shepperd S, Mukherjee S, Robson J, Vlaev I, Walsh N, et al. Treat-to-target in PsA: methods and necessity. RMD open. 2020;6(1).
5. Gudbjörnsson B, Krogh NS. Low dosage with escalating dosage of infliximab in psoriatic arthritis gives the same treatment results as standard dosage of adalimumab or etanercept: Results from the nationwide registry ICEBIO. Scandinavian Journal of Rheumatology. 2012;41:65-6.
6. Machado PM, Deodhar A. Treat-to-target in axial spondyloarthritis: gold standard or fools' gold? Current opinion in rheumatology. 2019;31(4):344-8.
7. Gudbjornsson B, Geirsson AJ, Krogh NS. Low starting dosage of infliximab with possible escalating dosage in psoriatic arthritis gives the same treatment results as standard dosage of adalimumab or etanercept: results from the nationwide Icelandic ICEBIO registry. Psoriasis (Auckland, NZ). 2018;8:13-9.

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Appendices

Appendix A: **Review protocol**

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020200164
1.	Review title	Treat to target
2.	Review question	In adults with active psoriatic arthritis, what is the clinical effectiveness of a treat to target strategy compared to a not treat to target strategy compared with usual care?
3.	Objective	This review seeks to assess whether there are benefits to a treat to target strategy over a usual care treatment strategy in people on biologic of targeted synthetic DMARDs.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Inclusion: Adults commencing b/tsDMARDS for the treatment of active psoriatic arthritis
7.	Intervention/Exposure/Test	Treat to target treatment strategy

		Treat to target management strategy. Defined as a strategy that defines a treatment target (for example, remission or low disease activity) and applies tight control (for example, monthly visits and action) and respective therapeutic adaptions to reach this target. The treatment strategy often follows a protocol.
8.	Comparator/Reference standard/Confounding factors	Standard Care Standard care typically consists of less frequent visits, and less clearly defined criteria for what constitutes a good outcome. Typically, it is patient/physician global assessments that drive management choices, and a degree of disease activity is accepted. It is typically a more reactive and less aggressive approach to disease management, and is usually not protocol driven.
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) • Radiological progression Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 Dactylitis

		• Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**<u>These outcomes are extracted if studies do not report ACR response criteria.</u>** <u>Arthritis</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous)

		PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) <u>Other outcomes</u> • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	None
18.	Anticipated or actual start date	18/07/20
19.	Anticipated completion date	27/07/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.

21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below..

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 08 July 2020	Exclusions, RCT, non-randomised studies
Embase (ProQuest)	1974 – 08 July 2020	Exclusions, RCT, non-randomised studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 7 of 12	None

Medline (ProQuest) and Embase (ProQuest) search terms

1.	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2.	EMB.EXACT.EXPLODE("psoriatic arthritis")
3.	TI,AB(Psoriasis or Psoriatic)
4.	TI,AB(arthrosis or *arthritis)
5.	S3 n/3 S4
6.	S1 or S2 or S5
7.	MESH.EXACT("Anecdotes as Topic") OR MESH.EXACT("Letter") OR EMB.EXACT("letter") OR RTYPE(letter) or RTYPE(note) or RTYPE(editorial) OR MESH.EXACT("Editorial") OR MESH.EXACT("News") OR MESH.EXACT("Historical Article") OR MESH.EXACT("Comment") OR MESH.EXACT("Case Report") OR EMB.EXACT("case report") OR EMB.EXACT("case study") OR TI(LETTER) OR TI(COMMENT*)
8.	EMB.EXACT("randomized controlled trial") OR MESH.EXACT("Randomized Controlled Trial") or TI,AB(random*)
9.	S7 NOT S8
10.	MESH.EXACT("Animals") OR EMB.EXACT("animal")
11.	MESH.EXACT("Humans") OR EMB.EXACT("human")
12.	S10 NOT S11
13.	MESH.EXACT.EXPLODE("Animals, Laboratory") OR MESH.EXACT.EXPLODE("Animal Experimentation") OR MESH.EXACT.EXPLODE("Models, Animal") OR MESH.EXACT.EXPLODE("Rodentia") OR EMB.EXACT("nonhuman") OR EMB.EXACT.EXPLODE("animal experiment") OR EMB.EXACT.EXPLODE("experimental animal") OR EMB.EXACT("animal model") OR EMB.EXACT.EXPLODE("rodent") OR TI(RAT) OR TI(RATS) OR TI(MOUSE) OR TI(MICE)
14.	S9 OR S12 OR S13
15.	S6 NOT S14

16.	TI,AB(tight* n/1 control*)
17.	TI,AB(t2t)
18.	TI,AB(treat* n/2 target* or treat n/2 goal* or therap* n/2 target* or therap* n/2 goal*)
19.	TI,AB(symptom* n/2 reduc* or symptom* n/2 improv* or symptom* n/2 control*)
20.	TI,AB(low disease activity)
21.	S16 OR S17 OR S18 OR S19 OR S20
22.	TI(trial)
23.	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
24.	TI,AB(doubl* n/1 blind*)
25.	TI,AB(singl* n/1 blind*)
26.	RTYPE(controlled clinical trial)
27.	RTYPE(randomized controlled trial)
28.	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
29.	EMB.EXACT.EXPLODE("crossover procedure")
30.	EMB.EXACT.EXPLODE("single blind procedure")
31.	EMB.EXACT.EXPLODE("randomized controlled trial")
32.	EMB.EXACT.EXPLODE("double blind procedure")
33.	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
34.	S15 and S21 AND S33
35.	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
36.	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
37.	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
38.	TI,AB(before n/2 after n/2 stud*)
39.	TI,AB(longitudinal or retrospective or prospective or cross sectional)
40.	TI,AB(study or studies or review or analys* or cohort* or data)
41.	S39 and S40
42.	S35 OR S36 OR S37 OR S38 OR S41
43.	S15 AND S21 AND S42
44.	S34 OR S43

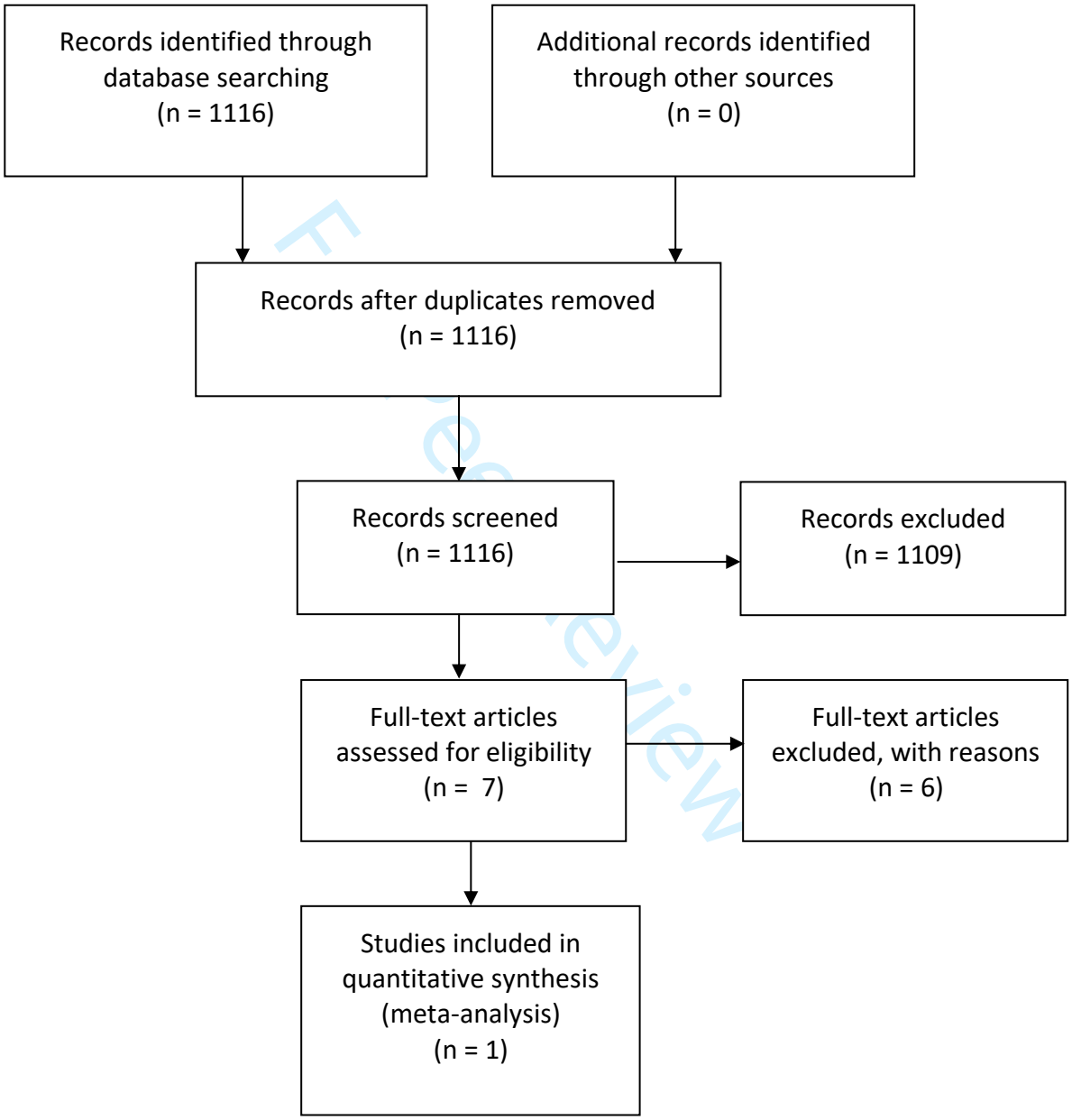
Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2.	arthrosis or *arthritis
#3.	Psoriasis or Psoriatic
#4.	#2 and #3

#5.	#1 or #4
#6.	(tight* next control*)
#7.	t2t
#8.	((mission or aiming or aim or aimed or aims or achiev* or sustain* or reach*) near/2 remission)
#9.	((treat* or therap*) near/2 (target* or goal*))
#10.	(symptom* near/2 (reduc* or improv* or control*))
#11.	low disease activity
#12.	#6 or #7 or #8 or #9 or #10 or #11
#13.	#5 and #12

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D: **Clinical evidence tables**

Study	TIght COntrol of Psoriatic Arthritis (TICOPA) trial. Coates 2014(1)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=206
Countries and setting	Conducted in UK; Setting: Multicentre clinical trial. People from eight secondary care rheumatology centres. 2008 – 2012.
Line of therapy	This was early therapy as the people had not previously received DMARDs.
Duration of study	Intervention + follow up: 48 week intervention period and safety follow-up for 52 weeks,
Method of assessment of guideline condition	Psoriatic arthritis diagnosed by a consultant rheumatologist. CASPAR criteria score 3+ in 91% and 2+ in 98%.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with recent onset (<24 months symptom duration) psoriatic arthritis who had never previously received treatment with disease-modifying anti-rheumatic drugs.
Exclusion criteria	Women who are pregnant, lactating, or planning pregnancy within 6 months of their last dose of protocol treatment. Use of any investigational agents within the previous 4 weeks or within five half-lives of the investigational agent, whichever is longer, before randomisation.
Age, gender and ethnicity	Age – Median (IQR): 46 (38-55) and 45 (36-51). Gender (M:F): 108/98. Ethnicity: 188 of white ethnic origin
Further population details	Current psoriasis in 85% Current enthesitis in 79% Current dactylitis in 30% Current nail disease in 60%
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: Treat to target: people seen by the study physician every 4 weeks and treated according to a predefined protocol. The target was minimal disease activity. The protocol begins with a single DMARD at a low dose and if the target is not met then it moves to higher doses. This is followed by 2 concurrent conventional DMARDs before moving to biologics. (n=105) Intervention 2: Usual care: People treated in a general rheumatology outpatient clinic supervised by a consultant rheumatologist. They were reviewed every 12 weeks but were seen more often if clinically indicated, with no formal measures of disease activity used in clinical decision making

Treat to target

Study	TIght COntrol of Psoriatic Arthritis (TICOPA) trial. Coates 2014(1)
Funding	Arthritis Research UK and Pfizer. The study states: The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: **Treat to target versus usual care**

- Mortality at 48 weeks. RoB: low
- Mean QUALYs at 48 weeks. RoB: h
- ACR20 at 48 weeks: RoB: low
- ACR50 at 48 weeks: RoB: low
- ACR70 at 48 weeks: RoB: low
- Radiological progression (via erosive disease) at 48 weeks. RoB: h
- Enthesitis score at 48 weeks. RoB: h
- Dactyltis score at 48 weeks. RoB: h
- BASDAI score at 48 weeks: RoB: h
- Psoriasis score (via PASI20) at 48 weeks. RoB: h
- Psoriasis score (via PASI75) at 48 weeks. RoB: h
- Serious adverse events at 48 weeks. RoB: low

ACR analysis was done on the intention-to-treat population with multiple imputation.

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Appendix E: **Forest plots**

Figure 2: Mortality at 48 weeks

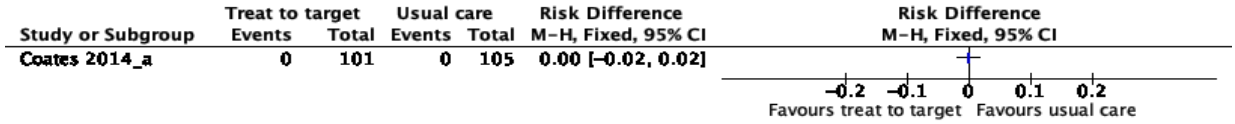


Figure 3: Mean QALYs at 48 weeks

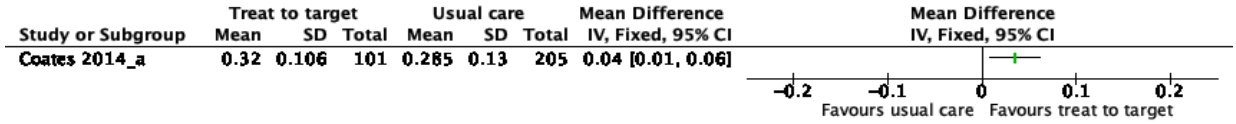


Figure 4: Radiological progression through presence of erosive disease at 48 weeks

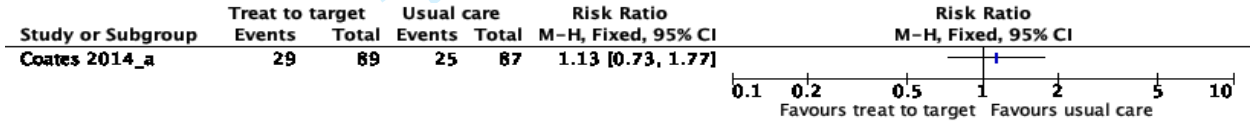
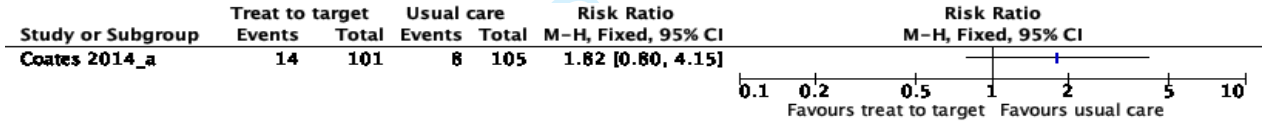


Figure 5 Serious adverse events within 48 weeks



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Appendix F: **Excluded studies**

Table 5: studies excluded from the evidence review

Study	Exclusion reason
Coates 2015(2)	Review paper
Coates 2013(3)	Conference abstract
Dures 2020(4)	Review paper
Gudbjörnsson 2012(5)	Conference abstract
Machado 2019(6)	Review paper
Gudbjörnsson 2018 (7)	Dose escalation but not treat to target

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Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on tapering treatment for people in clinical remission

BSR Guideline

Intervention evidence review

October 2020

Contents

1Tapering treatment for people in clinical remission

1.1 In adults with psoriatic arthritis, who have achieved clinical remission, what is the impact of bDMARD or tsDMARD tapering/dose reduction?

1.2 INTRODUCTION

Drug-induced remission indicates minimal disease activity while on medication. Drug-free remission, while rare, is complete relief from joint tenderness and swelling without the help of medication. A proposed move towards reduce medication use in remission is dose tapering. A concern is that this tapering will lead to symptom flares. This review seeks to assess whether tapering treatment in people in remission or low disease activity is an effective strategy.

1.3 PICO table

For full details, see the review protocol in Appendix A

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis who have achieved clinical remission while using b/tsDMARDs
Intervention	Dose tapering
Comparison	Maintaining existing treatment
Outcomes	**Critical** <u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u> • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Radiological progression <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) <u>Dactylitis</u> • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS20 (dichotomous)

	• ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain (continuous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous) **Important** <u>The outcomes below are extracted if studies do not report ACR response</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • PsARC score • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	Randomised Controlled Trials If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted to find RCTs or observational studies comparing a tapering treatment strategy to maintaining existing treatments in people who have achieved clinical remission from psoriatic arthritis using b/tsDMARDs.

One RCT(1) was included in this review.

1.4.2 Excluded studies

The table of Excluded studies can be found in Appendix G.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of RCT(s) included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
RETREAT (F) Moverley 2015(1)	Tapering - phased withdrawal of medication for PsA in a stepwise fashion (n=11) versus usual care (n=6)	N=17 adults with a diagnosis of PsA for more than 12 months and minimal disease activity after b/csDMARD treatment.	- MDA-flare within 24 week treatment period - Serious adverse events within 24 weeks	A number of the study population achieved minimal activity without the use of b/tsDMARDs UK study Funding: Arthritis Research UK

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Summary of studies included in the evidence review

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tapering	usual care	Relative (95% CI)	Absolute (95% CI)		

MDA-flare (follow up: 24 weeks; assessed with: People not being in MDA at any of 4 visits)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tapering	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	6/11 (54.5%)	0/6 (0.0%)	**RR 7.58** (0.50 to 115.26)	**550 more per 1,000** (from 210 more to 890 more) [d]	⨁◯◯◯ VERY LOW	CRITICAL

Serious adverse events (follow up: 24 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [e]	none	0/11 (0.0%)	0/6 (0.0%)	**RD 0.00** (-0.22 to 0.22)	**0 fewer per 1,000** (from 220 fewer to 220 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. A number of people in the study had not been treated with b/tsDMARDs prior to inclusion and the study was considered indirect evidence due to this population

c. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

d. Absolute risk calculated using the risk difference.

e. Imprecision not accurately assessed due to zero events in either treatment group

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and arthritis outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures capturing medication effects on other disease domains, such as enthesitis, dactylitis, axial Spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA, are available.

1.5.2 Benefits and harms

One RCT, involving 17 people with PsA was included in this review. . 2 outcomes were extracted and both were graded as very low quality. There was a clinically important benefit for continuing treatment for MDA flare and no clinical difference for serious adverse events.

The RCT included was a pilot study designed as a precursor to a major study covering tapering. Two members of the group were authors on this publication and could provide details of this particular study.

A question was asked about the population and whether they differed from a normal PsA population at all. It was stated that these people were from the TICOPA (TIght COntrol of Psoriatic Arthritis) trial and around 60% had polyarticular disease. They were not considered systematically different from a normal PsA population but the trial was very small and this was not formally analysed.

The trial itself was less about tapering, also called dose reduction, and could be better described as treatment withdrawal or cessation. In that sense the trial did not meet the protocol requirements for tapering of treatment.

The group agreed that the trial was small and did not adequately represent their understanding of dose tapering and therefore it was hard to draw any firm conclusions on tapering, or slower dose reduction, from the trial.

All of the clinicians present at the meeting indicated they utilised a form of dose tapering in their usual practice. However, this varied between dose reduction via a regular reduced dose or via longer time periods between doses. The latter is termed 'dose spacing' and increasing of this period might happened for a number of reasons. One of these reasons is that medications are licensed at fixed doses and reducing these is not possible due to limitations of what is provided by the manufacturers or unwillingness of CCGs to fund unlicensed lower doses. Therefore, a way to achieve a reduced dose is through increasing dose spacing.

Anecdotally and through their own experiences the group understood dose tapering to be effective in some cases. A group member indicated that there is poor observational data indicating the benefits of tapering, how this could occur, and that money could be saved.

Usual practice was stated to be that dose reduction could be proposed to people in long term remission or low disease activity. The rheumatologist might not consider the person suitable and may not propose it for them. The group consensus was that the outcomes for this were mainly

positive but clinicians should be ready to revert to a person's prior treatment if they do not respond well.

Shared decision making is thought to be very important for this process. People should not be forced to taper if they are unwilling as the evidence for a benefit is not strong enough. Putting in place programs to instigate tapering such as Bristol's B-TRIM is an effective protocol for this without mandating it for all.

The group agreed that people are often keen to try tapering and there is qualitative research that found people are often keen to be on the least amount of medication that allows them to feel well.

The group mentioned that most of the evidence that exists for tapering in b/tsDMARDs is for TNF inhibitors. This is because they are the mostly commonly utilised medications within the group. However, there is not enough evidence across groups to be able to make recommendations specific to any drug type.

The group agreed that there should be correspondence and involvement of all the specialists involved in the care of an individual in the decision to try dose tapering.

1.5.3 Cost effectiveness and resource use

1.5.4 Other factors the committee took into account

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Appendices

Appendix A. Review protocols

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020219011
1.	Review title	Tapering in psoriatic arthritis
2.	Review question	In adults with psoriatic arthritis, who have achieved clinical remission, what is the impact of bDMARD or tsDMARD tapering/dose reduction?
3.	Objective	In people who have achieved clinical remission, does it make sense to taper their biologic or targeted synthetic DMARD dose, leave their does unchanged, or to completely stop treatment.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.

5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with psoriatic arthritis who have achieved clinical remission using b/tsDMARDs
7.	Intervention/Exposure/Test	Dose tapering
8.	Comparator/Reference standard/Confounding factors	Maintaining existing treatment
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders. • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous)

		• Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) • Radiological progression <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 <u>Dactylitis</u> • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u>

		• Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**<u>These outcomes are extracted if studies do not report ACR response criteria.</u>** <u>Arthritis</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous)

		DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE)

		toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Tapering amongst people who have achieved imaging (ultrasound) remission vs clinical remission
18.	Anticipated or actual start date	20/10/2020
19.	Anticipated completion date	27/10/2020
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B. Literature search strategies

The literature searches for this review are detailed below.

For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 26 October 2020	RCT or observational studies
Embase (ProQuest)	1974 – 26 October 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Reviews issue 10 of 12, October 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4
6 S1 or S2 or S5
7 TI,AB("TNF inhibitor" or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
8 TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
9 TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
10 TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
11 TI,AB(Abatacept or apremilast)
12 TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
13 TI,AB(biologic* and DMARD)
14 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
15 EMB.EXACT.EXPLODE("drug dose reduction")
16 TI,AB(Taper*)
17 TI,AB(dose n/5 reduc*)

18	TI,AB(dose n/5 De-escalat*)
19	TI,AB(Treat* n/5 De-escalat*)
20	S15 OR S16 OR S17 OR S18 OR S19
21	TI(trial)
22	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
23	TI,AB(doubl* n/1 blind*)
24	TI,AB(singl* n/1 blind*)
25	RTYPE(controlled clinical trial)
26	RTYPE(randomized controlled trial)
27	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
28	EMB.EXACT.EXPLODE("crossover procedure")
29	EMB.EXACT.EXPLODE("single blind procedure")
30	EMB.EXACT.EXPLODE("randomized controlled trial")
31	EMB.EXACT.EXPLODE("double blind procedure")
32	S21 OR 22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
33	S6 and S14 and S20 AND S32
34	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
35	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
36	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
37	TI,AB(before n/2 after n/2 stud*)
38	TI,AB(longitudinal or retrospective or prospective or cross sectional)
39	TI,AB(study or studies or review or analys* or cohort* or data)
40	S38 and S39
41	S34 OR S35 OR S36 OR S37 OR S40
42	S6 AND S14 AND S20 AND S41
43	S33 OR S42

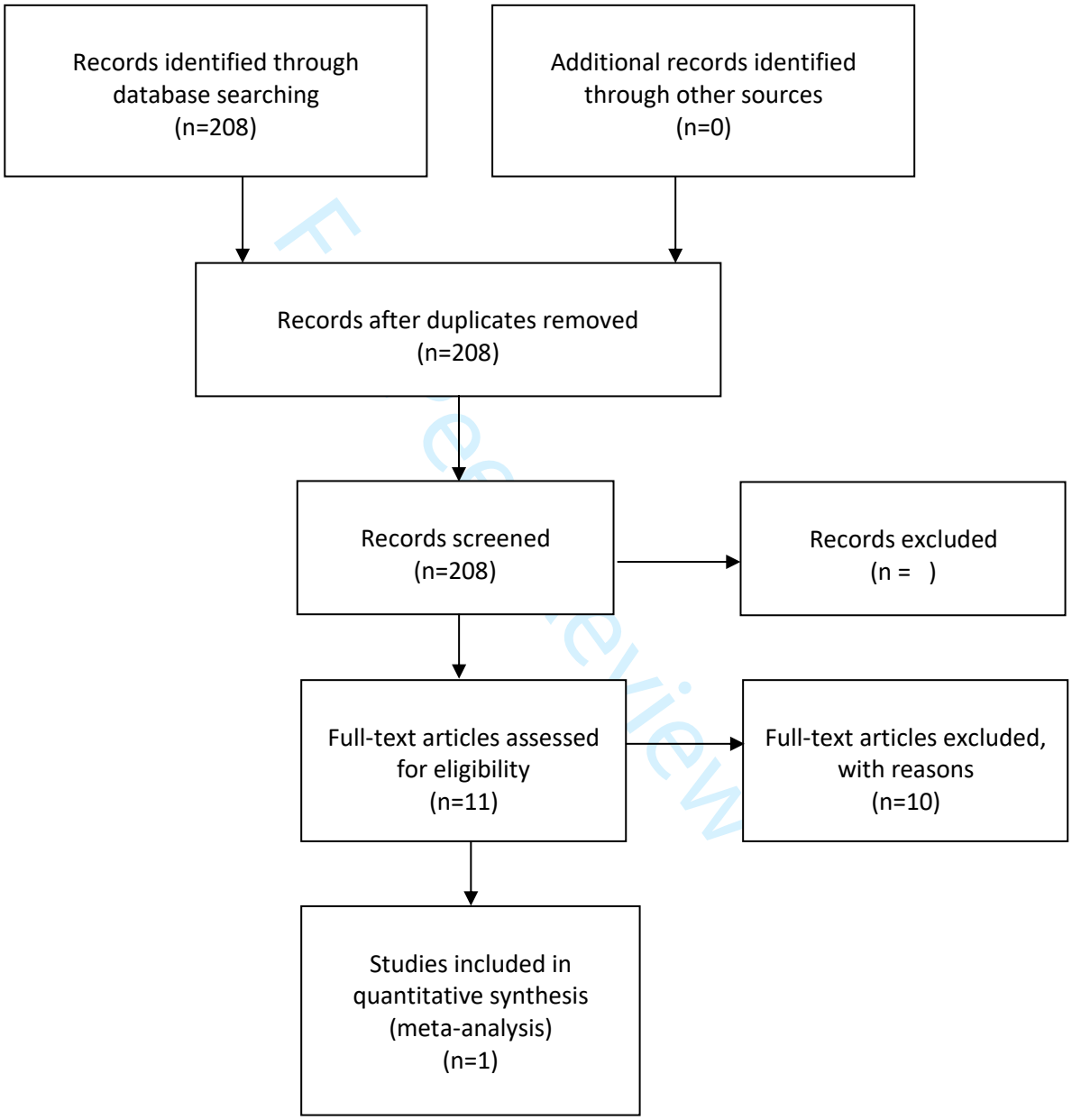
Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2	arthrosis or *arthritis
#3	Psoriasis or Psoriatic
#4	#2 and #3
#5	#1 or #4

#6	taper*
#7	dose near/5 (reduc* or de-escalat*)
#8	#6 or #7
#9	#5 and #8

Appendix C. Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D. **Clinical evidence tables**

Study	RETREAT (F) Moverley 2015(1)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=17
Countries and setting	Conducted in UK; Setting: Outpatient clinics
Line of therapy	Not applicable
Duration of study	Intervention and follow up: 4 months
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with a diagnosis of PsA for more than 12 months and in minimal disease activity. They were required to have stable disease for the preceding 6 months and a stable dose of b/csDMARD for that period.
Exclusion criteria	None stated
Age, gender and ethnicity	Age - Mean (SD): not detailed Gender (M:F): not detailed. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear 3. Form of shoulder replacement:: Mixed (Anatomical and reverse).
Indirectness of population	The population included people who were not using b/tsDMARDs and the study was considered indirect.
Interventions	(n=11) Intervention 1: Tapering – Phased withdrawal of medication for PsA in a stepwise fashion and stopping over 4-8 weeks. Concurrent medication/care: not detailed No indirectness (n=6) Intervention 2: Usual care Concurrent medication/care: Not detailed Indirectness: No indirectness
Funding	Arthritis Research UK

Tapering versus usual care:

- MDA-flare. People not being MDA at any visit at 24 weeks. RoB: vh
- Serious adverse events. RoB: vh

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Appendix E. **Forest plots**

Tapering versus usual care

Figure 2: MDA flare in 24 weeks

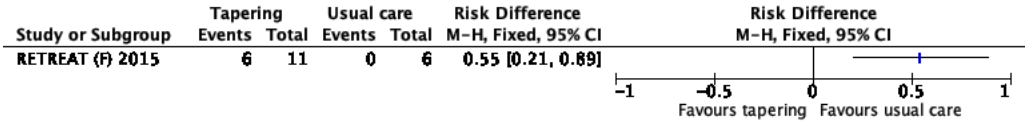
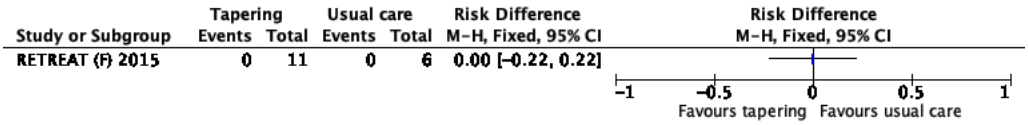


Figure 3: Serious adverse events at 24 weeks



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Appendix F. **Excluded studies**

Table 6: studies excluded from the evidence review

Study	Exclusion reason
Cantini 2012(2)	Study comparing dose reduction in people with psoriatic arthritis to people with rheumatoid arthritis
De Jong 2019(3)	Incorrect comparison: one group had not received b/tsDMARD treatment
de Stefano 2018(4)	Non-comparative study investigating dose reduction in people who have achieve remission
Fong 2016(5)	Non-comparative study of dose reduction in people with ankylosing spondylitis or psoriatic arthritis
Gossec 2020(6)	EULAR recommendations in a 2019 update. Included studies checked for inclusion in this review.
Huynh 2017(7)	Non-comparative study looking at outcomes in people who discontinued TNF inhibitors while in low disease activity
Inciarte-Mundo 2014(8)	Not in English
Janta 2015(9)	Unclear if all people in the study population were in clinical remission
Kerschbaumer 2020(10)	EULAR recommendations in a 2019 update. Included studies checked for inclusion in this review.
Michielsens 2020(11)	Protocol for an ongoing relevant randomised controlled trial: DRESS-PS

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Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on biosimilars compared to originators

BSR Guideline

Intervention evidence review

November 2020

Contents

1Biosimilars in psoriatic arthritis

1.1 In adults with psoriatic arthritis, who have responded to biologic and targeted synthetic DMARDs, what is the clinical effect of switching to a biosimilar drug compared to remaining on the originator drug

1.2 INTRODUCTION

A biosimilar is a biologic medical product highly similar to another already approved biological medicine. Biosimilar medications are more affordable treatments and healthcare providers may utilise them over originators on an economic basis. However the concern is that they are not as clinically effective as the originator or that altering medication may have an adverse effect on a person's disease control.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis who have responded to their current biologic or targeted synthetic DMARDs
Intervention	A person's biologic or targeted synthetic DMARD changed to a biosimilar
Comparison	A Person's biologic or targeted synthetic DMARD remains unchanged
Outcomes	**Critical** • Mortality (dichotomous) • Quality of life (continuous) Arthritis: . • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Radiological progression (continuous) Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous)

	• OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) **Important** Adverse Events • Serious adverse events (dichotomous) **The outcomes below are extracted if studies do not report ACR response.** • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • PsARC score • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous), • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	Randomised Controlled Trials (RCT's)- inclusion and exclusion criteria as stated above If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted to find RCTs or observational studies comparing commencing new b/tsDMARDs treatment with conventional DMARDs to commending without conventional DMARDs. 1 RCT(1) and one observational study(2) were included in this review.

1.4.2 Excluded studies

See Table 5: studies excluded from the evidence review on page 25

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
NOR-SWITCH: Jørgensen 2017(2)	Non-inferiority, double blind, RCT Current effective treatment, infliximab, switched to biosimilar: CT-P13 (n=16) versus current treatment maintained, no switch: infliximab (n=14) Trial continued for 52 weeks. Concurrent care: immunosuppressives or prednisolone were allowed.	N=482 adults with psoriatic arthritis, Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, or chronic plaque psoriasis on a stable treatment of infliximab for at least 6 months. Outcome were extracted where reported for the subgroup of people with psoriatic arthritis (n=30)	- Mortality at 52 weeks - Disease flare vis DAS28 during 52 weeks - Minimal disease activity via DAS28 remission at 52 weeks - PsAID: Psoriatic Arthritis Impact of Disease at 52 weeks.	Conducted in Norway at 25 hospital sites Funded by Norwegian Ministry of Health and Care Services.
DANBIO registry: Glintborg 2019(1)	Observational cohort study based on a nationwide registry. Current treatment, etanercept, switched to biosimilar: SB4 (n=351) versus current treatment maintained, no switch: etanercept (n=56)	N=2061 people with psoriatic arthritis, rheumatoid arthritis or axial spondylitis being treated with etanercept. Outcomes extracted for people with psoriatic arthritis (n=407)	- Treatment withdrawal by 52 weeks	Conducted in Denmark. In April 2016 a national guideline indicated that all people with inflammatory arthritis treated with etanercept should switch to biosimilar SB4. Study partly funded by a grant from Biogen

1.4.4 Quality assessment of clinical studies included in the evidence review

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch	no switch	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 52 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/16 (0.0%)	0/14 (0.0%)	**RD 0.00** (-0.12 to 0.12)	**0 fewer per 1,000** (from 120 fewer to 120 more)	⊕◯◯◯ VERY LOW	CRITICAL
Disease flare (follow up: 52 weeks; assessed with: change from baseline of Disease Activity Score in 28 joints of 1·2 or more with a minimum score of 3·2)												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [d]	none	8/16 (50.0%)	7/14 (50.0%)	**RR 1.00** (0.49 to 2.05)	**0 fewer per 1,000** (from 255 fewer to 525 more)	⊕◯◯◯ VERY LOW	CRITICAL
Minimal disease activity (follow up: 52 weeks; assessed with: DAS28 remission)												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [d]	none	6/16 (37.5%)	6/14 (42.9%)	**RR 0.88** (0.36 to 2.10)	**51 fewer per 1,000** (from 274 fewer to 471 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment withdrawal (follow up: 52 weeks; Adjusted for gender, age, methotrexate use (yes/no), remission (yes/no), comorbidities (≥1/0), ETA start year (1998-2010/2011-2016))												
1	observational studies	serious [a]	not serious	not serious	serious [d]	none	53/351 (15.1%)	25/56 (44.6%)	**HR 0.55** (0.28 to 1.07)	**169 fewer per 1,000** (from 294 fewer to 22 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Psoriatic Arthritis Impact of Disease (PsAID) (follow up: 52 weeks; assessed with: Lower is better; Scale from: 0 to 10)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch	no switch	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [d]	none	16	14	-	MD **0.5 lower** (1.33 lower to 0.33 higher)	⊕⊕◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Imprecision was considered very serious as there were no events in either group
c. Considered indirect evidence for the minimal disease activity as the DA28S score is utilised in this study
d. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
e. This is data adjusted for confounding factors but the absolute effect uses a raw control group risk

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1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures to capture medication effects on other psoriatic disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA, are available.

1.5.2 Benefits and harms

One RCT (NOR-SWITCH) and one observational study (DANBIO) were included in this evidence review. No clinical differences in mortality, disease flare, minimal disease activity or Psoriatic Arthritis Impact of Disease (PsAID) score were seen between biosimilar or originator drugs. However, a benefit for biosimilars was found for treatment withdrawal within 52 weeks. This was the single outcome from the DANBIO study.

The NOR-SWITCH study was not powered to find a benefit in people with psoriatic arthritis and the outcome measures used were mainly based on the Disease Activity Score for 28 joints (DAS28), a rheumatoid arthritis-derived measure, which is not appropriate for use in psoriatic arthritis.

The group agreed the review highlights a lack of evidence in terms of switching people from originators to biosimilars. As things stand there are a number of complicating issues in terms of biosimilars. Firstly, this tends to be a cost saving consideration rather than an efficacy consideration and thus the impetus for switching is financial.

Secondly, there have already been large switches from originators to biosimilars and these will be ongoing as more drugs have biosimilars developed. Indeed it may be that many people have never used the originator and were given a biosimilar in the first instance.

However, there are places where regular large-scale switches happen: 'sequential switching'. This could occur when tendering occurs and healthcare organisations could seek to sequentially change their patients to the cheapest biosimilar on a regular basis. The group stated opposition to these sequential changes because the financial benefits do not outweigh the challenges to patients as their PsA treatment will be altered without a clinical imperative. A lay member indicated that patients dislike being pressured into switching. The fear is that it won't have the same benefit going forward.

A member of the group spoke about the mixed experience of switching to biosimilars. For some there are disease flares but for some there are no large changes in their disease activity. To address these flares, an option is to switch back to the originator, which tends to resolve it, but there are people for whom this does not work. There are additional complications such as people who have many lines of therapy. These people may be less affected by the switch whereas those who are more reliant on the single line agent, which was switched may rely more heavily on the biosimilar.

It was indicated that switching back is rare but is a very important option in a person's care. Having said that the group understand that switching back is more common in PsA than rheumatoid arthritis and this should be recognised by clinicians.

In some cases it may be that a person is not switched back to the originator. For example if they have adverse events from the biosimilar it may be that local policy indicates a new biosimilar should be offered with a different safety profile to the former. The group agreed that the nature of the adverse event could be considered when agreeing a person's next molecule.

People may flare some time after switching and could believe a return to originator would solve this. However, it may not be that it was the switch that caused this. The disease may have changed, the drug may have lost its efficacy or they may have developed anti-drug antibodies. The group stated their intention was to leave room for physicians to use their expertise in this within this guideline's recommendations.

The group agreed it is important to support clinicians who push back on individual patients. Get out clauses should be available, as there are clinical scenarios whereby switching is not appropriate, for example, people with cancer or pregnant people.

In addition it is of great importance to liaise with a person's wider care team when altering treatment.

The group discussed the evidence and current BSR guidance on biosimilars. In 2018, BSR released a factsheet on biosimilars:
https://www.rheumatology.org.uk/Portals/0/Documents/Policy/Factsheets/Factsheet_Biosimilars_2018.pdf
It was a consensus document drafted by a working group of clinicians and was reviewed and signed off by the BSR Clinical Affairs Committee. The group agreed with all of the recommendations contained within the document, which encouraged shared decision-making, not undertaking sequential switching, but beginning with the most cost-effective medication.

British Association of Dermatologists (BAD) have a similar statement to BSR and it heavily promotes involvement of the patient in a discussion with the clinician.

In terms of monitoring movement from originator to biosimilar, a group member thought that most people would submit a Blueteq and that this would be useful for monitoring. Also, there are already recording mechanisms in place in biologics registers.

1.5.3 Cost effectiveness and resource use

There are benefits to using biosimilars in terms of cost and access to therapy. A group member indicated that the financial benefit rather than therapeutic benefit is the reason for considering utilising biosimilars. A member wondered whether the financial benefits of switching to a biosimilar may be offset by the number of flares that may happen due to the switch.

1.5.4 Other factors the committee took into account

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Appendices

Appendix A: **Review protocols**

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020219396
1.	Review title	Biosimilars in psoriatic arthritis
2.	Review question	In adults with psoriatic arthritis, who have responded to biologic and targeted synthetic DMARDs, what is the clinical effect of switching to a biosimilar drug compared to remaining on the originator drug
3.	Objective	In adults with psoriatic arthritis, who have responded well to a treatment, what is the clinical effect of changing to a biosimilar as compared to remaining on the originator drug
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with psoriatic arthritis who have responded to their current biologic or targeted synthetic DMARDs
7.	Intervention/Exposure/Test	Person's biologic or targeted synthetic DMARD changed to a biosimilar
8.	Comparator/Reference standard/Confounding factors	Person's biologic or targeted synthetic DMARD unchanged

9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) • Radiological progression <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 <u>Dactylitis</u> • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous)

		Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Adverse Events • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • Disease Assessment in PsA (continuous)

		Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Cochrane RoB (2.0) • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	None
18.	Start date	20/10/20
19.	Completion date	20/11/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update

23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 26 October 2020	RCTs or observational studies
Embase (ProQuest)	1974 – 26 October 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews Issue 10 of 12, October 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4
6 S1 or S2 or S5
7 TI,AB("TNF inhibitor" or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
8 TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
9 TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
10 TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
11 TI,AB(Abatacept or apremilast)
12 TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
13 TI,AB(biologic* and DMARD)
14 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
15 TI,AB(biosimilar*)
16 EMB.EXACT("biosimilar agent")
17 MESH.EXACT("Biosimilar Pharmaceuticals")

18 S15 OR S16 OR S17
19 TI(trial)
20 TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
21 TI,AB(doubl* n/1 blind*)
22 TI,AB(singl* n/1 blind*)
23 RTYPE(controlled clinical trial)
24 RTYPE(randomized controlled trial)
25 MESH.EXACT.EXPLODE("Clinical Trials as Topic")
26 EMB.EXACT.EXPLODE("crossover procedure")
27 EMB.EXACT.EXPLODE("single blind procedure")
28 EMB.EXACT.EXPLODE("randomized controlled trial")
29 EMB.EXACT.EXPLODE("double blind procedure")
30 S19 OR S20 S21 OR 22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
31 S6 and S14 and S18 AND S30
32 MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
33 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
34 TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
35 TI,AB(before n/2 after n/2 stud*)
36 TI,AB(longitudinal or retrospective or prospective or cross sectional)
37 TI,AB(study or studies or review or analys* or cohort* or data)
38 S36 and S37
39 S32 OR S33 Or S34 OR S35 OR S38
40 S6 AND S14 AND S18 AND S39
41 S31 OR S40

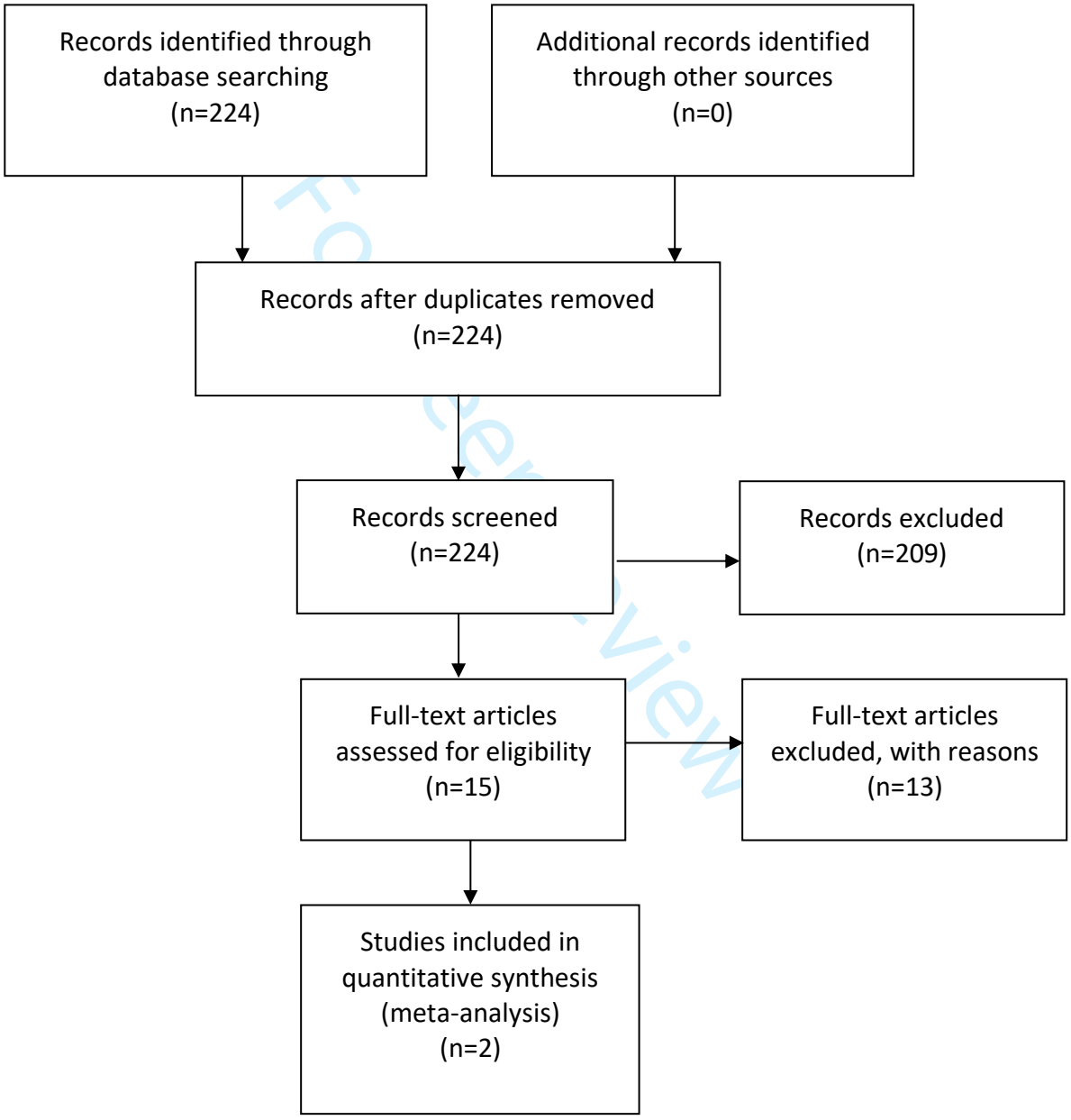
Cochrane Library (Wiley) search terms

#1 MeSH descriptor: [Arthritis, Psoriatic] this term only
#2 arthrosis or *arthritis
#3 Psoriasis or Psoriatic
#4 #2 and #3
#5 #1 or #4
#6 MeSH descriptor: [Biosimilar Pharmaceuticals] this term only
#7 biosimilar*
#8 #6 or #7

#9	#5 and #8

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D: **Clinical evidence tables**

Study	NOR-SWITCH: Jørgensen 2017(2)
Study type	Non-inferiority, double blind, RCT (Patient randomised; Parallel)
Number of participants	n=482
Countries and setting	Conducted in Norway; Setting: 25 hospital sites
Line of therapy	Not applicable
Duration of study	Intervention: 52 weeks
Method of assessment of guideline condition	Formal diagnosis required
Stratum	Overall
Subgroup analysis within study	Data extracted on subgroup of people with psoriatic arthritis. This was N=30 (6%) of the full study population.
Inclusion criteria	Adults with Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or chronic plaque psoriasis on a stable treatment of infliximab for at least 6 months.
Exclusion criteria	Major co-morbidities, such as severe malignancies, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases and/or other diseases including inflammatory conditions for which infliximab is contraindicated. Initiation of systemic corticosteroids or synthetic DMARDs or other medication which according to the investigator would interfere with the stability of the disease. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol impossible
Age, gender and ethnicity	In the subgroup of people with psoriatic arthritis: Age - Mean (SD): 59 (13) and 54 (8). Gender (M:F): 15/15. Ethnicity: not detailed
Further population details	EQ-5D: 0.7 (0.2) and 0.7 (0.2) Population details broken down by treatment group (infliximab followed by biosimilar): Concomitant immunosuppressives: 9 (64%) and 13 (81%) Concomitant prednisolone: 1 (7%) and 0 (0%) Physician's global assessment of disease activity (0-10): 1.3 (1.2) and 1.1 (1) Patient's global assessment of disease activity (0-10): 2.6 (2) and 2.7 (1.9) DAS28: 2.5 (1.4) and 2.2 (0.8) CDAI: 5.1 (4.2) and 4.1 (2.6) SDAI: 5.4 (4.3) and 4.4 (2.5) MHAQ: 0.3 (0.3) and 0.3 (0.4)

Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Treatment changed to b/tsDMARD biosimilar: Infliximab treatment changed to CT-P13. Concurrent medication/care: Immunosuppressives or prednisolone were allowed. Indirectness: No indirectness (n=14) Intervention 2: b/tsDMARD treatment continued: Infliximab treatment continued. Concurrent medication/care: Immunosuppressives or prednisolone were allowed. Indirectness: No indirectness.
Funding	Norwegian Ministry of Health and Care Services.

Biosimilar versus unchanged treatment in subgroup of people with PsA

- Mortality at 52 weeks RoB: h
- Disease flare during 52 weeks (change from baseline of Disease Activity Score in 28 joints of 1·2 or more with a minimum score of 3·2). RoB: h
- Minimal disease activity via DAS28 remission at 52 weeks RoB: h
- PsAID: Psoriatic Arthritis Impact of Disease at 52 weeks. RoB: h

Study	DANBIO registry: Glintborg 2019(1)
Study type	Observational cohort study based on a nationwide Denmark registry
Number of participants	n=2061
Countries and setting	Data from 18 department of rheumatology centres in Denmark
Line of therapy	Not applicable
Duration of study	The outcomes specify the time periods of interest in the registry data
Method of assessment of guideline condition	Not specified for psoriatic athritis
Stratum	Overall
Subgroup analysis within study	This is an analysis of outcomes in 407 (20%) of people in the with psoriatic arthritis
Inclusion criteria	People with psoriatic arthritis, rheumatoid arthritis or axial spondylitis being treated with etanercept. A Danish guideline in April 2016 stated that all people with inflammatory arthritis treated with originator etanercept (ETA) (Enbrel) must switch to SB4. The following cohorts were defined: switchers: patients who switched from ETA to SB4 between 1 April 2016 and 1 January 2017. Non-switchers: the group of ETA-treated patients who did not switch to SB4 during follow-up.
Exclusion criteria	None detailed
Age, gender and ethnicity	Details of 407 people with PsA: age - Median (IQR): 52 (43-61) and 52 (43-58). Gender (M:F): 216/191. Ethnicity: Not detailed
Further population details	Population details broken down by treatment group (biosimilar group followed by etanercept goup) In remission: 70% and 73% Concomitant methotrexate: 168 (48%) and 17 (30%) 1 or more comorbidities: 26% and 18%
Indirectness of population	No indirectness
Interventions	(n=351) Intervention 1: Treatment changed to b/tsDMARD biosimilar: The change was etanercept to SB4.

	Concurrent medication/care: this was dependent on the treating physician. Indirectness: No indirectness (n=56) Intervention 2: Treatment continued to be etanercept. Concurrent medication/care: this was dependent on the treating physician. Indirectness: No indirectness
Funding	The study was partly funded by a grant from Biogen

Biosimilar versus unchanged treatment in subgroup of people with PsA

- Treatment withdrawal at 52 weeks. RoB: h. Adjusted for gender, age, methotrexate use (yes/no), remission (yes/no), comorbidities (≥1/0), ETA start year (1998-2010/2011-2016)

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Appendix E: **Forest plots**

Figure 2: Mortality at 52 weeks

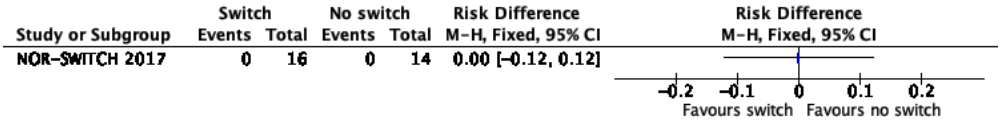


Figure 3: Disease flare during 52 weeks

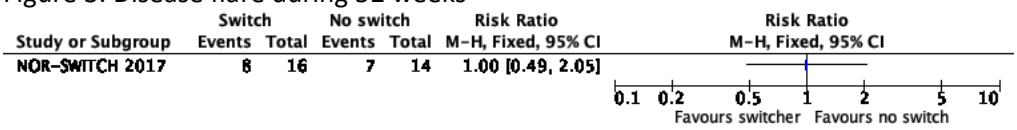


Figure 4:: DAS28 remission at 52 weeks

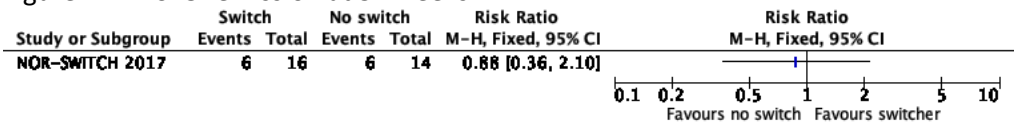


Figure 5: Treatment withdrawal at 52 weeks

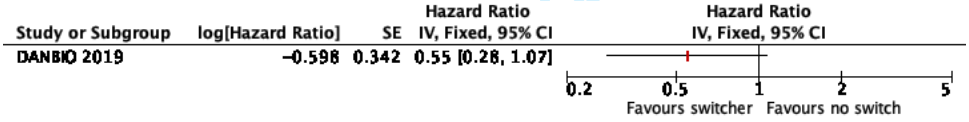
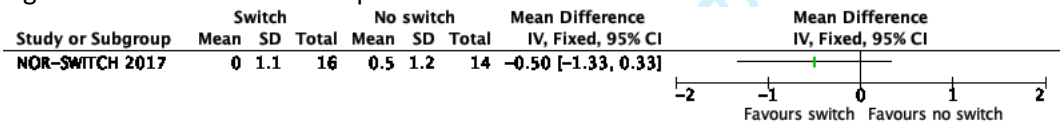


Figure 6: Psoriatic Arthritis Impact of Disease at 52 weeks



Appendix F: **Excluded studies**

Table 5: studies excluded from the evidence review

Study	Exclusion reason
Becciolini 2017(3)	Literature review around infliximab and biosimilar, CT-P13
Braun 2016(4)	Literature review around infliximab and biosimilar, CT-P13
Cantini 2019(5)	Literature review investigating evidence for biosimilars in people with psoriatic arthritis
Convertino 2020(6)	Unable to acquire paper
Feagan 2019(7)	Study included people with inflammatory rheumatic diseases but no subgroup analysis of people with psoriatic arthritis was presented.
Goll 2019(8)	Comparison of people who previously switched to CT-P13 to new switchers
Hercogová 2020(9)	People has not received the originator medication before the biosimilar used in the trial
Khandpur 2020(10)	Not a comparative study and people were not using the originator drug prior to beginning the trial
Kurizky 2019(11)	Not a comparative study
Perks 2017(12)	Description of the NOR-SWITCH trial and extension
Rojas-Giménez 2020(13)	Unable to acquire paper
Scherlinger 2018(14)	Study included people with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. Separate results were not presented for the psoriatic arthritis population.
Tweehuysen 2018(15)	Comparison of a historical cohort of people with inflammatory rheumatic disease using the originator to people witched to biosimilar. Separate results not presented for subgroup with psoriatic arthritis

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Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on whether to initiate b/tsDMARDs treatment with concurrent csDMARDs

BSR Guideline

Intervention evidence review

November 2020

Contents

1 Concurrent conventional DMARDs

1.1 In adults with active psoriatic arthritis commencing b/tsDMARDs, what is the clinical effect of concomitant conventional synthetic DMARD use compared to monotherapy?

1.2 INTRODUCTION

Some people are prescribed concomitant conventional synthetic (cs) DMARDs when beginning b/tsDMARDs but it is not universally undertaken. This review seeks to assess the clinical outcomes are improved by co-prescribing in people csDMARDs when a person first begins taking b/tsDMARDs.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with active psoriatic arthritis commencing biologic DMARDs or targeted synthetic DMARDs (b/tsDMARDs)
Intervention	Concomitant conventional DMARD therapy when commencing b/ts DMARDs
Comparison	Commencing b/tsDMARD monotherapy
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: . • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Radiological progression (continuous) Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Uveitis • VRQol (continuous)

	• Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) • IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) • Adverse Events • Serious adverse events (dichotomous) **Important** **These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • Disease Assessment in PsA (continuous) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	• Randomised Controlled Trials (RCT's) • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted to find RCTs or observational studies comparing people initiating b/tsDMARD treatment with concomitant csDMARDs to those initiating without concomitant csDMARDs. 1 RCT(1) and 2 observational studies(2, 3) were included in this review.

1.4.2 Excluded studies

See **Table 5** in Excluded studies in the appendix.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
RCT(s)				
SEAM-PsA: Mease 2019(1)	Etanercept and methotrexate (n=284) versus etanercept monotherapy (n=284) 48 week treatment period. Stable doses of corticosteroids and NSAIDs were permitted.	N=851 Adults who active PsA who were naïve to bDMARDs and had no prior use of methotrexate for PsA. 66% had enthesitis at baseline and 33% had dactylitis.	• Mortality at 48 weeks • SF36 physical component score at 24 weeks • SF36 mental component score at 24 weeks. • ACR20 response at 24 week • ACR50 response at 24 weeks • ACR70 response at 24 weeks. • Minimal disease activity at 24 weeks • Radiological progression at 48 weeks • Dactylitis resolution at 24 weeks • Enthesitis resolution at 24 weeks • SPARCC Enthesitis Index at 24 weeks • People achieving clear/almost clear on sPGA-psoriasis at 24 weeks • Serious adverse events at 48 weeks	There was a third treatment group where people received methotrexate monotherapy. This group was not relevant for this evidence review. Study funded by Amgen Conducted in 92 hospitals across North America, South America, Europe, and Africa.

Study	Intervention and comparison	Population	Outcomes	Comments
Observational studies				
NCT01111240: Behrens 2016(2)	Retrospective analysis of data from a multicentre, prospective, noninterventional study. Reported for 2 groups, those with or without axial involvement. Adalimumab with methotrexate (n=131 axial, n=501 no axial) versus adalimumab monotherapy (n=165 axial, n=568 no axial)	N=1455 People with PsA who enrolled into a non-interventional study between August 2005 and December 2009 who initiated adalimumab monotherapy or adalimumab plus methotrexate therapy. Groups varied in prior methotrexate use, enthesitis at baseline, and psoriasis body surface area at baseline.	Stepwise regression analyses utilised using 36 explanatory variables. • DAS28 at 24 months. • Target Lesion Score at 24 months • Withdrawal for any reason during study time period	People may have been exposed to other TNF inhibitors prior to joining this study. Conducted in Germany across 355 centres. Funded by AbbVie Deutschland GmbH and Co.
Thomas 2020(3)	Retrospective analysis of data from five cohorts TNF inhibitor therapy	N=2294 The study ran from 2000 to 2015 in 2 hospital cohorts and 3 biologics registries. Adults with PsA who were naïve to TNF inhibitor treatment and were prescribed a TNF inhibitor with or without concomitant csDMARD therapy.	To account for confounding they used database-specific propensity score (PS) models. • Change in DAS28 - unclear time period. • Discontinuation of treatment during the first year of treatment	Conducted in Czech Republic, Italy, UK, Greece, Switzerland; Setting: 2 hospital cohorts and 3 biologics registries The study required individual patient data for the comparative effectiveness analyses modelling, and so only included people from the UK, Italian, and Swiss cohorts. Funded by an award from Pfizer.

1.4.4 Quality assessment of clinical studies included in the evidence review

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concomitant DMARDs	monotherapy	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 48 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	0/284 (0.0%)	0/282 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (follow up: 24 weeks; assessed with: Change in SF-36 mental component score; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	256	256	-	MD **0.5 higher** (1.16 lower to 2.16 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Quality of life (follow up: 24 weeks; assessed with: Change in SF-36 physical component score; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	256	256	-	MD **0.2 higher** (1.46 lower to 1.86 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
ACR20 response (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	184/283 (65.0%)	173/284 (60.9%)	**RR 1.07** (0.94 to 1.21)	**43 more per 1,000** (from 37 fewer to 128 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ACR50 response (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concomitant DMARDs	monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	117/256 (45.7%)	114/257 (44.4%)	**RR 1.03** (0.85 to 1.25)	**13 more per 1,000** (from 67 fewer to 111 more)	⨁⨁◯◯ LOW	CRITICAL
ACR70 response (follow up: 24 weeks)												
1	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	71/256 (27.7%)	75/257 (29.2%)	**RR 0.95** (0.72 to 1.25)	**15 fewer per 1,000** (from 82 fewer to 73 more)	⨁◯◯◯ VERY LOW	CRITICAL
Minimal disease activity (follow up: 24 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	101/283 (35.7%)	102/284 (35.9%)	**RR 0.99** (0.80 to 1.24)	**4 fewer per 1,000** (from 72 fewer to 86 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Radiological progression (follow up: 48 weeks; assessed with: Change in mTSS/SHS: van der Heijde modified Total Sharp Score; Scale from: 0 to 528)												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	226	225	-	MD **0.03 higher** (0.07 lower to 0.13 higher)	⨁⨁◯◯ LOW	CRITICAL
Absence of enthesitis (follow up: 24 weeks; assessed with: Enthesitis resolution at week 24 in people with enthesitis at baseline)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concomitant DMARDs	monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	85/179 (47.5%)	91/173 (52.6%)	**RR 0.90** (0.73 to 1.11)	**53 fewer per 1,000** (from 142 fewer to 58 more)	⊕⊕◯◯ LOW	CRITICAL
Absence of dactylitis (follow up: 24 weeks; assessed with: Dactylitis resolution vi Leeds Dactylitis Index in people with dactylitis at baseline)												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	69/87 (79.3%)	68/89 (76.4%)	**RR 1.04** (0.89 to 1.22)	**31 more per 1,000** (from 84 fewer to 168 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Enthesitis score (follow up: 24 weeks; assessed with: SPARCC Enthesitis Index: Spondyloarthritis Research Consortium of Canada Enthesitis index; Scale from: 0 to 16)												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	179	173	-	MD **0.1 higher** (0.74 lower to 0.94 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Psoriasis score (follow up: 24 weeks; assessed with: People achieving clear/almost clear status in the static Physician's Global Assessment (sPGA) in people with psoriasis at baseline)												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	125/161 (77.6%)	120/166 (72.3%)	**RR 1.07** (0.95 to 1.22)	**51 more per 1,000** (from 36 fewer to 159 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Psoriasis score (follow up: 24 weeks; assessed with: Change in Target Lesion Score; Scale from: 0 to 15)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concomitant DMARDs	monotherapy	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	very serious [b]	not serious	not serious	not serious	none	237	263	-	MD **0.85 higher** (0.09 higher to 1.6 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events (assessed with: Withdrawal from study/ discontinuation of treatment due to adverse events and/or lack of efficacy)												
3	observational studies	very serious [b]	not serious	not serious	serious [c]	none	223/1396 (16.0%)	247/1382 (17.9%)	**RR 0.89** (0.75 to 1.05)	**20 fewer per 1,000** (from 45 fewer to 9 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Disease activity (follow up: 24 months; assessed with: Change in DAS28; Scale from: 0 to 9.4)												
2	observational studies	very serious [b]	not serious	not serious	not serious	none	286	288	-	MD **0.05 lower** (0.31 lower to 0.21 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Disease activity comparison reported for monotherapy versus concomitant therapy (assessed with: Rate of change of DAS28 prior to a person's censoring date)												
1	observational studies	very serious [b]	not serious	not serious	not serious	none	-/0	-/0	**RR 0.98** (0.95 to 1.03)	Unclear[d]	⊕◯◯◯ VERY LOW	IMPORTANT

a. Imprecision considered very serious because there were no events in either study arm
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
c. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
d. Data adjusted for confounding factors and absolute effect cannot be calculated

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and arthritis disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures capable of capturing medication effects on other disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA, are available.

1.5.2 Benefits and harms

1 RCT and 2 observational studies were included in this evidence review. All of the studies were large and the observational studies controlled for confounding factors. The studies all utilised a TNF inhibitor as their b/tsDMARD treatment and the csDMARD was etanercept in one case, adalimumab in another, and it varied in the last.

All outcomes across all of the studies indicated no clinical difference in efficacy between initiating b/tsDMARDs as monotherapy or co-prescribing with a csDMARD. These outcomes included mortality, quality of life, measures of disease activity, and measures of other manifestations of the disease, such a psoriasis and enthesitis. The outcomes varied from high to very low quality but most outcomes sat at the higher quality end.

The group understand the evidence in the review indicate there is not a clinically important benefit for routine use of co-prescribed csDMARDs when a person starts b/tsDMARD treatment. However, there are important aspects of this care not covered in the evidence review and the group included these aspects in the conversation. This includes drug survival, treatment of other manifestations of PsA, and also not leaving a person untreated prior to the b/tsDMARD taking effect or in case the b/tsDMARD is not effective.

The group discussed other data they are aware of around csDMARDs increasing the longevity of TNF inhibitors when co-prescribed. This is thought to be the medication stopping formation of anti-drug antibodies. Also, it is unknown if this effect is similar for other b/tsDMARDs as there are no studies investigating the co-prescription. Therefore drug survival is a positive link to co-prescription that the evidence review did not evaluate. This benefit has been highlighted in these studies.

One other reason mentioned for keeping people on a csDMARD while starting a b/tsDMARD is not to leave people unsupported while determining whether the b/tsDMARD will be effective. Even if the csDMARD has insufficient efficacy it still offers some efficacy to the person.

The group discussed care in their centres. The consensus of the group was that unless people are contraindicated, they tend to leave the person on csDMARD therapy after escalation to biologic therapy. However, the evidence is very limited for most of this and it is more erring on the side of caution rather than being certain of a benefit, and taking an analogous approach to that used in

rheumatoid arthritis and other related conditions such as Crohn's diseases and acute anterior uveitis.

Also linked to csDMARD co-prescription, in response to flaring joint disease a member of the group indicated an option they would consider is stepping-up csDMARD treatment in a person who is already using b/tsDMARDs. This is instead of switching a person's b/tsDMARD treatment as it may not appear warranted for some less severe flares.

A lay member of the group indicated they had dropped methotrexate therapy after escalation and had problems. They went back to co-prescribed methotrexate and the situation improved.

It was mentioned that people may be receiving the csDMARD for reasons outside of their disease activity. For example, a person's skin / IBD / uveitis may require treatment and may be an important focus of their csDMARD treatment. There could be an argument for continuing this treatment as it potentially could be effective from a dermatology perspective but not for other measures of disease activity. It is possible for people to get skin flares when their effective csDMARD is withdrawn. Having said that, the group were keen to state that methotrexate can be stopped in people who previously had psoriasis symptoms without it necessarily causing a skin flare.

The group agreed that they wanted to offer a more nuanced approach and provide a framework that rheumatologists and other linked healthcare professionals can utilise to make decisions on whom to offer co-prescription of csDMARDs. They were aware the evidence does not support csDMARD co-prescription in all people but they are aware of many people for whom co-prescription would be a benefit. This benefit could be in terms of treating other manifestations, or to promote drug persistence, or to act as a bridge to the next advanced therapy commencing. This guideline supports healthcare professionals offering co-prescription where it makes sense based on these factors.

However, if people are co-prescribed csDMARDs alongside their b/tsDMARD, there should be a conversation around stepping down csDMARDs when the b/tsDMARD is established and a person has achieved low disease activity. Routinely it is expected that most people could eventually stop all csDMARD treatment.

The group spoke about existing NICE recommendations and possible future recommendations. One mentioned was tofacitinib [TA543] where it is recommended by NICE for people with psoriatic arthritis when co-prescribed with methotrexate. The group agreed not to challenge these licensing recommendations.

The group agreed that this should be revisited when more data is available on other modes of action.

1.5.3 Cost effectiveness and resource use

1.5.4 Other factors the committee took into account

1

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Appendices

Appendix A: **Review protocols**

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020221117
1.	Review title	Concomitant DMARDs in psoriatic arthritis
2.	Review question	In adults with active psoriatic arthritis commencing b/ts DMARDs, what is the clinical effect of concomitant conventional synthetic DMARD use compared to monotherapy.
3.	Objective	To investigate whether people benefit from co-prescription of conventional DMARDs when commencing b/ts DMARDs
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with active psoriatic arthritis commencing b/ts DMARDs
7.	Intervention/Exposure/Test	Concomitant conventional DMARD therapy when commencing b/tsDMARD therapy
8.	Comparator/Reference standard/Confounding factors	Commencing b/tsDMARD monotherapy
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

		• Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) • Radiological progression Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous)

		• ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) • Psoriasis Area Severity Index (PASI)- 0-72 score • Investigator Global Assessment (IGA)- (0-5) score • Body Surface Area (BSA)- (0-100) score <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**<u>These outcomes are extracted if studies do not report ACR response criteria.</u>** <u>Arthritis</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) <u>Other outcomes</u> • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)

14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using an appropriate checklist. For Intervention reviews: • Cochrane RoB (2.0)
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Subgroup analysis by b/tsDMARD treatment group (TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, Abatacept, Apremilast, JAK inhibitors) and by csDMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine, azathioprine)
18.	Anticipated or actual start date	20/10/20
19.	Anticipated completion date	30/11/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 20 October 2020	RCTs or observational studies
Embase (ProQuest)	1974 – 20 October 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 10 of 12, October 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2	EMB.EXACT.EXPLODE("psoriatic arthritis")
3	TI,AB(Psoriasis or Psoriatic)
4	TI,AB(arthrosis or *arthritis)
5	S3 n/3 S4
6	S1 or S2 or S5
7	TI,AB("TNF inhibitor*" or "Tumor necrosis factor inhibitor*" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
8	TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
9	TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
10	TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
11	TI,AB(Abatacept or apremilast)
12	TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
13	TI,AB(biologic* and DMARD)
14	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
15	TI,AB(concomitant or combination)
16	TI,AB(disease modifying antirheumatic drug* or *DMARD* or methotrexate or ciclosporin or cyclophosphamide or hydroxychloroquineor leflunomide or mycophenolate or sulfasalazine)
17	S15 and S16
18	TI(trial)
19	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)

20 TI,AB(doubl* n/1 blind*)

21 TI,AB(singl* n/1 blind*)

22 RTYPE(controlled clinical trial)

23 RTYPE(randomized controlled trial)

24 MESH.EXACT.EXPLODE("Clinical Trials as Topic")

25 EMB.EXACT.EXPLODE("crossover procedure")

26 EMB.EXACT.EXPLODE("single blind procedure")

27 EMB.EXACT.EXPLODE("randomized controlled trial")

28 EMB.EXACT.EXPLODE("double blind procedure")

29 S18 OR S19 OR S20 OR S21 OR 22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28

30 S6 and S14 and S17 AND S29

31 MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")

32 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)

33 TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)

34 TI,AB(before n/2 after n/2 stud*)

35 TI,AB(longitudinal or retrospective or prospective or cross sectional)

36 TI,AB(study or studies or review or analys* or cohort* or data)

37 S35 and S36

38 S31 OR S32 OR S33 OR S34 OR S37

39 S6 AND S14 AND S17 AND S38

40 S30 OR S39

Cochrane Library (Wiley) search terms

#1 MeSH descriptor: [Arthritis, Psoriatic] this term only

#2 arthrosis or *arthritis

#3 Psoriasis or Psoriatic

#4 #2 and #3

#5 #1 or #4

#6 concomitant

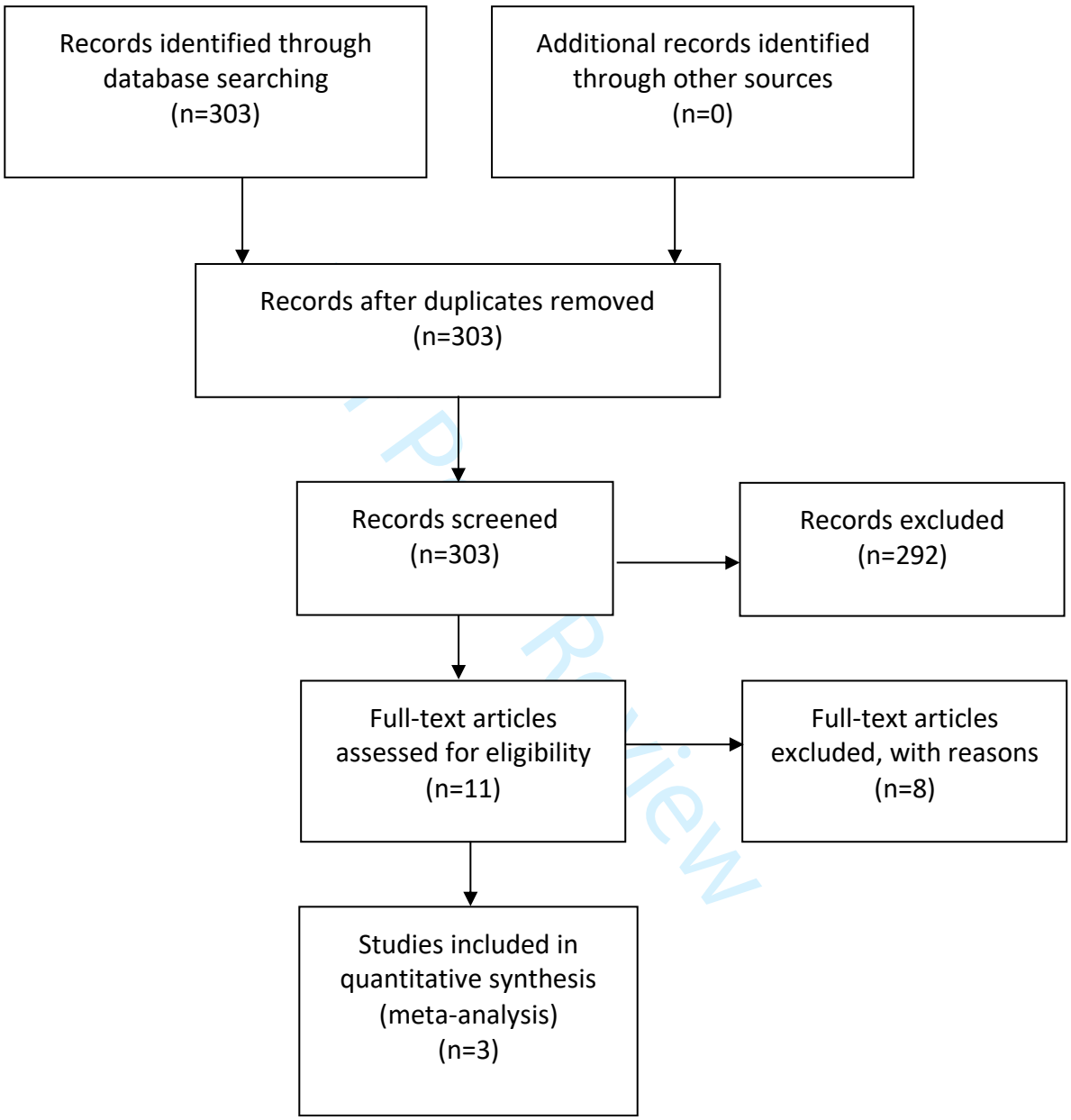
#7 DMARD* or disease modifying antirheumatic drug*

#8 #6 and #7

#9 #5 and #8

Appendix C: **Clinical evidence selection**

Figure 1: Flow chart of clinical study selection



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Appendix D: **Clinical evidence tables**

Study	SEAM-PsA: Mease 2019(1)
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=851
Countries and setting	Conducted in USA, Argentina, Bulgaria, Canada, Chile, Czech Republic, France, Greece, Hungary, Latvia, Mexico, Poland, Portugal, Puerto Rico, Russia, South Africa, Spain, UK; Setting: 92 hospital centres
Line of therapy	Not applicable
Duration of study	Intervention plus follow-up: 48 weeks week of treatment and 30 days follow-up
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This study included 3 treatment groups, etanercept + methotrexate, etanercept alone, and methotrexate alone. This evidence review looks at the comparison of the former two treatment groups.
Inclusion criteria	Adults who active PsA who were naïve to bDMARDs and no prior use of methotrexate for PsA. If people were receiving nonsteroidal antiinflammatory drugs (NSAIDs), the dose had to be stable ≥2 weeks prior to initiation of the study. If people were receiving oral corticosteroids, the dose had to be stable (not to exceed the equivalent of 10 mg prednisone per day) ≥4 weeks prior to initiation of the study.
Exclusion criteria	People had to test negative for hepatitis B surface antigen and hepatitis B core antibody, test negative for hepatitis C antibody, have no known history of active tuberculosis, and test negative for tuberculosis during screening. Women had to test negative for pregnancy if not at least 2 years postmenopausal. People were excluded if they had a known history of alcoholic hepatitis, nonalcoholic steatohepatitis, or immunodeficiency syndromes.
Age, gender and ethnicity	Age – Mean (SD): 49 (13) and 49 (14) and 48 (13). Gender (M:F): 419/432. Ethnicity: 90% white
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 548 (64%) Enthesitis at baseline: 576 (68%) Dactylitis at baseline: 284 (33%)
Indirectness of population	No indirectness
Interventions	(n=284) Intervention 1: Concomitant conventional DMARD therapy when commencing b/ts DMARDs – Etanercept was administered at a dosage of 50 mg/week by subcutaneous injection. Methotrexate, supplied as 2.5-mg tablets in capsules, and was initiated at a dosage of 10 mg/week and titrated up to 20 mg/week over a 4-week period. Concurrent medication/care: Folic acid was administered at 5–7 mg/week. People entering the study taking oral corticosteroids had to remain on a stable dose up to week 24. Those taking acetaminophen, narcotic analgesics, or NSAIDs had to remain on a stable dose up to week 24 and could not take these agents within 12 hours (24 hours for oxycontin) before a scheduled study visit. Indirectness: No indirectness (n=284) Intervention 2: Commencing b/ts DMARDS monotherapy - Etanercept was administered at a dosage of 50 mg/week by subcutaneous injection. Concurrent medication/care: Folic acid was administered at 5–7 mg/week.

Concurrent conventional DMARDs

	People entering the study taking oral corticosteroids had to remain on a stable dose up to week 24. Those taking acetaminophen, narcotic analgesics, or NSAIDs had to remain on a stable dose up to week 24 and could not take these agents within 12 hours (24 hours for oxycontin) before a scheduled study visit. Indirectness: No indirectness
Funding	Amgen

TNF inhibitor versus placebo

- Mortality at 48 weeks. RoB: low
- SF36 physical component score at 24 weeks. RoB: low
- SF36 mental component score at 24 weeks. RoB: low
- ACR20 response at 24 weeks. RoB: low
- ACR50 response at 24 weeks. RoB: low
- ACR70 response at 24 weeks. RoB: low
- Minimal disease activity at 24 weeks. RoB: low
- Dactylitis resolution at 24 weeks. RoB: h
- Enthesitis resolution at 24 weeks. RoB: h
- People achieving clear/almost clear on sPGA-psoriasis at 24 weeks. RoB: h
- Serious adverse events at 48 weeks. RoB: low
- Radiological progression at 48 weeks. RoB: low
- SPARCC Enthesitis Index at 24 weeks. BoB: low

Study	NCT01111240: Behrens 2016(2)
Study type	Retrospective analysis of data from a multicentre, prospective, noninterventional study
Number of participants	n=1455
Countries and setting	Conducted in Germany; Setting: 355 centres: 234 rheumatology centres, 101 dermatology centres, 20 general practices
Recruitment	All people enrolled into a non-interventional study between August 2005 and December 2009 who initiated adalimumab monotherapy or adalimumab plus methotrexate therapy.
Duration of study	Assessment over a 24 month period
Method of assessment of guideline condition	Diagnosis of PsA and active disease as judged by a clinician
Stratum	Overall
Subgroup analysis within study	The treatment groups were divided into those with axial involvement and those without.
Inclusion criteria	People with PsA prescribed adalimumab.
Exclusion criteria	People who had previously received adalimumab were excluded as were people who were prescribed concomitant therapy with a csDMARD other than methotrexate.
Age, gender and ethnicity	Age - Mean (SD): 50 (12). Gender (M:F): 754/701. Ethnicity: Not stated
Further population details	2 concomitant therapy groups (axial and no axial) followed by 2 Monotherapy groups (axial and no axial) Psoriasis body surface area: 9.4% and 8% / 10.6% and 11%

	Prior methotrexate use: 95% and 92% / 75% and 82% Enthesitis at baseline: 47% and 29% / 35% and 25% Dactylitis at baseline: 42% and 46% / 42% and 44%
Indirectness of population	No indirectness
Interventions	(n=131 (axial) and n=501 (no axial)) Intervention 1: Concomitant conventional DMARD therapy when commencing b/ts DMARDs - adalimumab with methotrexate. Concurrent medication: not detailed. Indirectness: No indirectness (n=165 (axial) and 568 (no axial)) Intervention 2: b/tsDMARD monotherapy – Adalimumab Concurrent medication: not detailed. Indirectness: No indirectness
Funding	Supported by AbbVie Deutschland GmbH and Co.

Stepwise regression analyses (forward selection and backward elimination) were performed on key outcome measures (change from month 0 to month 24 in DAS28, TJC, SJC, TLS, and BSA) using 36 explanatory variables:
Baseline values for body surface area, target lesions score, DAS28, Funktionsfragebogen Hannover questionnaire (self reported patient function), tender joint count, swollen joint count, erythrocyte sedimentation rate, C-reactive protein, age, body mass index, disease duration of psoriasis, disease duration of arthritis, number of doctor visits in the last 3 months, number of previous DMARDs, number of actual DMARDs, years of DMARD treatment, physician assessment of global disease activity, patient assessment of global disease activity, fatigue (11-point scale), pain (11-point scale), minutes of morning stiffness, number of previous biologic therapies, gender, hospitalization in the last 12 months, employment status, erosive joint disease, rheumatoid factor seropositivity, concomitant MTX therapy, concomitant systemic glucocorticoid therapy, concomitant analgesic therapy, concomitant non-steroidal anti-inflammatory drug therapy, osteoporosis, mental disorder/depression, type II diabetes, axial involvement, limitations due to arthritis ≥ 7 days.

Concomitant conventional DMARD therapy when commencing b/ts DMARDs versus commencing b/ts DMARDS monotherapy

- DAS28 at 24 months. RoB: vh
- Target Lesion Score. RoB: vh
- Withdrawal for any reason. RoB: vh

Study	Thomas 2020(3)
Study type	Retrospective analysis of data from five cohorts
Number of participants	n=2294
Countries and setting	Conducted in Czech Republic, Italy, UK, Greece, Switzerland; Setting: 2 hospital cohorts and 3 biologics registries
Recruitment	
Duration of study	The study period ran from January 2000 to December 2015.
Method of assessment of guideline condition	Diagnosis of PsA as judged by a clinician
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults with PsA who were naïve to TNF inhibitor treatment and had now been prescribed a TNF inhibitor.

Concurrent conventional DMARDs

Exclusion criteria	Not detailed.
Age, gender and ethnicity	Patient characteristics were reported by cohort. To avoid long lists of numbers the range of values is presented here. Age - Median: 45-51 . Gender: approximately 50%M/F. Ethnicity: Not stated
Further population details	There appeared to be variations in baseline population details between the two groups but the population details were presented separately for each of the 5 cohorts and it was not possible to draw any general trends from this.
Indirectness of population	No indirectness
Interventions	(n=1514) Intervention 1: Concomitant conventional DMARD therapy when commencing b/ts DMARDs - TNF inhibitor combination therapy with a csDMARD. Concurrent medication: not detailed. Indirectness: No indirectness (n=780) Intervention 2: b/tsDMARD monotherapy – TNF inhibitor monotherapy Concurrent medication: not detailed. Indirectness: No indirectness
Funding	Nonrestricted investigator-initiated award from Pfizer.

The regression models were adjusted for age at TNFi initiation and sex. Differences between rates of improvement in the 2 treatment groups were obtained by including an interaction term between time and treatment group in the regression models. To account for any confounding by indication, they developed database-specific propensity score (PS) models, using all available baseline data, to calculate the individual PS for treatment to monotherapy or combination therapy. All covariates that were not explicitly included in the model were included in the PS models, including clinical characteristics such as disease duration.

The study required individual patient data for the comparative effectiveness analyses modelling, and so only included people from the UK, Italian, and Swiss databases.

Concomitant conventional DMARD therapy when commencing b/ts DMARDs versus commencing b/ts DMARDS monotherapy

- Change in DAS28 unclear time period. RoB: vh.
- Discontinuation of treatment during the first year RoB: vh

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Appendix E: **Forest plots**

Figure 2: Mortality at week 48

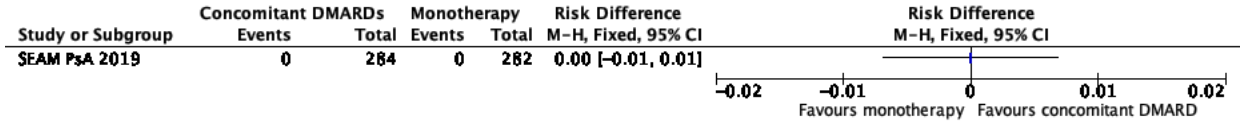


Figure 3: Change in SF-36 mental component score at 24 weeks

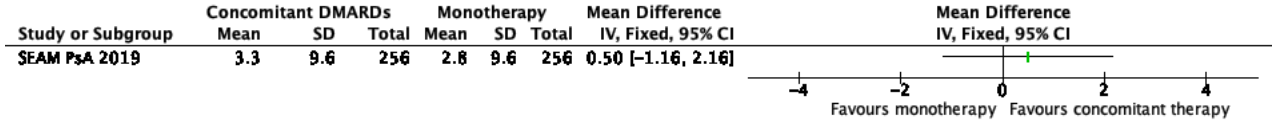


Figure 4: Change in SF-36 physical component score 24 weeks

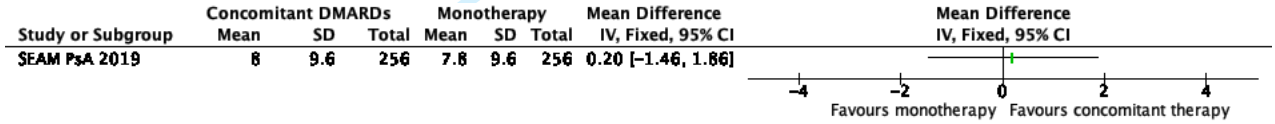


Figure 5: Mortality at ACR20 response at week 24

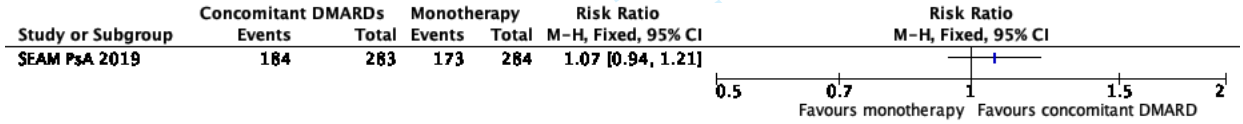


Figure 6: ACR50 response at week 24

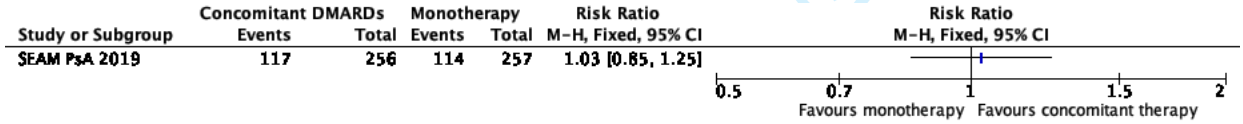


Figure 7: ACR70 response at week 24

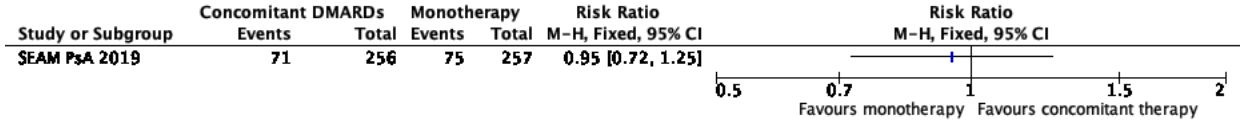


Figure 8: Minimal disease activity (≥ 5 of 7 criteria) at 24 weeks

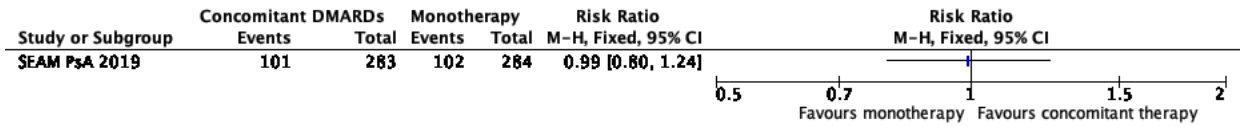


Figure 9: mTSS/SHS: van der Heijde modified Total Sharp Score (0-528) at 48 weeks

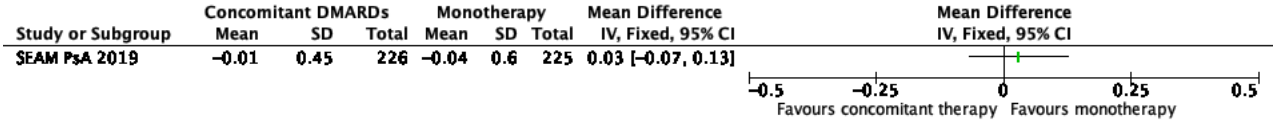


Figure 10: Enthesitis resolution at week 24 in people with enthesitis at baseline

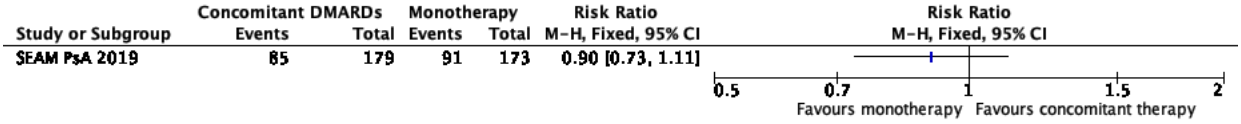


Figure 11: Dactylitis resolution at 24 weeks. Data are reported for people with dactylitis at baseline

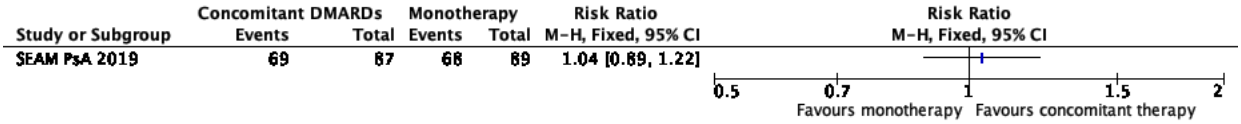


Figure 12: SPARCC Enthesitis Index: Spondyloarthritis Research Consortium of Canada Enthesitis index (score 0-16) at week 24

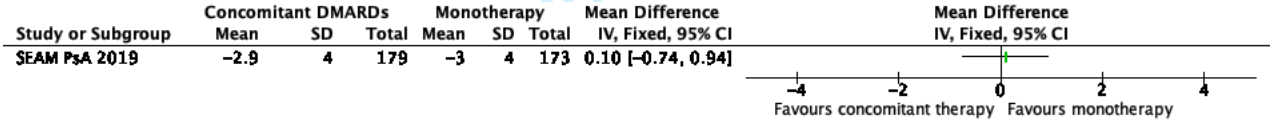


Figure 13: People achieving clear/almost clear status at 24 weeks in people with psoriasis at baseline

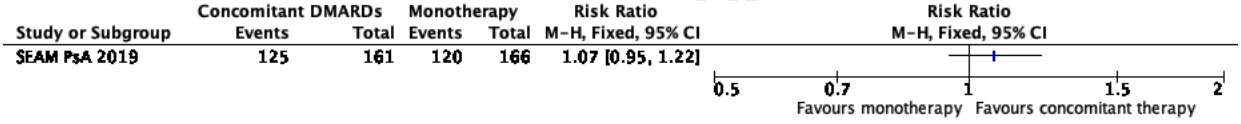


Figure 14: Change in Target Lesion Score at 24 months

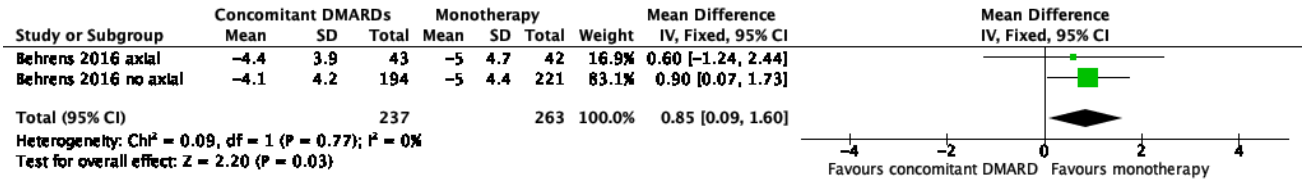


Figure 15: Withdrawal from study/ discontinuation of treatment due to adverse events and/or lack of efficacy

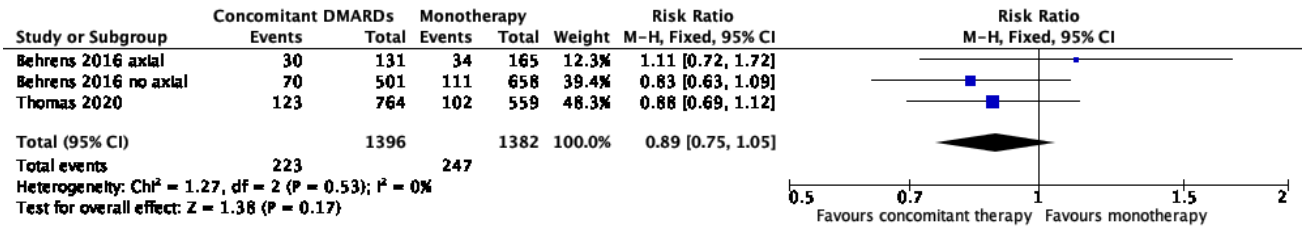


Figure 16: Change in DAS28 at 24 months

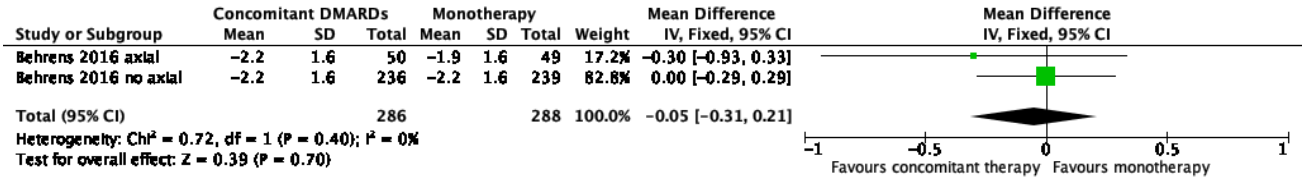
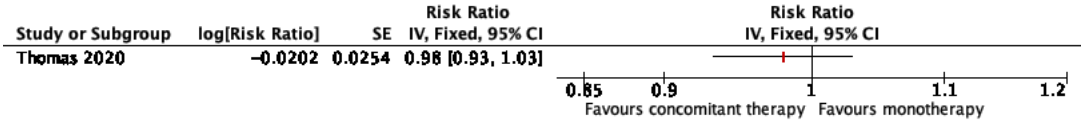


Figure 17: Rate of change of DAS28 prior to a person's censoring date



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Appendix F: **Excluded studies**

Table 5: studies excluded from the evidence review

Study	Exclusion reason
Behrens 2019(4)	Review including data from an included study
Behrens 2018(5)	Observational study where it was unclear if people were recruited before initiation of b/tsDMARD therapy and no accounting for confounding factors
Coates 2017(6)	Observational study which does not account for confounding factors
Fagerli 2014(7)	Efficacy data not adjusted for confounding factors but risk factor analysis performed for treatment cessation at 3 years
Mease 2019(8)	Observational study with a focus on treatment patterns from registry data
Mease 2015(9)	Multivariate Cox regression models were used to identify predictors of TNFi persistence and time to remission.
Nash 2018(10)	Observational study which does not account for confounding factors
Walsh 2018(11)	Observational study which does not account for confounding factors

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Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on sequence of biologic and targeted synthetic DMARD treatment after treatment failure

BSR Guideline

Intervention evidence review

October 2020

Contents

1Sequencing of biologic and targeted synthetic DMARD treatment after treatment failure

1.1 In adults with PsA who have had an inadequate response to, or failed treatment with, one or more biologic or targeted synthetic DMARDs, which biologic and targeted synthetic DMARDs are the most clinically effective subsequent treatment?

1.2 INTRODUCTION

People can be unresponsive or have an inadequate response to a b/tsDMARD medication, or develop an inadequate response to a b/tsDMARD to which they had previously responded. These people are switched to a different b/tsDMARD but it is unclear what the best next step is. This review seeks to answer what the next b/tsDMARD treatment should be after an inadequate response or treatment failure.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis an inadequate response to, or failed treatment with, one or more biologic or targeted synthetic DMARDs
Intervention	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept Apremilast JAK inhibitors
Comparison	Comparison of interventions Placebo
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life including SF-36, PsAQoL (continuous) Arthritis • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Psoriasis in those with psoriasis at baseline • Psoriasis score (PASI / IGA / BSA) (continuous) **Important** Arthritis • Radiological progression (continuous)

	Adverse Events • Serious adverse events (dichotomous) **The outcomes below are extracted if studies do not report ACR response.** • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous), • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	RCTs If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search we conducted to find studies comparing a person with psoriatic arthritis (PsA) initial biologic and targeted synthetic DMARDs (b/tsDMARDs) treatment. In addition data extraction and quality assessment undertaken by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was utilised to aid in the completion of this review.

8 RCTs were included in the review. These studies covered 4 comparisons versus placebo and 0 active control comparisons. In all cases the medication to which people were not responding or were intolerant were TNF inhibitors.

Comparisons in people who are not responding or are intolerant to at least one TNF inhibitor:

- Apremilast versus placebo: 2 RCTs
- IL-17 inhibitor versus placebo: 4 RCTs
- IL-23 inhibitors versus placebo: 1 RCT
- JAK inhibitor versus placebo: 1 RCT

1.4.2 Excluded studies

See the list of excluded studies in Appendix G: Excluded studies

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Apremilast versus placebo				
PALACE 1: Kavanaugh 2014{Kavanaugh, 2014 #276}	Apremilast (n=336) versus placebo (n=168) for 24 weeks. Concurrent stable treatment with csDMARDs, NSAIDs and corticosteroids was permitted. Early escape possible for people in either group at week 16.	N=504 Outcomes in the subgroup of people who for whom bDMARD failed. N=45 (9%). Adults with active PsA despite previous treatment with csDMARDs and/or bDMARDs.	- ACR20 at week 16.	Multicentre study in North America, Australasia, Europe, and Africa. Funding: Study sponsored by Celgene Corp.
PALACE 3: Edwards 2016(7)	Apremilast (n=336) versus placebo (n=169) for 24 weeks. Concurrent stable treatment with csDMARDs, NSAIDs and corticosteroids was permitted. Early escape possible for people in either group at week 16.	N=505 Outcomes in the subgroup of people who for whom TNF inhibitors failed. N=44 (9%). Adults with active PsA despite previous treatment with csDMARDs and/or bDMARDs.	- ACR20 at 16 weeks	Multicentre study in North America, Australasia, and Europe. Funding: Study sponsored by Celgene Corp.
IL-17 inhibitor versus placebo:				
FUTURE 2. McInnes 2015{McInnes, 2015 #440}, Kavanaugh 2016{Kavanaugh, 2016 #390}, Coates 2018{Coates, 2018 #449}	Secukinumab (n=195) versus placebo (n=63) for 24 weeks. Concomitant use of MTX permitted.	N=397 This is an analysis of 139 (35%) people with prior inadequate response to TNF inhibitors	- Quality of life (change in SF-36 mental component) - ACR20 response at 24 weeks. - ACR50 response at 24 weeks. - ACR70 response at 24 weeks.	Multicentre study across Europe, North America, Australasia and Asia. Funding: Novartis

Study	Intervention and comparison	Population	Outcomes	Comments
		Adults with active PsA despite previous treatment with conventional therapy.	- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 16 weeks. - Enthesitis resolution at 24 weeks. - Dactylitis resolution at 24 weeks. - PASI response: ≥90% improvement at week at 24 weeks. - PASI response: ≥75% improvement at week at 24 weeks.	
FUTURE 3: Nash 2018{Nash, 2018 #447}	Secukinumab (n=189) versus placebo (n=93) for 24 weeks. Concomitant use of oral glucocorticoids or MTX permitted.	N=414 This is an analysis of 132 (32%) people with prior inadequate response to TNF inhibitors Adults with active PsA despite previous treatment with csDMARDs, NSAIDs or TNF inhibitors.	- ACR20 at 24 weeks - ACR50 at 24 weeks	Multicentre study across Europe, North America, and Australasia. Funding: Novartis
FUTURE 4: Kivitz 2019{Kivitz, 2019 #451}	Secukinumab (n=173) versus placebo (n=87) for 24 weeks. Concomitant use of NSAIDs, oral glucocorticoids or MTX permitted. At week 16 people in the placebo group could have early escape to secukinumab treatment.	N=341 This is an analysis of 81 (24%) people with prior inadequate response to TNF inhibitors Adults with active PsA despite previous treatment with cs/bDMARDs and/or NSAIDs.	- ACR20 at 16 weeks - ACR50 at 16 weeks	Multicentre study across Europe, North America, and Australasia. Funding: Novartis

Study	Intervention and comparison	Population	Outcomes	Comments
FUTURE 5: Mease 2018{Mease, 2018 #443}	Secukinumab (n=469) versus placebo (n=234) for 24 weeks. Concomitant use of NSAIDs, oral glucocorticoids or MTX permitted. At week 16 people in the placebo group could have early escape to secukinumab treatment.	N=996 This is an analysis of 295 (30%) people with prior inadequate response to TNF inhibitors Adults with active PsA despite previous treatment with csDMARDs, NSAIDs or TNF inhibitors.	- ACR20 at 16 weeks. - ACR50 at 16 weeks. - ACR70 at 16 weeks.	Multicentre study across Europe, North America, South America, and Asia. Funding: Novartis
IL-23 inhibitors versus placebo:				
DISCOVER 1: Deodhar 2020{Deodhar, 2020 #193}	Guselkumab (n=255) versus placebo (n=126) for 24 weeks. Background treatment with csDMARDs, corticosteroids, or NSAIDs allowed. Early escape possible for people in either group at week 16.	N=381 overall Data extracted for subgroup of people with inadequate response to previous TNF inhibitor: N=44 (12%). People with active PsA with inadequate response (IR) to conventional treatment.	- ACR20 at 24 weeks - ACR50 at 24 weeks - ACR70 at 24 weeks	Multicentre study across Europe, North America, South America, and Asia. Funding: Janssen Research and Development. 12 people in this study were previously exposed to apremilast and therefore this it is considered indirect evidence.
JAK inhibitor versus placebo				
OPAL Beyond: Gladman 2017{Gladman, 2017 #381}, Strand 2019{Strand, 2019 #406}	Tofacitinib (n=263) versus placebo (n=131) for 12 weeks. People were allowed a stable dose of a csDMARD	N=394 Adults with a active PsA and inadequate response to at least 1 TNF inhibitor	- Mortality at 12 weeks. - ACR20 at week 12. - ACR50 at week 12 - ACR70 at week 12 - MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks - Enthesitis absence at 12 weeks in people with enthesitis at baseline	Multicentre study across Europe, North America, Central America, Asia, and Australasia. Funding: Pfizer

Study	Intervention and comparison	Population	Outcomes	Comments
			- LEI: Leeds Enthesitis Index at 12 weeks in people with enthesitis at baseline - Dactylitis resolution at 12 weeks in people with dactylitis at baseline. - PASI response: ≥75% improvement at week 12 - Serious adverse events at 12 weeks	

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Apremilast versus placebo in people for whom TNF inhibitors failed

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apremilast	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response (follow up: 16 weeks)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	14/59 (23.7%)	2/30 (6.7%)	**RR 3.45** (0.84 to 14.15)	**163 more per 1,000** (from 11 fewer to 877 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 4: IL-17 inhibitors versus placebo in people for whom TNF inhibitors failed

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/245 (0.0%)	0/118 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow up: 12 weeks; assessed with: Change in Short Form-36 Health Survey, Physical Component Score; Scale from: 0 to 100)												
5	randomised trials	not serious	not serious	not serious	serious [a]	none	349	153	-	MD **3.6 higher** (1.51 higher to 5.68 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life (follow up: 12 weeks; assessed with: Change in Short Form-36 Health Survey, Mental Component Score; Scale from: 0 to 100)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	245	118	-	MD **4.35 higher** (1.51 higher to 7.19 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response (follow up: range 12 weeks to 24 weeks)												
5	randomised trials	serious [b]	not serious	not serious	not serious	none	291/688 (42.3%)	56/322 (17.4%)	**RR 2.46** (1.91 to 3.16)	**254 more per 1,000** (from 158 more to 376 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response (follow up: range 12 weeks to 24 weeks)												
5	randomised trials	serious [b]	not serious	not serious	not serious	none	172/688 (25.0%)	17/322 (5.3%)	**RR 4.75** (2.94 to 7.66)	**198 more per 1,000** (from 102 more to 352 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR70 response (follow up: range 12 weeks to 24 weeks)												
3	randomised trials	serious [b]	not serious	not serious	not serious	none	74/546 (13.6%)	8/251 (3.2%)	**RR 4.13** (2.06 to 8.28)	**100 more per 1,000** (from 34 more to 232 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Minimal disease activity (follow up: range 12 weeks to 16 weeks; assessed with: ≥ 5 of 7 criteria)												
2	randomised trials	not serious	not serious	not serious	not serious	none	60/315 (19.0%)	7/152 (4.6%)	**RR 4.13** (1.94 to 8.82)	**144 more per 1,000** (from 43 more to 360 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Dactylitis resolution in people with dactylitis at baseline. (follow up: range 12 weeks to 24 weeks)												
2	randomised trials	very serious [b]	not serious	not serious	serious [a]	none	46/81 (56.8%)	6/24 (25.0%)	**RR 2.26** (1.12 to 4.58)	**315 more per 1,000** (from 30 more to 895 more)	⊕◯◯◯ VERY LOW	CRITICAL
Enthesitis absence/resolution in people with enthesitis at baseline (follow up: range 12 weeks to 24 weeks)												
2	randomised trials	serious [b]	very serious [c]	not serious	serious [a]	none	83/221 (37.6%)	22/92 (23.9%)	**RR 2.26** (0.39 to 13.07)	**301 more per 1,000** (from 146 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Enthesitis score in people with enthesitis at baseline (follow up: range 12 weeks to 24 weeks; assessed with: LEI: Leeds Enthesitis Index ; Scale from: 0 to 6)												
2	randomised trials	serious [b]	not serious	not serious	serious [a]	none	152	69	-	MD **0.45 lower** (1.17 lower to 0.27 higher)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Bath Ankylosing Spondylitis Disease Activity Index. (BASDAI) in people with baseline BASDAI>4 at baseline (follow up: 24 weeks; assessed with: Change score; Scale from: 0 to 10)												
2	randomised trials	serious [b]	not serious	not serious	serious [a]	none	199	96	-	MD **1.6 lower** (2.31 lower to 0.89 lower)	⊕⊕◯◯ LOW	CRITICAL
Psoriasis score (follow up: range 12 weeks to 24 weeks; assessed with: PASI response: ≥90% improvement)												
2	randomised trials	serious [b]	not serious	not serious	not serious	none	75/186 (40.3%)	9/79 (11.4%)	**RR 3.77** (2.00 to 7.12)	**316 more per 1,000** (from 114 more to 697 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	11/245 (4.5%)	4/118 (3.4%)	**RR 1.32** (0.43 to 4.07)	**11 more per 1,000** (from 19 fewer to 104 more)	⊕⊕◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
c. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used

Table 5: IL-23 inhibitors versus placebo in people for whom TNF inhibitors failed

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-23 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	20/32 (62.5%)	3/12 (25.0%)	**RR 2.50** (0.91 to 6.91)	**375 more per 1,000** (from 22 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
ACR50 response (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/32 (21.9%)	0/12 (0.0%)	**RR 5.91** (0.36 to 96.19)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
ACR70 response (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/32 (12.5%)	0/12 (0.0%)	**RR 3.55** (0.21 to 61.32)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: JAK inhibitors versus placebo in people for whom TNF inhibitors failed

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 12 weeks; assessed with: Short Form-36 Health Survey, Physical Function score ; Scale from: 0 to 100)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	244	117	-	MD **2.85 higher** (1.17 higher to 4.54 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 12 weeks; assessed with: Short Form-36 Health Survey, Mental Function score; Scale from: 0 to 100)												
2	randomised trials	not serious	not serious	not serious	not serious	none	263	131	-	MD **1.64 higher** (0.48 lower to 3.76 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR20 response (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	127/263 (48.3%)	31/131 (23.7%)	**RR 2.04** (1.46 to 2.84)	**246 more per 1,000** (from 109 more to 435 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR50 response (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	76/263 (28.9%)	19/131 (14.5%)	**RR 1.99** (1.26 to 3.15)	**144 more per 1,000** (from 38 more to 312 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR70 response (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	41/263 (15.6%)	13/131 (9.9%)	**RR 1.57** (0.87 to 2.83)	**57 more per 1,000** (from 13 fewer to 182 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Minimal disease activity (follow up: 12 weeks; assessed with: ≥ 5 of 7 criteria)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	58/263 (22.1%)	19/131 (14.5%)	**RR 1.52** (0.95 to 2.44)	**75 more per 1,000** (from 7 fewer to 209 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Enthesitis resolution in people with enthesitis at baseline (follow up: 12 weeks)												
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	65/182 (35.7%)	20/93 (21.5%)	**RR 1.66** (1.08 to 2.56)	**142 more per 1,000** (from 17 more to 335 more)	⨁⨁◯◯ LOW	CRITICAL
Enthesitis score in people with enthesitis at baseline (follow up: 12 weeks; assessed with: LEI: Leeds Enthesitis Index; Scale from: 0 to 6)												
2	randomised trials	serious [b]	not serious	not serious	serious [a]	none	165	93	-	MD **0.8 lower** (1.26 lower to 0.34 lower)	⨁⨁◯◯ LOW	CRITICAL
Dactylitis resolution in people with dactylitis at baseline (follow up: 12 weeks)												
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	67/131 (51.1%)	18/64 (28.1%)	**RR 1.82** (1.19 to 2.78)	**231 more per 1,000** (from 53 more to 501 more)	⨁⨁◯◯ LOW	CRITICAL
Psoriasis score in people with psoriasis at baseline (follow up: 12 weeks; assessed with: PASI response: ≥75% improvement)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	not serious	none	52/161 (32.3%)	12/86 (14.0%)	**RR 2.31** (1.31 to 4.10)	**183 more per 1,000** (from 43 more to 433 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Serious adverse events (follow up: 12 weeks)

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	4/263 (1.5%)	3/131 (2.3%)	**RR 0.66** (0.15 to 2.92)	**8 fewer per 1,000** (from 19 fewer to 44 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and arthritis disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures capable of capturing medication effects on other disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA, are available.

1.5.2 Benefits and harms

8 RCTs were found each in a population of people who did not respond or were intolerant to TNF inhibitors. The comparisons for the subsequent treatment were apremilast (2 RCTs), IL-17 inhibitor (4 RCTs), IL-23 inhibitor (1 RCT), and JAK inhibitor (1 RCT) each versus placebo. Therefore there were no active controlled comparisons. The outcomes were similar between groups in that response to joint disease outcomes indicated a clinically important benefit of the intervention in all cases. The IL-17 inhibitor trials reported mortality and alongside the JAK inhibitor trials reported quality of life outcomes. No clinical difference was found for any of these. Both also offered dactylitis and enthesitis outcomes and found a benefit of the intervention for these. The IL-17 inhibitor trials also had an axial spondylarthritis outcome that indicated a benefit of the intervention. In terms of safety, the IL-17 inhibitor trial found a harm of the treatment for serious adverse events and the JAK inhibitor trial found a benefit for this outcome.

The group commented that the evidence around JAK inhibitors was from a single study of tofacitinib. It may not be appropriate to make recommendations on the class based only on a single medication in the class. It was specifically mentioned that JAK inhibitor effectiveness is thought to vary within class.

In terms of the evidence found, there was no entirely standard definition of what defines medication failure and this likely varied from study to study. It is often an inadequate treatment response at the discretion of the enrolling physician.

Overall, the group agreed there is very little evidence to state an order of treatment when a certain medication has failed. All the evidence is for TNF inhibitor failure but all the medications found appeared to be broadly effective in the outcomes they reported.

A member of the group mentioned that the recommendation could be made for the cheapest next medication. However, the group agreed that a more appropriate response to the lack of evidence is to rely on the limited evidence available and also to rely on the expertise of the MDT to make decisions based on a variety of contributing factors.

One thing to note is that all of the groups of medications evaluated in this guideline have shown effectiveness in b/tsDMARD naive people. These are TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors , IL17 inhibitors, abatacept, apremilast , and JAK inhibitors.

The evidence for the guideline indicates all the treatments evaluated in the trials (apremilast, IL-17 inhibitor, IL-23 inhibitor, JAK inhibitor) are effective after failure of TNF inhibitors but without head to head data it is hard to know which are most effective. The group discussed whether certain drugs which appear to be more effective versus placebo should be prioritised. The group spoke about network meta-analysis (NMA) for this question and whether that could shed light on this. One problem is that evidence for this clinical question is all versus placebo and there are no closed loops. This limits the usefulness of NMA and the assessment of consistency of the evidence.

Therefore the group decided to allow more freedom to prescribe to the MDT which capitalises on their knowledge of the medical history of each specific patient. There are a number of aspects that could be utilised in this decision-making.

An important aspect is the level of failure of the previous medication. In some cases people have a treatment which is partially effective but a decision is taken to try a new mode of action to optimize their treatment. Their response to this new mode of action then informs whether they should stick with it or change back to their previous partially effective mode of action. Also health professionals are presented with a limited line of therapies and it may be necessary to try a previous therapy in some situations where it offers an acceptable outcome.

A trust was mentioned who required an individual funding request when reverting back to a previous treatment that was deemed to have insufficient efficacy for the patient. A number of these have been declined. Unfortunately this discourages an aspirational treatment approach to achieve remission / MDA as part of nationally agreed T2T approaches in PsA. Both the clinician and patient are therefore "boxed-in" to accept the current status, rather than aspire for better, in case a different agent is not as efficacious. Also people have been known to not agree to a change in treatment because return to the previous treatment cannot be assured.

A lay member agreed that it is really important to be able to pick the appropriate drug for the situation based on the patient's needs rather than being overly prescriptive in this guideline.

In terms of practice, the group agreed not to define a single time point for when to assess a medication is deemed not be effective and should be altered. This varies on a person by person and medication by medication basis.

After multiple b/tsDMARDs have failed then it may be that other case factors such as adherence and their diagnosis should be considered. There are occasions where people try multiple biologics and it turns out they had osteoarthritis (OA) rather than PsA. Alternatively their treatment has been escalated due to pain syndromes, but there is no disease activity to warrant this change.

1.5.3 Cost effectiveness and resource use

1.5.4 Other factors the committee took into account

References

Appendices

Appendix A: **Review protocols**

Table 7: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020212858
1.	Review title	b/tsDMARD sequencing in psoriatic arthritis
2.	Review question	In adults with PsA who have had an inadequate response to, or failed treatment with, one or more biologic or targeted synthetic DMARDs, which biologic and targeted synthetic DMARDs are the most clinically effective subsequent treatment?
3.	Objective	A person may go through a sequence of differing medications until an effective treatment is found. This question seeks to inform the order these treatments should be prescribed in.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	Adults commencing b/tsDMARDS for the treatment of active psoriatic arthritis
6.	Population	Inclusion: Adults with psoriatic arthritis an inadequate response to, or failed treatment with, one or more biologic or targeted synthetic DMARDs

		The population will be stratified by the failed biologic or targeted synthetic DMARDs
7.	Intervention/Exposure/Test	Subsequent treatment with: TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept Apremilast JAK inhibitors
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions Placebo
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Not applicable
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less)

		• Radiological progression Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondylarthritis Research Consortium of Canada (SPARCC)- 0-16 Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous)

		IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Adverse Events • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I

		• Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Primary inefficacy (people who never responded the b/tsDMARD) Secondary inefficacy (people who lose response to a previously effective b/tsDMARD)
18.	Anticipated or actual start date	01/10/20
19.	Anticipated completion date	15/10/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

British Society for Rheumatology

Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 12 June 2020	Exclusions
Embase (ProQuest)	1974 – 12 June 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12	None

Medline (ProQuest) and Embase (ProQuest) search terms

1. .	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2.	EMB.EXACT.EXPLODE("psoriatic arthritis")
3.	TI,AB(Psoriasis or Psoriatic)
4.	TI,AB(arthrosis or *arthritis)
5.	S3 n/3 S4
6.	S1 or S2 or S5
7.	MESH.EXACT("Anecdotes as Topic") OR MESH.EXACT("Letter") OR EMB.EXACT("letter") OR RTYPE(letter) or RTYPE(note) or RTYPE(editorial) OR MESH.EXACT("Editorial") OR MESH.EXACT("News") OR MESH.EXACT("Historical Article") OR MESH.EXACT("Comment") OR MESH.EXACT("Case Report") OR EMB.EXACT("case report") OR EMB.EXACT("case study") OR TI(LETTER) OR TI(COMMENT*)
8.	EMB.EXACT("randomized controlled trial") OR MESH.EXACT("Randomized Controlled Trial") or TI,AB(random*)
9.	S7 NOT S8
10.	MESH.EXACT("Animals") OR EMB.EXACT("animal")
11.	MESH.EXACT("Humans") OR EMB.EXACT("human")
12.	S10 NOT S11
13.	MESH.EXACT.EXPLODE("Animals, Laboratory") OR MESH.EXACT.EXPLODE("Animal Experimentation") OR MESH.EXACT.EXPLODE("Models, Animal") OR MESH.EXACT.EXPLODE("Rodentia") OR EMB.EXACT("nonhuman") OR EMB.EXACT.EXPLODE("animal experiment") OR EMB.EXACT.EXPLODE("experimental animal") OR EMB.EXACT("animal model") OR EMB.EXACT.EXPLODE("rodent") OR TI(RAT) OR TI(RATS) OR TI(MOUSE) OR TI(MICE)
14.	S9 OR S12 OR S13
15.	S6 NOT S14

16.	TI,AB("TNF inhibitor" or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
17.	TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
18.	TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
19.	TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
20.	TI,AB(Abatacept)
21.	TI,AB(apremilast)
22.	TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
23.	S16 OR S17 OR S18 OR S19 OF S20 OR S21 OR S22
24.	TI(trial)
25.	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
26.	TI,AB(doubl* n/1 blind*)
27.	TI,AB(singl* n/1 blind*)
28.	RTYPE(controlled clinical trial)
29.	RTYPE(randomized controlled trial)
30.	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
31.	EMB.EXACT.EXPLODE("crossover procedure")
32.	EMB.EXACT.EXPLODE("single blind procedure")
33.	EMB.EXACT.EXPLODE("randomized controlled trial")
34.	EMB.EXACT.EXPLODE("double blind procedure")
35.	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
36.	S15 and S23 AND S35
37.	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
38.	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
39.	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
40.	TI,AB(before n/2 after n/2 stud*)
41.	TI,AB(longitudinal or retrospective or prospective or cross sectional)
42.	TI,AB(study or studies or review or analys* or cohort* or data)
43.	S41 and S42
44.	S37 OR S38 OR S39 OR S40 OR S43
45.	S15 AND S23 AND S44
46.	S36 OR S45

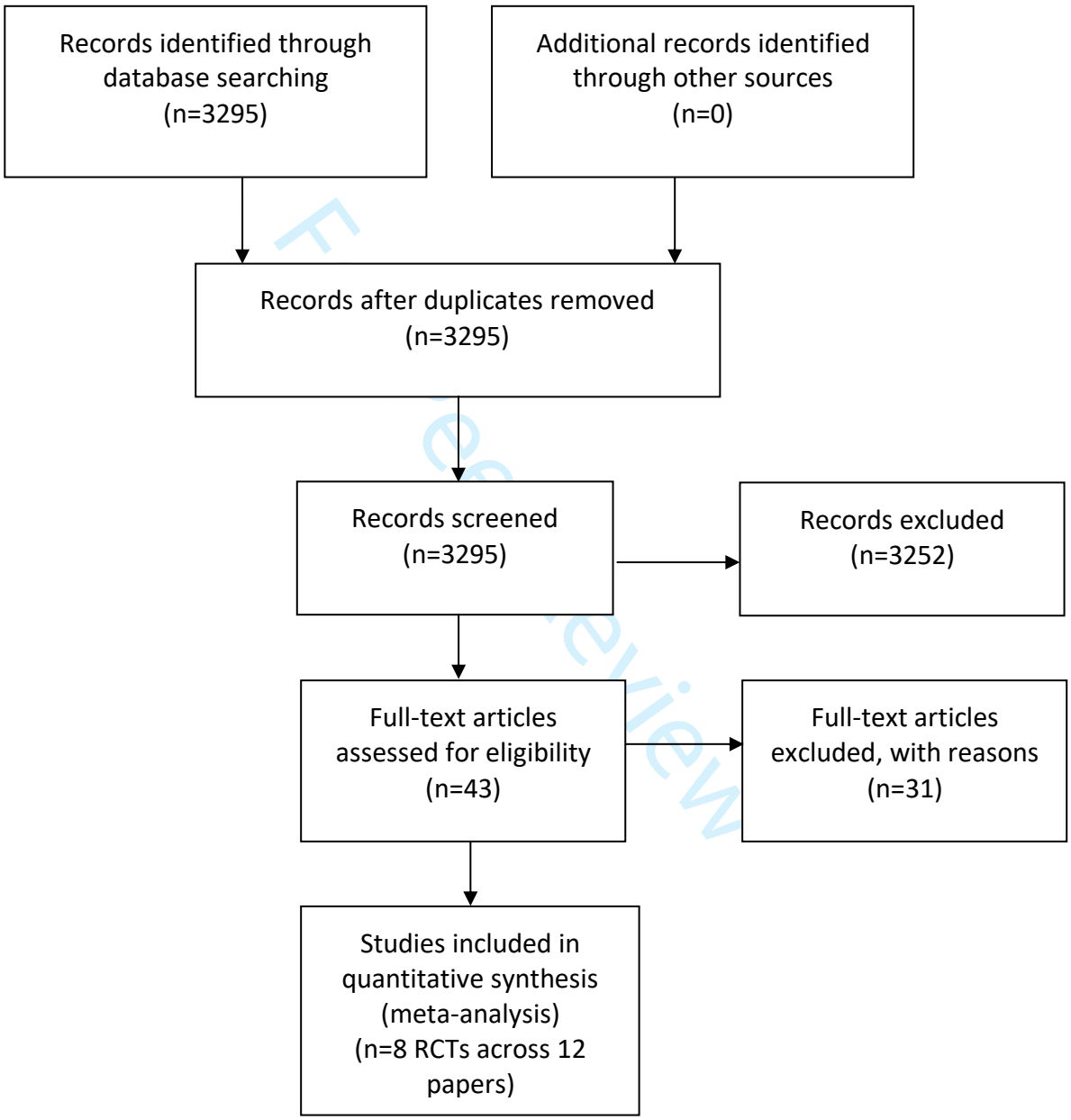
Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] explode all trees

#2	Psoriasis or Psoriatic
#3	arthrosis or *arthritis
#4	#2 and #3
#5	#1 or #4
#6	TNF inhibitor or "Tumor necrosis factor inhibitor" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab
#7	IL-12/23 inhibitor or IL12/23 inhibitor or Ustekinumab or briankizumab
#8	IL23 inhibitor or IL-23 inhibitor or guselkumab or tildrakizumab or risankizumab or mirikizumab
#9	IL17 inhibitor or IL-17 inhibitor or Ixekizumab or secukinumab or brodalumab or Bimekizumab
#10	Abatacept
#11	apremilast
#12	JAK inhibitors or “Janus kinase inhibitor” or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or tofacitinib
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#5 and #13

Appendix C: **Clinical evidence selection**

Figure 1: Flow chart of clinical study selection



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Appendix D: **Clinical evidence tables**

Study	DISCOVER 1: Deodhar 2020{Deodhar, 2020 #193}
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=381
Countries and setting	Conducted in Australia, Canada, Czech Republic, Germany, Hungary, Malaysia, Poland, South Korea, Russia, Spain, Taiwan, Ukraine, USA; Setting: 86 sites
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks while placebo controlled
Method of assessment of guideline condition	Formal classification criteria not stated.
Stratum	Overall
Subgroup analysis within study	Data extracted on subgroup of people with inadequate response to previous TNF inhibitor: N=44 (12%). It is possible up to 12 of these people were previously exposed to apremilast.
Inclusion criteria	People with psoriatic arthritis and displaying at least three tender and at least three swollen joints and CRP concentration of 0·3 mg/dL or more. They had a current or documented history of psoriasis and had demonstrated inadequate response to or intolerance of standard treatment, including at least 4 months of apremilast (if discontinued >4 weeks before receiving study treatment), at least 3 months of non-biologic DMARDs (limited to methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day), or at least 4 weeks of NSAIDs for psoriatic arthritis. Background use of stable doses of one selected nonbiologic DMARD, oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), and NSAIDs or other analgesics was permitted. People had to meet criteria for screening laboratory testing and tuberculosis history, testing, and treatment (for latent tuberculosis)
Exclusion criteria	People with other inflammatory diseases and those who had previously received biologics other than TNF inhibitors were excluded.
Age, gender and ethnicity	Age - Mean (SD): 48 (12) and 49 (11). Gender (M:F): 195/186. Ethnicity: 349 were white
Further population details	Enthesitis at baseline: 222 Dactylitis at baseline: 142
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: IL-23 inhibitor – the study contained 2 guselkumab intervention groups administered every 4 weeks or 8 weeks. Guselkumab was administered as a 100-mg subcutaneous injection. At week 16, all patients with

	less than 5% improvement in both swollen and tender joint counts were eligible for early escape—i.e. they continued with study treatment but the investigator could initiate or increase the dose of NSAIDs or other analgesics (up to the regional marketed dose approved), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), or non-biologic DMARDs (per study inclusion criteria). Indirectness: No indirectness (n=87) Intervention 2: Placebo. At week 16, all patients with less than 5% improvement in both swollen and tender joint counts were eligible for early escape—i.e. they continued with study treatment but the investigator could initiate or increase the dose of NSAIDs or other analgesics (up to the regional marketed dose approved), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), or non-biologic DMARDs (per study inclusion criteria). Indirectness: No indirectness.
Funding	Janssen Research and Development.

IL-23 inhibitor versus placebo in subgroup without previous TNF inhibitor use

- ACR20 at 24 weeks. RoB: h
- ACR50 at 24 weeks. RoB: h
- ACR75 at 24 weeks. RoB: h

Study	FUTURE 2. McInnes 2015{McInnes, 2015 #440}, Kavanaugh 2016{Kavanaugh, 2016 #390}, Coates 2018{Coates, 2018 #449}
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=397
Countries and setting	Conducted in 76 centres in USA, Australia, Belgium, Canada, Czech Republic, Germany, Poland, Puerto Rico, Russia, Thailand, UK.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 year study but randomisation was broken after 24 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 139 (35%) people with prior inadequate response to TNF inhibitors
Inclusion criteria	People with PsA fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) and active disease, defined as ≥ 3 tender and ≥ 3 swollen joints, despite previous treatment with conventional therapy.
Exclusion criteria	Patients were excluded if they had previously received biologics other than TNF inhibitors, or had received > 3 TNF inhibitors. Where applicable, TNF inhibitors were discontinued for 4–10 weeks before randomization.
Age, gender and ethnicity	Age - Mean (SD): 47 (12) and 49 (12). Gender (M:F): 122/136. Ethnicity: Not detailed

Further population details	Dactylitis: 95 (78 and 17) Enthesitis: 161 (119 and 42) Psoriasis ≥ 3% of BSA: 130 (99 and 31)
Indirectness of population	No indirectness
Interventions	(n=104) Intervention 1: IL-17 inhibitor – People were randomised to either secukinumab 300 mg (n=67), 150 mg (n=63), 75 mg (n=65) at baseline, and weeks 1, 2, 3, and 4, and every 4 weeks thereafter. Concurrent medication/care: Concomitant methotrexate (MTX; ≤ 25 mg per week) was permitted. Indirectness: No indirectness (n=35) Intervention 2: Placebo at baseline, and weeks 1, 2, 3, and 4, and every 4 weeks thereafter. At week 16 they were randomised to either 300 mg or 150 mg secukinumab. Concurrent medication/care: Concomitant methotrexate (MTX; ≤ 25 mg per week) was permitted. Indirectness: No indirectness
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people who were TNFi-IR

- Quality of life (change in SF-36 mental component): RoB: h
- ACR20 response at 24 weeks. RoB: h
- ACR50 response at 24 weeks. RoB: h
- ACR70 response at 24 weeks. RoB: h
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 16 weeks. RoB: h
- Enthesitis resolution at 24 weeks. RoB: h
- Dactylitis resolution at 24 weeks. RoB: h
- PASI response: ≥90% improvement at week at 24 weeks. RoB: h
- PASI response: ≥75% improvement at week at 24 weeks. RoB: h

Study	FUTURE 3: Nash 2018{Nash, 2018 #447}
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=414
Countries and setting	Conducted in 77 centres in USA, Australia, Bulgaria, Canada, Czech Republic, Germany, Italy, Netherlands, Puerto Rico, Russia, Spain, Switzerland, UK.
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks double blind, placebo controlled treatment period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 132 (32%) people with prior inadequate response to TNF inhibitors
Inclusion criteria	Adults with active PsA despite treatment with NSAIDs, cDMARDs or TNF inhibitors.

Exclusion criteria	Previous use of any biological agent other than anti-TNF agents or the use of > 3 anti-TNF agents; active inflammatory diseases other than PsA; active infection in the 2 weeks before randomization, or a history of ongoing, chronic, or recurrent infections, or evidence of tuberculosis infection; history of malignant disease within the past 5 years (excluding basal cell carcinoma or actinic keratosis, in-situ cervical cancer, or noninvasive malignant colon polyps); and pregnancy.
Age, gender and ethnicity	Age - Mean (SD): 49 (13) and 50 (12) and 50 (13). Gender (M:F): 187/227. Ethnicity: White: 392 (95%), Asian: 9 (2%), American Indian or Alaska Native: 2 (0%), Other: 11 (3%)
Further population details	Dactylitis at baseline: 118(29%) Enthesitis at baseline: 281 (68%) Psoriasis ≥ 3% of BSA: 189 (46%)
Indirectness of population	No indirectness
Interventions	(n=88) Intervention 1: IL-17 inhibitor – 2 treatment groups. These were secukinumab 300 mg or secukinumab150 mg. People self-administered via autoinjector at baseline, weeks 1, 2, 3, 4 followed by treatment every 4 weeks from week 4. Concurrent medication/care: Concomitant use of oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and methotrexate (MTX; ≤ 25 mg/week) was allowed if the dose was stable for at least 2 weeks and 4 weeks before randomization, respectively. Indirectness: No indirectness (n=44) Intervention 2: Placebo - People self-administered via autoinjector at baseline, weeks 1, 2, 3, 4 followed by treatment every 4 weeks from week 4. Concurrent medication/care: Concomitant use of oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and methotrexate (MTX; ≤ 25 mg/week) was allowed if the dose was stable for at least 2 weeks and 4 weeks before randomization, respectively. Indirectness: No indirectness Early escape: At week 16, people were classified either as responders (≥ 20% improvement from baseline in both tender joint count (TJC) and swollen joint count (SJC)) or nonresponders. People in the placebo group were re-randomized to receive secukinumab 300 or 150 mg s.c. every 4 weeks at week 16.
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people who are TNFi-IR

- ACR20 response at 24 weeks. RoB: vh
- ACR50 response at 24 weeks. RoB: vh

Study	FUTURE 4: Kivitz 2019{Kivitz, 2019 #451}
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=341
Countries and setting	Conducted in 64 centres in USA, Australia, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Italy, Poland, Russia, Sweden, UK.

Sequencing of biologic and targeted synthetic DMARD treatment after treatment failure

Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks double blind, placebo controlled treatment period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 81 (24%) people with prior inadequate response to TNF inhibitors
Inclusion criteria	Adults with active PsA despite treatment with NSAIDs or c/bDMARDs.
Exclusion criteria	Previous exposure to secukinumab or any other biologic drug directly targeting the IL-17 or IL17 receptor. Also excluded were patients with active infection in the 2 weeks before randomization or those with a history of ongoing, chronic or recurrent infections, or evidence of tuberculosis infection or with active inflammatory diseases other than psoriatic arthritis. People with a history of malignant disease within the past 5 years (excluding basal cell carcinoma or actinic keratoses, in situ cervical cancer or non-invasive malignant colon polyps) and those having chest X-ray/magnetic resonance imaging (MRI) with evidence of an ongoing infectious or malignant process, obtained within 3 months prior to screening.
Age, gender and ethnicity	Age - Mean (SD): 48 (12) and 50 (12) and 49 (12). Gender (M:F): 143/198. Ethnicity: Not detailed
Further population details	Dactylitis at baseline: 122 (36%) Enthesitis at baseline: 216 (63%) Psoriasis ≥ 3% of BSA: 171 (50%)
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: IL-17 inhibitor – 2 treatment groups: loading/no loading. Secukinumab 150 mg load at weeks 0, 1, 2 and 3 followed by dosing every 4 weeks starting at week 4 or secukinumab treatment at baseline followed by secukinumab dosing every 4 weeks from week 4. Concurrent medication/care: People on prescribed NSAIDs were required to be on a stable dose for at least 2 weeks before randomization and were required to remain on a stable dose up to week 24. Patients could continue to receive the following medications at a stable dose for at least 2 weeks: prednisone or equivalent (B 10 mg/day); methotrexate (B 25 mg/week). Indirectness: No indirectness (n=27) Intervention 2: Placebo - Concurrent medication/care: People on prescribed NSAIDs were required to be on a stable dose for at least 2 weeks before randomization and were required to remain on a stable dose up to week 24. Patients could continue to receive the following medications at a stable dose for at least 2 weeks: prednisone or equivalent (B 10 mg/day); methotrexate (B 25 mg/week). Indirectness: No indirectness Early escape: At week 16, people were classified either as responders in the placebo group received secukinumab 150 mg every 4 weeks at week 16.
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people with prior inadequate response to TNF inhibitors

- ACR20 response at 16 weeks. RoB: h
- ACR50 response at 16 weeks. RoB: h

Study	FUTURE 5: Mease 2018{Mease, 2018 #443}
Study type	Multicentre RCT (Patient randomised; Parallel)
Number of participants	n=996
Countries and setting	Conducted in 172 centres in USA, Argentina, Austria, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Guatemala, Hungary, India, Ireland, Israel, Italy, Latvia, Lithuania, Mexico, Netherlands, Philippines, Russia, Spain, Sweden, Thailand, UK, Vietnam.
Line of therapy	Not applicable
Duration of study	Intervention: 24 weeks double blind, placebo controlled treatment period
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of 295 (30%) people with prior inadequate response to TNF inhibitors
Inclusion criteria	People with PsA fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) and active disease, defined as ≥ 3 tender and ≥ 3 swollen joints, despite previous treatment with NSAIDs, cDMARDs, of TNF Inhibitors. .
Exclusion criteria	Patients were excluded if they had previously received biologics other than TNF inhibitors, or had received > 3 TNF inhibitors. Where applicable, TNF inhibitors were discontinued for 4–10 weeks before randomization.
Age, gender and ethnicity	Age - Mean (SD): 49 (12). Gender (M:F): 500/496. Ethnicity: White: 816 (82%), Asian: 113 (11%), American Indian or Alaska Native: 6 (1%), Unknown: 4 (0%), Other: 47 (5%)
Further population details	Dactylitis at baseline: 389 (39%) Enthesitis at baseline: 602 (60%) Psoriasis ≥ 3% of BSA: 514 (52%)
Indirectness of population	No indirectness
Interventions	(n=197) Intervention 1: IL-17 inhibitor – 3 treatment groups. These were secukinumab 300 mg with loading dose (LD), secukinumab150 mg with LD, secukinumab 150 mg without LD. People self-administered their own treatment using prefilled syringes at baseline, weeks 1, 2 and 3 followed by treatment every 4 weeks from week 4. Patients in the secukinumab 150 mg without LD arm were administered placebo at weeks 1, 2 and 3 to conceal treatment allocation. Concurrent medication/care: Concomitant corticosteroids (≤10 mg/day prednisone or equivalent), NSAIDs and methotrexate (≤25 mg/week) were allowed, provided the dose was stable and remained so for the first 24 weeks of the study. Indirectness: No indirectness (n=98) Intervention 2: Placebo at baseline, and weeks 1, 2, 3, and 4, and every 4 weeks thereafter. People self-administered their own treatment using prefilled syringes at baseline, weeks 1, 2 and 3 followed by treatment every 4

	weeks from week 4. At week 16, people with <20% improvement from baseline in tender and swollen joint counts (SJCs) were switched in a double-blind manner to receive secukinumab 300 mg or 150 mg, preassigned at original randomisation. Concurrent medication/care: Concomitant corticosteroids (≤10 mg/day prednisone or equivalent), NSAIDs and methotrexate (≤25 mg/week) were allowed, provided the dose was stable and remained so for the first 24 weeks of the study. Indirectness: No indirectness
Funding	Novartis pharmaceuticals Corporation.

IL-17 inhibitor versus placebo in people with prior inadequate response to TNF inhibitors

- ACR20 response at 16 weeks. RoB: h
- ACR50 response at 16 weeks. RoB: h
- ACR70 response at 16 weeks. RoB: h

Study	OPAL Beyond: Gladman 2017{Gladman, 2017 #381}, Strand 2019{Strand, 2019 #406}
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=394
Countries and setting	Conducted in USA, Australia, Belgium, Brazil, Czech Republic, France, Germany, Mexico, Poland, Russia, Slovakia, Spain, Taiwan, UK; Setting: 125 centres.
Line of therapy	Not applicable
Duration of study	Intervention: Randomised, double blind treatment period for 12 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	Adults who had received a diagnosis of psoriatic arthritis at least 6 months previously and had previously had an inadequate response to at least one TNF inhibitor. .
Exclusion criteria	Not detailed.
Age, gender and ethnicity	Age - Mean (SD): 49 (13) and 50 (12) and 51 (11). Gender (M:F): 176/218. Ethnicity: White race: 363 (92%)
Further population details	Enthesitis (LEI) at baseline: 275 (70%) Dactylitis at baseline: 194 (49%) Psoriasis involvement of body surface area ≥ 3% at baseline: 247 (63%)
Indirectness of population	None
Interventions	(n=263) Intervention 1: JAK inhibitor – Two tofacitinib groups where people either used a dose of 5 mg or 10 mg taken orally twice daily. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide Indirectness: No indirectness

	(n=131) Intervention 2: Placebo. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide. Indirectness: No indirectness
Funding	Pfizer

JAK inhibitor versus placebo

- Mortality at 12 weeks. RoB: low
- ACR20 response at week 12. RoB: low
- ACR50 response at week 12: RoB: low
- ACR70 response at week 12: RoB: low
- MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks. RoB: low
- Enthesitis absence at 12 weeks in people with enthesitis at baseline. RoB: h
- LEI: Leeds Enthesitis Index at 12 weeks in people with enthesitis at baseline. RoB: h
- Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline. RoB: h
- PASI response: ≥75% improvement at week 12. RoB: h
- Serious adverse events at 12 weeks. RoB: low

Study	PALACE 1: Kavanaugh 2014{Kavanaugh, 2014 #276}
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=504
Countries and setting	Conducted in USA, Australia, Austria, Canada, France, Germany, Hungary, New Zealand, Poland, Russia, South Africa, Spain, UK. Setting: 92 centres
Line of therapy	Not applicable
Duration of study	Intervention: placebo controlled for 24 weeks with “early escape” at 16 weeks.
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Outcomes in the subgroup of people who for whom bDMARD failed. N=45 (9%).
Inclusion criteria	Adults with a documented diagnosis of active PsA with duration ≥ 6 months. They were required to have had previous treatment with cDMARDs and/or bDMARDs. People using cDMARDs must have been on a stable dose for 16 weeks prior to entering the study.
Exclusion criteria	Failure of more than three agents for PsA (DMARDs or biologics) or >1 TNF inhibitor. People were also excluded if they had a history of or current (1) inflammatory, rheumatic or autoimmune joint disease other than PsA; (2) erythrodermic, guttate or generalised pustular psoriasis; (3) were functional class IV, defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis; (4) had used phototherapy

	or DMARDs other than methotrexate, leflunomide or sulfasalazine within 4 weeks of randomisation; (5) had used adalimumab, etanercept, golimumab, infliximab, certolizumab pegol or tocilizumab within 12 weeks of randomisation or alefacept or ustekinumab within 24 weeks of randomisation; or (6) had prior treatment with apremilast. Topical therapy for psoriasis within 2 weeks of randomisation was not permitted. Patients with active tuberculosis or a history of incompletely treated tuberculosis could not participate.
Age, gender and ethnicity	Age - Mean (SD): 51 (12) and 48 (11) and 51 (120). Gender (M:F): 249/255. Ethnicity: Not detailed
Further population details	Psoriasis involvement of body surface area ≥ 3% at baseline: 227 (45%) Baseline cDMARD use: 327 (65%) Enthesitis at baseline: 315 (62%) Dactylitis at baseline: 197 (39%)
Indirectness of population	No indirectness
Interventions	(n=336, of whom 27 had had bDMARD failure). Intervention 1: Apremilast – people were randomised to either 20 mg BID or 30 mg BID. Dose titrated over first week until target does reached. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. Indirectness: No indirectness (n=168, of whom 18 had had bDMARD failure) Intervention 2: Placebo – Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. Indirectness: No indirectness Early escape: People whose swollen and tender joint counts had not improved by ≥20% were considered non-responders at week 16 and were required to enter the protocol defined early escape. People receiving placebo were re-randomised (1:1) to apremilast 20 mg BID or 30 mg BID, while those on apremilast remained on their initial apremilast dose.
Funding	Study sponsored by Celgene Corp.

Apremilast versus placebo in people who were bDMARD naive

- ACR20 response at week 16. RoB: vh

Study	PALACE 3: Edwards 2016{Edwards, 2016 #204}
Study type	RCT (Patient randomised; Parallel)

Number of participants	n=505
Countries and setting	Conducted in USA, Australia, Canada, Finland, Germany, Italy, France, Korea, Lithuania, Poland. Romania, Russia, Slovakia, Spain, Switzerland, UK. Study conducted across 91 centres.
Line of therapy	Not applicable
Duration of study	Intervention: placebo controlled for 24 weeks with “early escape” at 16 weeks.
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Outcomes in the subgroup of people who for whom bDMARD failed. N=44 (9%).
Inclusion criteria	Adults with a documented diagnosis of PsA with duration ≥ 6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR). They had to have ≥ 3 swollen and ≥ 3 tender joints despite prior treatment with csDMARD and/or bDMARD or concurrent treatment with csDMARD.
Exclusion criteria	People with prior therapeutic failure of > 3 agents for PsA (csDMARD or bDMARD) or > 1 TNF inhibitor were ineligible. People could not have used phototherapy within 4 weeks, bDMARD (including adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab) within 12 weeks, or alefacept and ustekinumab within 24 weeks of randomization. Other exclusions were prior apremilast treatment, active tuberculosis (TB), history of incompletely treated TB, or significant infection within 4 weeks of screening, erythrodermic, guttate, or generalized pustular psoriasis.
Age, gender and ethnicity	Age - Mean (SD): 50 (12) and 50 (12). Gender (M:F): 236/269. Ethnicity: 481 white, 15, Asian, 2 black, 6 other.
Further population details	Baseline cDMARD use: 306 Baseline enthesitis: 318 Baseline dactylitis: 222
Indirectness of population	No indirectness
Interventions	(n=336, of whom 32 had had bDMARD failure) Intervention 1: Apremilast – people were randomised to either 20 mg BID or 30 mg BID. Dose titrated over first week until target does reached. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. These were permitted as background therapy, except ≤ 24 h before each study visit: low-potency topical glucocorticoids for treatment of face, axillae, and groin psoriatic lesions, coal tar shampoo

	and/or salicylic acid scalp preparations for scalp lesions, and nonmedicated emollient for body lesions. Topical therapies for psoriasis, except those permitted for background therapy, were not allowed, including topical glucocorticoids, topical retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin; immunosuppressive systemic therapy, including cyclosporine, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, and fumaric acid esters; and phototherapy (ultraviolet B, psoralen + ultraviolet A). Indirectness: No indirectness (n=169, of whom 12 had had bDMARD failure) Intervention 2: Placebo – no details of blinding. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. These were permitted as background therapy, except ≤ 24 h before each study visit: low-potency topical glucocorticoids for treatment of face, axillae, and groin psoriatic lesions, coal tar shampoo and/or salicylic acid scalp preparations for scalp lesions, and nonmedicated emollient for body lesions. Topical therapies for psoriasis, except those permitted for background therapy, were not allowed, including topical glucocorticoids, topical retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin; immunosuppressive systemic therapy, including cyclosporine, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, and fumaric acid esters; and phototherapy (ultraviolet B, psoralen + ultraviolet A). Indirectness: No indirectness
Funding	Study sponsored by Celgene Corp.

Apremilast versus placebo in people who were bDMARD naïve.

- ACR20 response at 16 weeks: RoB: vh

Study	SPIRIT-P2: Nash 2017{Nash, 2017 #438}
Study type	RCT (Patient randomised; Parallel)
Number of participants	n=363
Countries and setting	Conducted in USA, Australia, Czech Republic, France, Germany, Italy, Poland, Spain, Taiwan, UK; Setting: 109 centres
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind period of treatment
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Adults with a diagnosis of PsA for at least 6 months who had inadequate response or were intolerant to TNF inhibitors. They also must have been treated with csDMARDs and have had a history of plaque psoriasis.
Exclusion criteria	History of malignant disease within the past 5 years (other than non-melanoma skin cancer successfully treated and with limited recurrences within 5 years before baseline); recent (4–24 weeks before baseline depending on infection type and severity) history of ongoing, chronic, or recurrent infections; and present ulcerative colitis or Crohn's disease
Age, gender and ethnicity	Age - Mean (SD): 52 (10) and 53 (14) and 52 (12). Gender (M:F): 169/194. Ethnicity: White: 332, Asian: 21, Other: 9.
Further population details	People with psoriasis ≥3% of body surface area at baseline: 203 (56%) Methotrexate use at baseline: 149 (41%) Enthesitis at baseline: 221 (61%) Dactylitis at baseline: 62 (17%)
Indirectness of population	No indirectness
Interventions	(n=245) Intervention 1: IL-17 inhibitor – : 2 treatment groups of either ixekizumab 80 mg every 2 weeks or every 4 weeks. Administered via subcutaneous injection. People were administered a starting dose of 160 mg given as two injections at week 0. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness (n=118) Intervention 3: Placebo– : Administered via subcutaneous injection. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness Early escape in all treatment groups with an inadequate response at week 16, distinguished by predefined tender and swollen joint count criteria (i.e., inadequate responders), were required to add or modify concomitant drugs
Funding	Eli Lilly and Company.

IL-17 inhibitor versus placebo

- Mortality
- ACR20 response at 12 weeks. RoB: low
- ACR50 response at 12 weeks. RoB: low
- ACR70 response at 12 weeks. RoB: low
- Minimal disease activity at 12 weeks. RoB: low
- Dactylitis resolution (LDI-B = 0) at 12 weeks. RoB: h
- LEI: Leeds Enthesitis Index at 12 weeks in people with enthesitis at baseline
- Enthesitis absence (LEI=0) at 12 weeks. RoB: h
- BASDAI: Bath Ankylosing Spondylitis Disease Activity Index in people with baseline BASDAI>4
- PASI response: ≥75% improvement at week 12. RoB: h
- PASI response: ≥100% improvement at week 12. RoB: h
- Change in SF-36 PCS: Short Form-36 Health Survey, Physical Component Score at 12 weeks. RoB: h

- Change in SF-36 PCS: Short Form-36 Health Survey, Mental Component Score at 12 weeks. RoB: h
- Serious adverse events at 24 weeks. RoB: low

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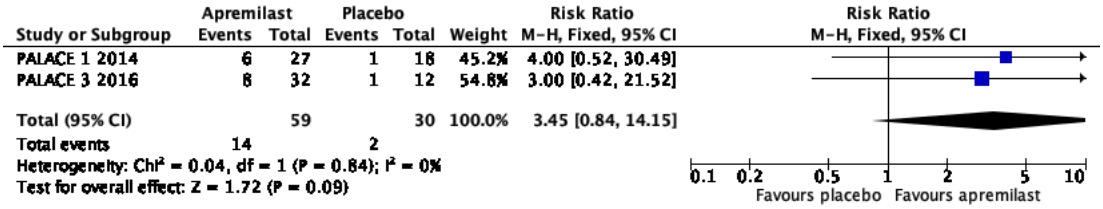
Appendix E: **Forest plots**

E.1 Apremilast versus placebo

Figure 2: ACR20 response at week 16/24



E.2 IL-17 inhibitors versus placebo

Figure 3: Mortality at 24 weeks

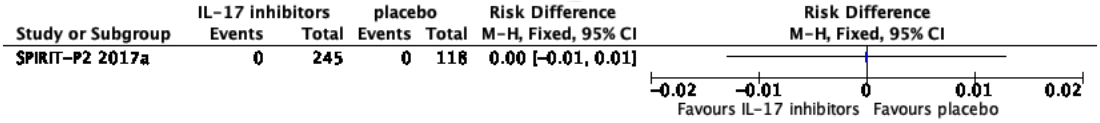


Figure 4: Change in SF-36 physical component score at 12 weeks

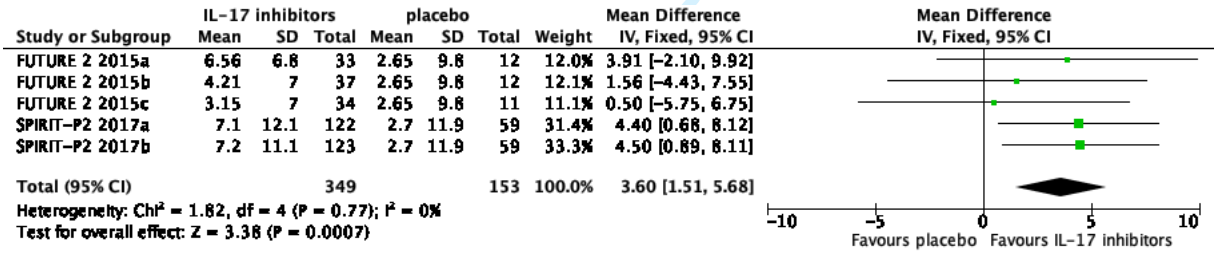


Figure 5: Change in SF-36 Mental Component Score at 12 weeks

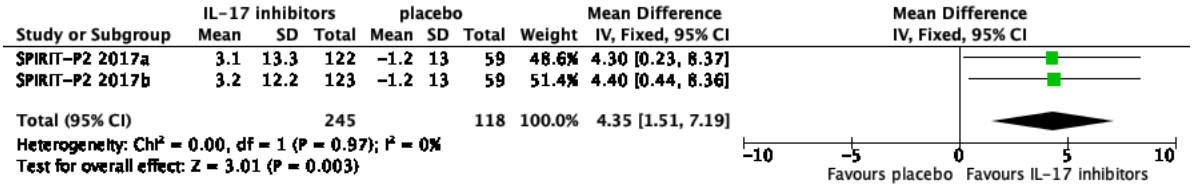


Figure 6: ACR20 response at 12/24 weeks

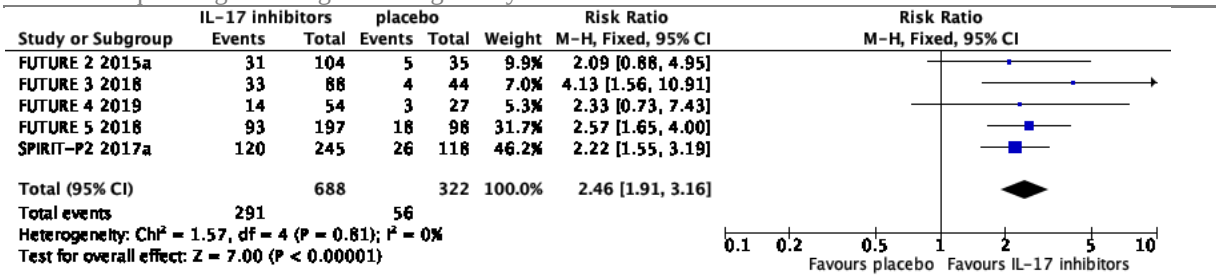


Figure 7: ACR50 response at week 12/24

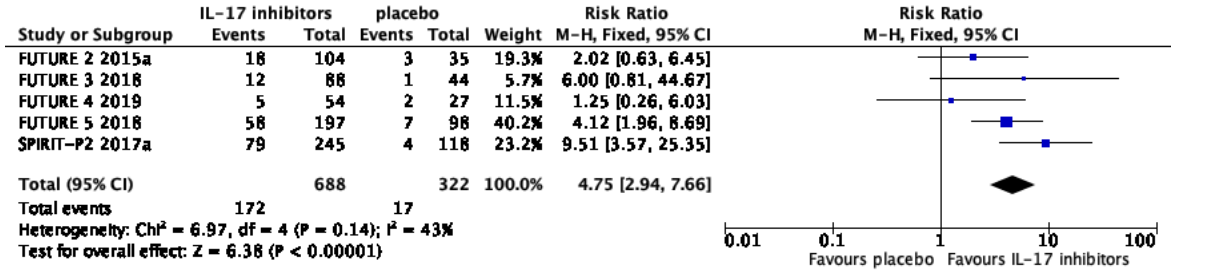


Figure 8: ACR70 response at week 12/24

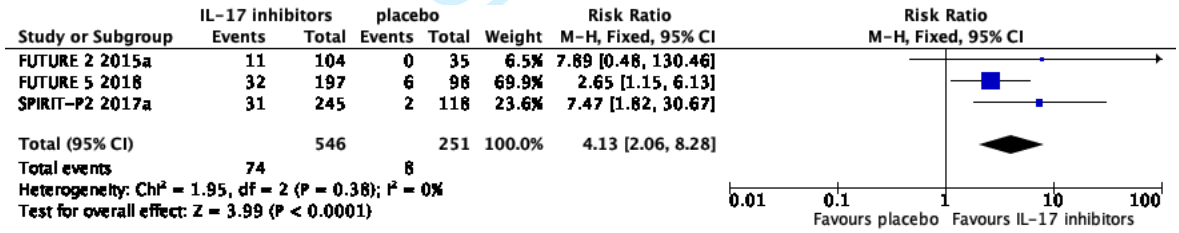


Figure 9: MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12/16 weeks

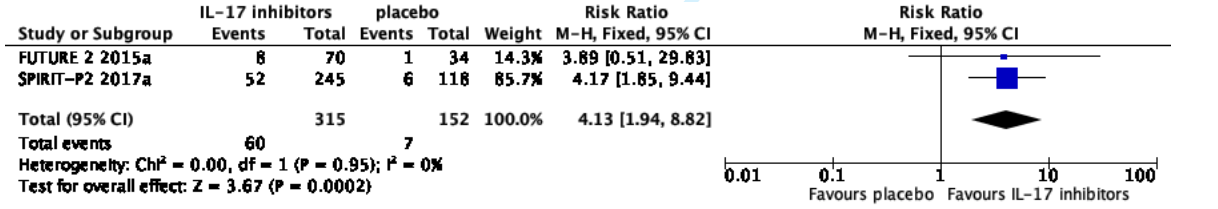


Figure 10: Dactylitis resolution at 12/24 weeks. Data are reported for people with dactylitis at baseline.

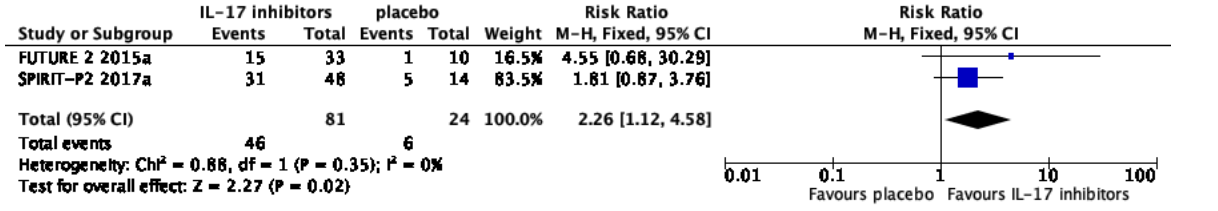


Figure 11: Enthesitis absence/resolution at 12/24 weeks in people with enthesitis at baseline

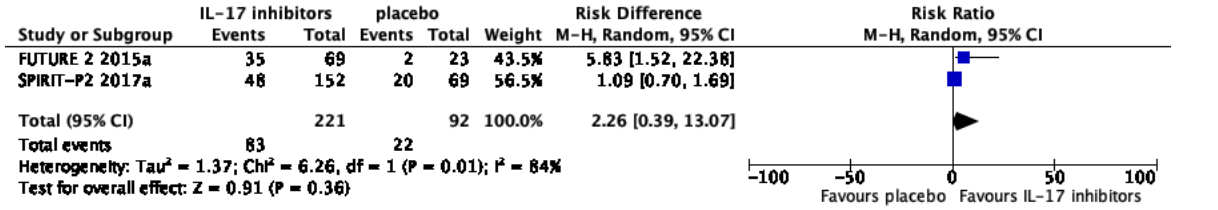


Figure 12: LEI: Leeds Enthesitis Index at 12 weeks in people with enthesitis at baseline

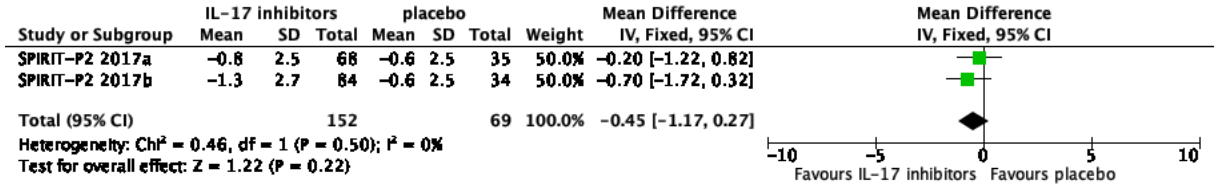


Figure 13: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index in people with baseline BASDAI>4

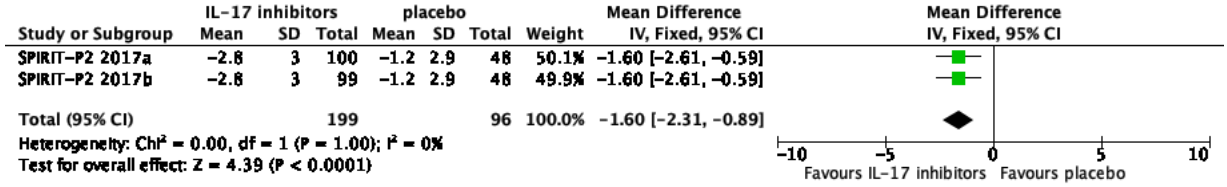


Figure 14: PASI response: ≥90% improvement at week 12/24

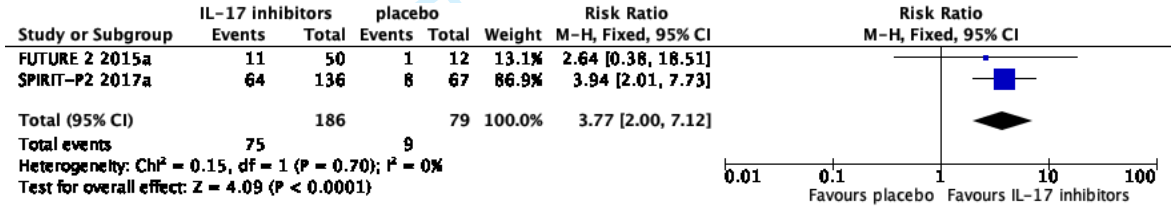
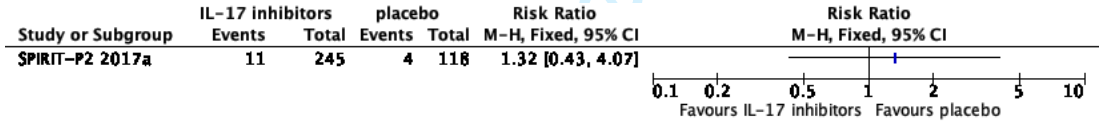


Figure 15: Serious adverse events at 24 weeks



E.3 IL-23 inhibitors versus placebo

Figure 16: ACR20 response at week 24

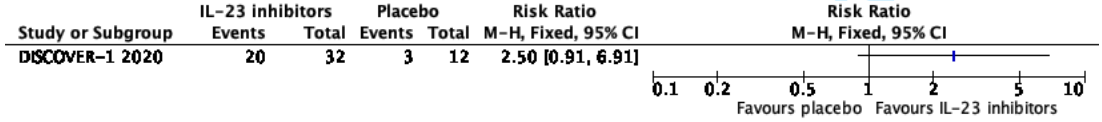


Figure 17: ACR50 response at week 24

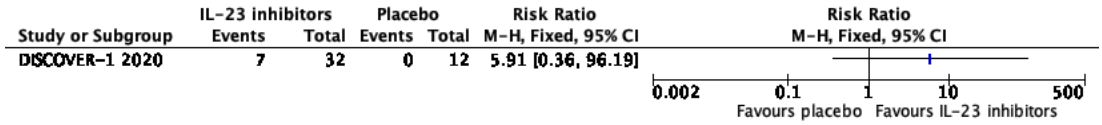
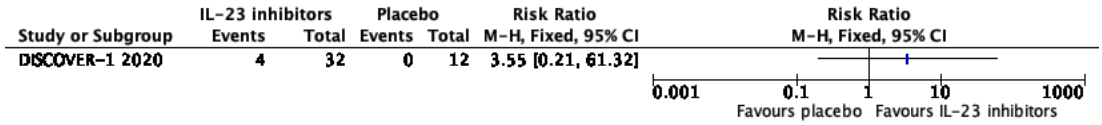


Figure 18: ACR70 response at week 24



E.4 JAK inhibitors versus placebo

Figure 19: Short Form-36 Health Survey, Physical Function score at 12 weeks

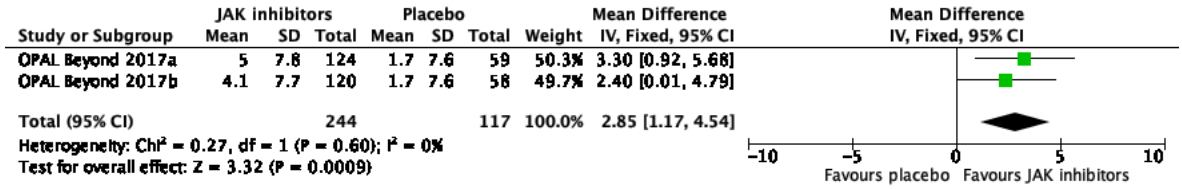


Figure 20: Short Form-36 Health Survey, Mental Function score at 12 weeks

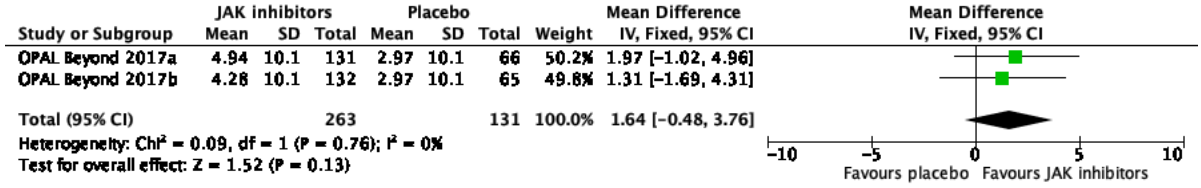


Figure 21: ACR20 response at week 12

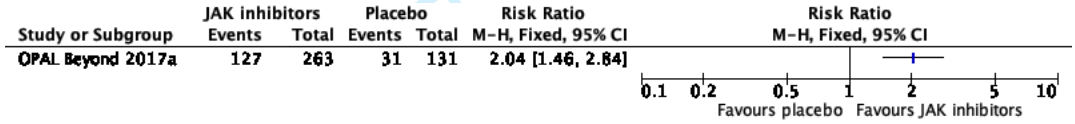


Figure 22: ACR50 response at week 12

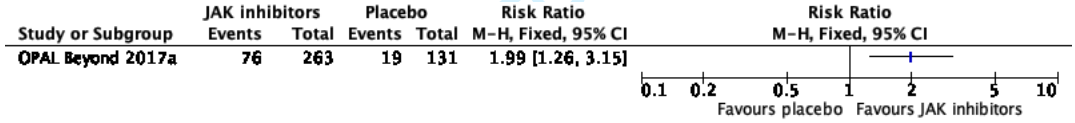


Figure 23: ACR70 response at week 12

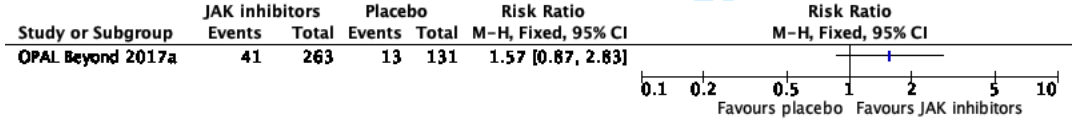


Figure 24: MDA: Minimal disease activity (≥ 5 of 7 criteria) at 12 weeks

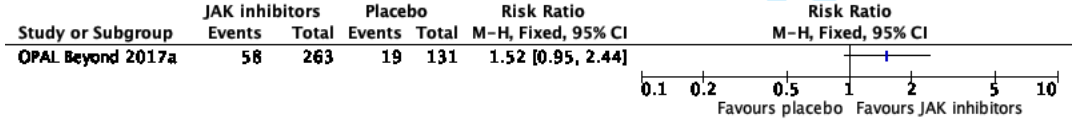


Figure 25: Enthesitis resolution at 12 weeks in people with enthesitis at baseline

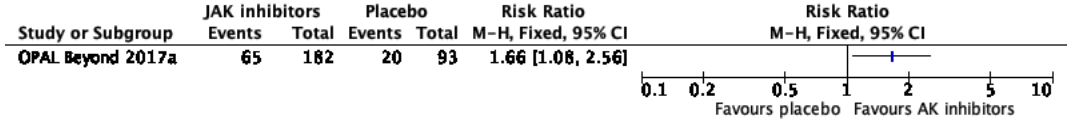


Figure 26: LEI: Leeds Enthesitis Index at 12 weeks in people with enthesitis at baseline

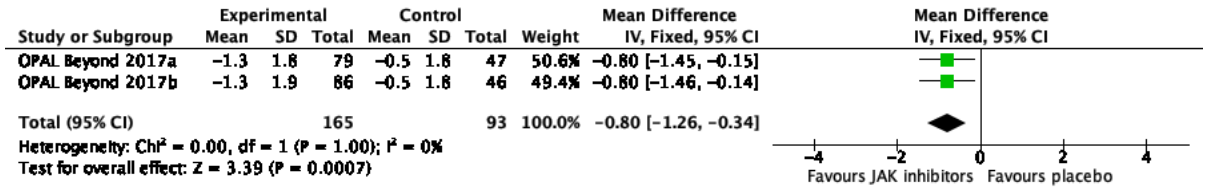


Figure 27: Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline

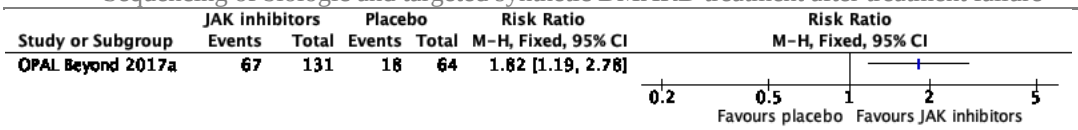


Figure 28: PASI response: ≥75% improvement at week 12

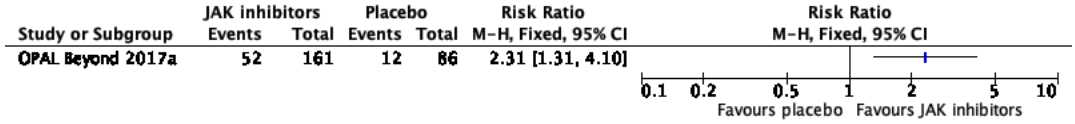
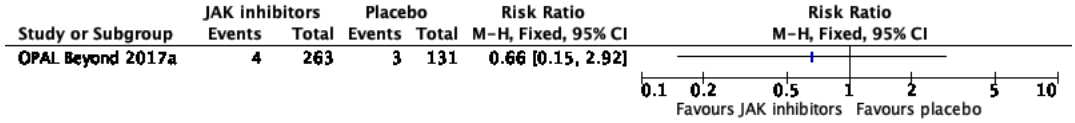


Figure 29: Serious adverse events at 12 weeks



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Appendix F: **Excluded studies**

Table 9: studies excluded from the evidence review

Study	Exclusion reason
Cantini 2017{#361}	Systematic review with different inclusion criteria however included studies were checked for this review
Conti 2007{#362}	Observational study without adjustment for confounding factors
Cutolo 2016{#188}	Results were not stratified by the specific b/ts DMARD to which a person had inadequate response or was intolerant
Delaunay 2005{#363}	Observational study of people with ankylosing spondylitis of whom only 2 had psoriatic arthritis
Deodhar 2018{#192}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Deodhar 2020{#193}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Edwards 2016{#204}	Results were not stratified by the specific b/ts DMARD to which a person had inadequate response or was intolerant
Fagerli 2013{#364}	Observational study without adjustment for confounding factors
Gladman 2014{#379}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Gottlieb 2009{#231}	Results were not stratified by the specific b/ts DMARD to which a person had inadequate response or was intolerant
Gottlieb 2015{#235}	Unable to obtain
Haberhauer 2010{#384}	Unable to obtain
Kavanaugh 2014{#278}	Includes a mix of people who were exposed to bDMARDs and people who are bDMARD naive
Langley 2018{#396}	Trial of people with psoriasis without relevant psoriatic arthritis subgroup analysis
Langley 2019{#395}	Trial of people with psoriasis without relevant psoriatic arthritis subgroup analysis
Mease 2011{#445}	No separate results presented for people who had had inadequate response or intolerance to b/tsDMARD
Mease 2014{#306}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Mease 2014{#448}	Results were not stratified by the specific b/ts DMARD to which a person had inadequate response or was intolerant
Mease 2015{#439}	No separate results presented for people who had had inadequate response or intolerance to b/tsDMARD

Study	Exclusion reason
Mease 2017{Mease, 2017 #354}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Mease 2018{#293}	No separate results presented for people who had had inadequate response or intolerance to b/tsDMARD
Merola 2017{#397}	Review of studies investigating people switching biologics. Studies investigated for inclusion in this review.
Ogdie 2020{#325}	Systematic review with different inclusion criteria however included studies were checked for this review
Onuora 2014{#400}	Review paper
Orbai 2019{#327}	No separate results presented for people who had had inadequate response or intolerance to b/tsDMARD
Ritchlin 2014{#442}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Ritchlin 2014{#442}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Spadaro 2010{#405}	Observational study of switching TNF inhibitors without adjustment for confounding
Strand 2018{#344}	Unable to obtain
Strand 2018{#345}	Some people had previous exposure to TNF inhibitors but outcomes in subgroup with inadequate response or intolerance were not detailed
Torii 2010{#349}	Population included people with plaque psoriasis, a number of whom had psoriatic arthritis. Prior bDMARD and tsDMARD treatment unclear.

British Society for Rheumatology

Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on biologic and targeted synthetic DMARDs in people with PsA who are overweight or obese

BSR Guideline

Intervention evidence review

December 2020

Contents

1 b/tsDMARDs in people with PsA who are overweight or obese

1.1 In adults with active psoriatic arthritis who are overweight, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, apremilast or JAK inhibitors, in comparison to each other or placebo?

1.2 INTRODUCTION

Being overweight or obese places extra pressure on a person's joints, meaning it can contribute to the symptoms of psoriatic arthritis. It is also thought to contribute to inflammation and stops some PsA medications from working as well as they could. This review seeks to find which medications are best in people who are overweight or obese.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis (PsA) who are overweight or obese
Intervention	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept apremilast JAK inhibitors
Comparison	Comparison of interventions or placebo
Outcomes	**Critical** <u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: . • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Radiological progression (continuous) <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) <u>Dactylitis</u> • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS20 (dichotomous) • ASAS40 (dichotomous)

	ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Uveitis • VRQol (continuous) Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) • IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) • Adverse Events • Serious adverse events (dichotomous) **Important** **These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • Disease Assessment in PsA (continuous) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	Randomised Controlled Trials (RCT's)- inclusion and exclusion criteria as stated above If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted to find RCTs or observational studies comparing b/tsDMARDs in people with PsA who are overweight or obese people. 3 papers(1-3) reporting subgroup analysis from 7 RCTs were included in the review. All 3 papers were conference abstracts.

1.4.2 Excluded studies

See **Table 8** in Excluded studies in the appendix.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
OPAL Broaden/Beyond: Ritchlin 2019(1)	JAK inhibitor : tofacitinib versus placebo. Concomitant therapy: people were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide	N=710 including people who were underweight or normal weight Adults with PsA who had an inadequate response to at least 1 csDMARD for one RCT or an inadequate response to at least 1 TNF inhibitor in the other. Overweight: 238 (34%) Obese (class 1): 186 (26%) Obese (class 2, 3): 125 (18%) Over 90% of the population were white.	• Change in SF36 physical function score at 12 weeks • Change in SF36 mental function score at 12 weeks • ACR20 response at 12 weeks • ACR50 response at 12 weeks • ACR70 response at 12 weeks • Enthesitis absence at 12 weeks in people with enthesitis at baseline • Dactylitis resolution at 12 weeks in people with dactylitis at baseline • Serious adverse events at 12 weeks	Analysis of data of subgroups from OPAL Broaden and OPAL Beyond RCTs. OPAL Broaden included a treatment group using TNF inhibitors but this data was not presented. Conducted in North America, Europe, and Asia Trial funded by Pfizer Inc. and medical writing support funded by Pfizer Inc.
PALACE 1/2/3 Schett 2014(2)	Apremilast (n=344 overweight and n=425 obese) versus placebo (n=152 overweight and n=231 obese) Concomitant therapy: stable doses of csDMARDs, NSAIDs, and corticosteroids were permitted.	N=1493 including those of normal weight or underweight. Adults with PsA who had previous treatment with csDMARDs and/or bDMARDs.	• ACR20 response at 16 weeks	Analysis of data of subgroups from PALACE 1, PALACE 2 and PALACE 3 RCTs Conducted in North America, Europe and Asia. Trials were sponsored by Celgene Corp. However funding not stated for this analysis.

Study	Intervention and comparison	Population	Outcomes	Comments
SPIRIT-P1/P2: Eder 2019(3)	IL-17 inhibitor: Ixekizumab (n=175 overweight/obese) versus placebo (n=184 overweight/obese) Concomitant therapy: stable doses of allowed csDMARDs, oral corticosteroids, opiates and/or NSAIDs permitted.	N=453 including those normal weight and underweight Adults with active PsA who for one study were naïve to biologic DMARD treatment and in the other had inadequate response or intolerance to TNF inhibitors. Results reported in 3 weight categories and these were the numbers by treatment group. Overweight: 157 (35%) Obese (class 1, 2): 158 (35%) Obese (class 3): 44 (13%)	• ACR20 response at 24 weeks • ACR50 response at 24 weeks • ACR70 response at 24 weeks • Minimal disease activity at 24 weeks Missing data were imputed using nonresponder imputation (NRI)	Analysis of data of subgroups from SPIRIT-P1 and SPIRIT-P2 RCTs Conducted in North/Central America, Europe, Asia The trials were funded and sponsored by Eli Lilly and Company. However funding not stated for this analysis

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Apremilast versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apremilast	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response in overweight/obese people (follow up: 16 weeks)												
4	randomised trials	very serious [a]	not serious	not serious	not serious	none	265/769 (34.5%)	69/383 (18.0%)	**RR 1.93** (1.53 to 2.44)	**168 more per 1,000** (from 95 more to 259 more)	⊕⊕◯◯ LOW	CRITICAL
ACR20 response in overweight subgroup (follow up: 16 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apremilast	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	114/344 (33.1%)	24/152 (15.8%)	**RR 2.10** (1.41 to 3.12)	**174 more per 1,000** (from 65 more to 335 more)	⨁⨁◯◯ LOW	CRITICAL
ACR20 response in class 1 obese subgroup (follow up: 16 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	83/226 (36.7%)	28/125 (22.4%)	**RR 1.64** (1.13 to 2.37)	**143 more per 1,000** (from 29 more to 307 more)	⨁◯◯◯ VERY LOW	CRITICAL
ACR20 response in class 2 obese subgroup (follow up: 16 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	40/132 (30.3%)	10/66 (15.2%)	**RR 2.00** (1.07 to 3.74)	**152 more per 1,000** (from 11 more to 415 more)	⨁◯◯◯ VERY LOW	CRITICAL
ACR20 response in class 3 obese subgroup (follow up: 16 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	28/67 (41.8%)	7/40 (17.5%)	**RR 2.39** (1.15 to 4.95)	**243 more per 1,000** (from 26 more to 691 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 4: IL-17 inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
Minimal disease activity in overweight/obese people (follow up: 24 weeks; assessed with: ≥ 5 of 7 criteria)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	49/175 (28.0%)	13/184 (7.1%)	**RR 4.13** (2.34 to 7.29)	**221 more per 1,000** (from 95 more to 444 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Minimal disease activity in overweight subgroup (follow up: 24 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	25/67 (37.3%)	9/90 (10.0%)	**RR 3.73** (1.87 to 7.46)	**273 more per 1,000** (from 87 more to 646 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Minimal disease activity in class 1/2 obese subgroup (follow up: 24 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	21/84 (25.0%)	4/74 (5.4%)	**RR 4.63** (1.66 to 12.86)	**196 more per 1,000** (from 36 more to 641 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Minimal disease activity in class 3 obese subgroup (follow up: 24 weeks; assessed with: ≥ 5 of 7 criteria)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/24 (12.5%)	0/20 (0.0%)	**RR 5.88** (0.32 to 107.49)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
ACR20 response in overweight/obese people (follow up: 24 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	95/175 (54.3%)	42/184 (22.8%)	**RR 2.36** (1.75 to 3.18)	**310 more per 1,000** (from 171 more to 498 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response in overweight subgroup (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	37/67 (55.2%)	19/90 (21.1%)	**RR 2.62** (1.66 to 4.12)	**342 more per 1,000** (from 139 more to 659 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR20 response in class 1/2 obese subgroup (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	47/84 (56.0%)	18/74 (24.3%)	**RR 2.30** (1.47 to 3.59)	**316 more per 1,000** (from 114 more to 630 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR20 response in class 3 obese subgroup (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	11/24 (45.8%)	5/20 (25.0%)	**RR 1.83** (0.76 to 4.40)	**208 more per 1,000** (from 60 fewer to 850 more)	⨁◯◯◯ VERY LOW	CRITICAL
ACR50 response in overweight/obese people (follow up: 24 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	64/175 (36.6%)	16/184 (8.7%)	**RR 4.29** (2.59 to 7.11)	**286 more per 1,000** (from 138 more to 531 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR50 response in overweight subgroup (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	29/67 (43.3%)	10/90 (11.1%)	**RR 3.90** (2.04 to 7.43)	**322 more per 1,000** (from 116 more to 714 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ACR50 response in class 1/2 obese subgroup (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	29/84 (34.5%)	6/74 (8.1%)	**RR 4.26** (1.87 to 9.68)	**264 more per 1,000** (from 71 more to 704 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response in class 3 obese subgroup (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/24 (25.0%)	0/20 (0.0%)	**RR 10.92** (0.65 to 182.71)	**250 more per 1,000** (from 430 fewer to 70 more) [c]	⊕◯◯◯ VERY LOW	CRITICAL
ACR70 response in overweight/obese people (follow up: 24 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	40/175 (22.9%)	2/184 (1.1%)	**RR 15.30** (4.76 to 49.21)	**155 more per 1,000** (from 41 more to 524 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR70 response in overweight/obese people (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	20/67 (29.9%)	2/90 (2.2%)	**RR 13.43** (3.25 to 55.50)	**276 more per 1,000** (from 50 more to 1,000 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR70 response in class 1/2 obese people (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	18/84 (21.4%)	0/74 (0.0%)	**RR 32.65** (2.00 to 532.49)	**210 more per 1,000** (from 120 more to 300 more) [c]	⊕⊕⊕◯ MODERATE	CRITICAL
ACR70 response in class 3 obese subgroup (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-17 inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/24 (8.3%)	0/20 (0.0%)	**RR 4.20** (0.21 to 82.72)	**80 more per 1,000** (from 50 fewer to 220 more) [c]	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
c. Absolute effect calculate from the risk difference

Table 5: JAK inhibitor versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life: SF36 PCS in overweight/obese people (follow up: 12 weeks; assessed with: Change in SF36 physical component summary; Scale from: 0 to 100)												
6	randomised trials	serious [a]	not serious	not serious	serious [b]	none	374	175	-	MD **2.56 higher** (1.08 higher to 4.03 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life: SF36 PCS in overweight subgroup (follow up: 12 weeks; assessed with: Change in SF36 physical component summary; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	166	72	-	MD **2.94 higher** (0.69 higher to 5.2 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life: SF36 PCS in class 1 obese subgroup (follow up: 12 weeks; assessed with: Change in SF36 physical component summary; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	123	63	-	MD **4.04 higher** (1.56 higher to 6.52 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life: SF36 PCS in class 2/3 obese subgroup (follow up: 12 weeks; assessed with: Change in SF36 physical component summary; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	85	40	-	MD **0.55 lower** (3.68 lower to 2.57 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life: SF36 MCS in overweight/obese people (follow up: 12 weeks; assessed with: Change in SF36 mental component summary; Scale from: 0 to 100)												
6	randomised trials	serious [a]	not serious	not serious	not serious	none	374	175	-	MD **1.77 higher** (0.01 lower to 3.55 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life: SF36 MCS in overweight subgroup (follow up: 12 weeks; assessed with: Change in SF36 mental component summary; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	166	72	-	MD **2.16 higher** (0.33 lower to 4.65 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life: SF36 MCS in class 1 obese subgroup (follow up: 12 weeks; assessed with: Change in SF36 mental component summary ; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	123	63	-	MD **1.56 higher** (1.53 lower to 4.64 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life: SF36 MCS in class 2/3 obese subgroup (follow up: 12 weeks; assessed with: Change in SF36 mental component summary ; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	85	40	-	MD **0.95 higher** (3.56 lower to 5.46 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response in obese/overweight people (follow up: 12 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	194/361 (53.7%)	49/160 (30.6%)	**RR 1.76** (1.37 to 2.26)	**233 more per 1,000** (from 113 more to 386 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response in overweight subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	86/162 (53.1%)	22/66 (33.3%)	**RR 1.59** (1.10 to 2.31)	**197 more per 1,000** (from 33 more to 437 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response in class 1 obese subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	69/119 (58.0%)	18/60 (30.0%)	**RR 1.93** (1.28 to 2.93)	**279 more per 1,000** (from 84 more to 579 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR20 response in class 2/3 obese subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	39/80 (48.8%)	9/34 (26.5%)	**RR 1.84** (1.01 to 3.37)	**222 more per 1,000** (from 3 more to 627 more)	⊕⊕◯◯ LOW	CRITICAL
ACR50 response in overweight/obese people (follow up: 12 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	118/361 (32.7%)	20/160 (12.5%)	**RR 2.63** (1.70 to 4.06)	**204 more per 1,000** (from 88 more to 382 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response in overweight subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	54/162 (33.3%)	9/66 (13.6%)	**RR 2.44** (1.28 to 4.66)	**196 more per 1,000** (from 38 more to 499 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response in class 1 obese subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	45/119 (37.8%)	7/60 (11.7%)	**RR 3.24** (1.56 to 6.75)	**261 more per 1,000** (from 65 more to 671 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 response in class 2/3 obese subgroup (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	19/80 (23.8%)	4/34 (11.8%)	**RR 2.02** (0.74 to 5.49)	**120 more per 1,000** (from 31 fewer to 528 more)	⊕◯◯◯ VERY LOW	CRITICAL
ACR70 response in overweight/obese people (follow up: 12 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	58/361 (16.1%)	12/160 (7.5%)	**RR 2.18** (1.20 to 3.94)	**89 more per 1,000** (from 15 more to 221 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ACR70 response in overweight subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26/162 (16.0%)	4/66 (6.1%)	**RR 2.65** (0.96 to 7.29)	**100 more per 1,000** (from 2 fewer to 381 more)	⊕⊕◯◯ LOW	CRITICAL
ACR70 response in class 1 obese subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23/119 (19.3%)	6/60 (10.0%)	**RR 1.93** (0.83 to 4.49)	**93 more per 1,000** (from 17 fewer to 349 more)	⊕⊕◯◯ LOW	CRITICAL
ACR70 response in class 2/3 obese subgroup (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	9/80 (11.3%)	2/34 (5.9%)	**RR 1.91** (0.44 to 8.39)	**54 more per 1,000** (from 33 fewer to 435 more)	⊕◯◯◯ VERY LOW	CRITICAL
Absence of enthesitis in overweight/obese people with enthesitis at baseline (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	92/244 (37.7%)	25/110 (22.7%)	**RR 1.67** (1.14 to 2.45)	**152 more per 1,000** (from 32 more to 330 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of enthesitis in subgroup who were overweight with enthesitis at baseline (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	43/109 (39.4%)	8/43 (18.6%)	**RR 2.12** (1.09 to 4.13)	**208 more per 1,000** (from 17 more to 582 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of enthesitis in subgroup who were class 1 obese with enthesitis at baseline												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	31/77 (40.3%)	12/40 (30.0%)	**RR 1.34** (0.78 to 2.32)	**102 more per 1,000** (from 66 fewer to 396 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of enthesitis in subgroup who were class 2/3 obese with enthesitis at baseline (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	18/58 (31.0%)	5/27 (18.5%)	**RR 1.68** (0.70 to 4.04)	**126 more per 1,000** (from 56 fewer to 563 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of dactylitis in overweight/obese people with dactylitis at baseline (follow up: 12 weeks)												
3	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	92/193 (47.7%)	29/97 (29.9%)	**RR 1.62** (1.15 to 2.27)	**185 more per 1,000** (from 45 more to 380 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of dactylitis in subgroup who were overweight with dactylitis at baseline (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitor	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	42/96 (43.8%)	10/43 (23.3%)	**RR 1.88** (1.04 to 3.39)	**205 more per 1,000** (from 9 more to 556 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of dactylitis in subgroup who were class 1 obese with dactylitis at baseline (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [a]	none	32/56 (57.1%)	10/32 (31.3%)	**RR 1.83** (1.04 to 3.21)	**259 more per 1,000** (from 13 more to 691 more)	⨁◯◯◯ VERY LOW	CRITICAL
Absence of dactylitis in subgroup who were class 2/3 obese with dactylitis at baseline (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	18/41 (43.9%)	9/22 (40.9%)	**RR 1.07** (0.58 to 1.97)	**29 more per 1,000** (from 172 fewer to 397 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

1.5.1 The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures to capture medication effects on other psoriatic disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA.

1.5.2 Benefits and harms

3 conference abstracts reporting subgroup analysis from 7 RCTs were included in the review. 3 medications were covered in the comparisons; Apremilast, IL-17 inhibitors, and JAK inhibitors, all versus placebo. Each reported an overarching effect in people who were overweight/obese but they also reported the results in sub-subgroups of people who were overweight and those at certain levels of obesity.

All 3 medications indicated a clinical benefit for peripheral arthritis symptoms both for all overweight / obese people and also when drilling down into the sub-subgroups. The IL-17 inhibitor trials also reported quality of life data and this indicated no difference between the groups. However this is similar to data presented for people who are not overweight/obese.

The JAK inhibitor study reported absence of enthesitis and dactylitis as an outcome. Most of the results indicated a benefit of JAK inhibitor but one results for absence of dactylitis in people who are class 2/3 obese indicated no clinical difference.

The group agreed that all the medications evaluated in the trials appeared similarly efficacious versus placebo. However it was not possible to differentiate between the treatments given the evidence as it stands. Given the lack of data, the group did not want to overly limit the treatment options that can be offered . Therefore the group agreed that treatment options for overweight/obese people were identical to those offered to the general PsA population. Also it is important to mention that the people with PsA who are overweight/obese outnumber those of normal weight and therefore the data in the other efficacy reviews in the guideline will contain a significant representation from this group.

However it is understood by the group that people who are overweight/obese more commonly have more severe disease and at the higher levels of obesity respond less well to treatment. However despite the efficacy being lessened, this does not indicate not offering systemic treatment for people who are morbidly obese.

1.5.3 Cost effectiveness and resource use

1.5.4 Other factors the committee took into account

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Appendix A: **Review protocol**

Table 6: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020223047
1.	Review title	Obesity and psoriatic arthritis
2.	Review question	In adults with active psoriatic arthritis who are overweight, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, apremilast or JAK inhibitors, in comparison to each other or placebo?
3.	Objective	To find the most effective biologic or targeted synthetic DMARD in people with psoriatic arthritis who are overweight or obese.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with psoriatic arthritis who are overweight or obese
7.	Intervention/Exposure/Test	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors Abatacept apremilast

		JAK inhibitors
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions or placebo
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders including but not limited to sex, smoking, alcohol, line of biologic therapy • Cross sectional studies, Conference abstracts, letters, will not be considered
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	BMI can be used to further categorise states of healthy BMI/ overweight/ obesity/ morbid obesity
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 <u>Dactylitis</u>

		• Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> Induction of IBD remission (dichotomous) Maintenance of IBD remission (dichotomous) IBD clinical response (dichotomous) <u>Adverse Events</u> Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**<u>These outcomes are extracted if studies do not report ACR response criteria.</u>** <u>Arthritis</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous)

		PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) <u>Other outcomes</u> • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group <u>http://www.gradeworkinggroup.org/</u>
17.	Analysis of sub-groups	BMI category (~~Healthy/~~ overweight / obese)
18.	Anticipated or actual start date	15/11/20
19.	Anticipated completion date	15/12/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.

21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 25 November 2020	RCTs or observational studies
Embase (ProQuest)	1947 – 25 November 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 11 of 12, November 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4
6 S1 or S2 or S5
7 TI,AB("TNF inhibitor*" or "Tumor necrosis factor inhibitor*" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
8 TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
9 TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
10 TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
11 TI,AB(Abatacept or apremilast)
12 TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
13 TI,AB(biologic* and DMARD)
14 TI,AB(targeted n/3 DMARD*)
15 TI,AB(tsDMARD*)
16 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

MESH.EXACT.EXPLODE("Overweight") OR MESH.EXACT.EXPLODE("Weight Reduction Programs") OR EMB.EXACT.EXPLODE("body weight management")
17 OR EMB.EXACT.EXPLODE("obesity")
18 TI,AB(Overweight OR obese OR obesity OR fat OR diet OR exercise OR “high BMI”)
19 TI,AB(loss OR reduc* OR lose)
20 TI,AB(weight OR BMI)
21 S19 AND S20
22 S17 OR S18 OR S21
23 TI(trial)
24 TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
25 TI,AB(doubl* n/1 blind*)
26 TI,AB(singl* n/1 blind*)
27 RTYPE(controlled clinical trial)
28 RTYPE(randomized controlled trial)
29 MESH.EXACT.EXPLODE("Clinical Trials as Topic")
30 EMB.EXACT.EXPLODE("crossover procedure")
31 EMB.EXACT.EXPLODE("single blind procedure")
32 EMB.EXACT.EXPLODE("randomized controlled trial")
33 EMB.EXACT.EXPLODE("double blind procedure")
34 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
35 S6 and S16 and S22 AND S34

MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR
36 EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
37 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)

TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or
38 epidemiologic* n/1 studies or epidemiologic* n/1 data)
39 TI,AB(before n/2 after n/2 stud*)
40 TI,AB(longitudinal or retrospective or prospective or cross sectional)
41 TI,AB(study or studies or review or analys* or cohort* or data)
42 S40 and S41
43 S36 OR S37 OR S38 OR S39 OR S42
44 S6 AND S16 AND S22 AND S43

45 S35 OR S44

Top up search completed on 28 November 2020

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4
6 S1 or S2 or S5
7 MESH.EXACT.EXPLODE("Weight Reduction Programs") OR EMB.EXACT.EXPLODE("body weight management")
8 TI,AB(loss OR reduc* OR lose)
9 TI,AB(weight OR BMI)
10 S8 AND S9
11 S7 OR S10
12 TI(trial)
13 TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
14 TI,AB(doubl* n/1 blind*)
15 TI,AB(singl* n/1 blind*)
16 RTYPE(controlled clinical trial)
17 RTYPE(randomized controlled trial)
18 MESH.EXACT.EXPLODE("Clinical Trials as Topic")
19 EMB.EXACT.EXPLODE("crossover procedure")
20 EMB.EXACT.EXPLODE("single blind procedure")
21 EMB.EXACT.EXPLODE("randomized controlled trial")
22 EMB.EXACT.EXPLODE("double blind procedure")
23 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
24 S6 and S11 and S23
25 MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
26 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
27 TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
28 TI,AB(before n/2 after n/2 stud*)

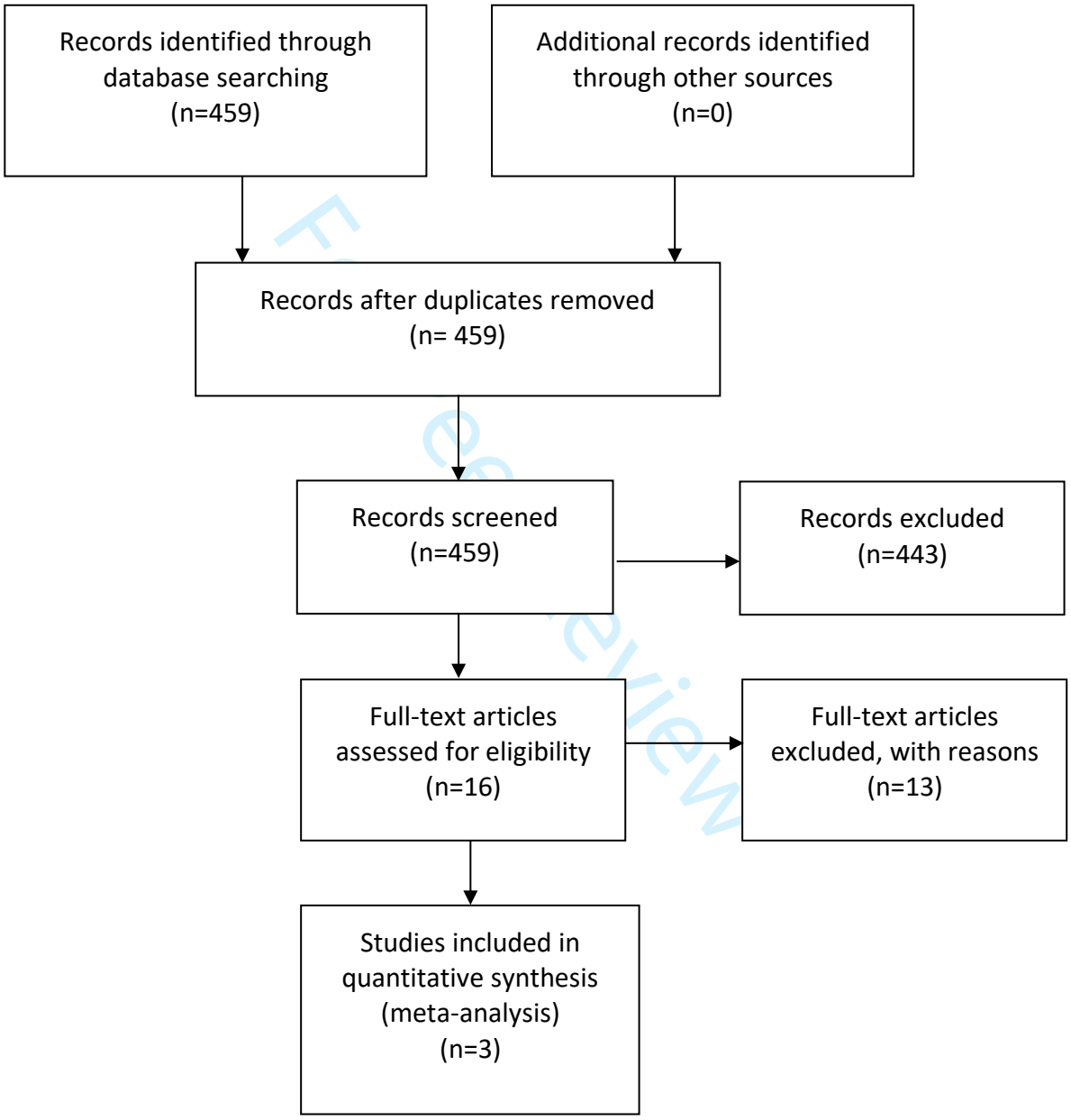
29 TI,AB(longitudinal or retrospective or prospective or cross sectional)
30 TI,AB(study or studies or review or analys* or cohort* or data)
31 S29 and S30
32 S25 OR S26 OR S27 OR S28 OR S31
33 S6 AND S11 AND S32
34 S24 OR S33

Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2	arthrosis or *arthritis
#3	Psoriasis or Psoriatic
#4	#2 and #3
#5	#1 or #4
#6	MeSH descriptor: [Weight Reduction Programs] explode all trees
#7	MeSH descriptor: [Overweight] explode all trees
#8	Overweight OR obese OR obesity OR fat OR diet OR exercise OR “high BMI”
#9	loss OR reduc* OR lose
#10	weight AND BMI
#11	#9 and #10
#12	#6 or #7 or #8 or #11
#13	#5 and #12

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D: **Clinical evidence tables**

Study	OPAL Broaden/Beyond: Ritchlin 2019(1)
Study type	Subgroup analysis using data from 2 double blind RCTs
Number of participants	n=710
Countries and setting	Conducted in North America, Europe, and Asia
Line of therapy	Not applicable
Duration of study	Intervention: Randomised treatment for 12 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	None
Inclusion criteria	This varies by study. Adults who had received a diagnosis of psoriatic arthritis at least 6 months previously. OPAL Broaden recruited people who previously had an inadequate response to at least one conventional synthetic DMARD. OPAL Beyond recruited people who had an inadequate response to at least 1 TNF inhibitor.
Exclusion criteria	Varies by study.
Age, gender and ethnicity	This appeared to be reported by trial: Age – mean age: 44.5 or 50. Gender: 49.5% or 65.6% female. Ethnicity: 92.5% or 96.8% white
Further population details	Overweight (BMI 25-30): 238 Obese (class 1): 186 Obese (class 2/3): 125
Indirectness of population	No indirectness
Interventions	(n=472) Intervention 1: JAK inhibitor – Two tofacitinib groups where people either used a dose of 5 mg or 10 mg taken orally twice daily. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide Indirectness: No indirectness

	(n=219) Intervention 2: Placebo - placebo subcutaneously injected at week 0, week 4, and then every 8 weeks. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide. Indirectness: No indirectness
Funding	Trial funded by Pfizer Inc. and medical writing support funded by Pfizer Inc.

Analysis of populations separated where possible into overweight, obese (class 1), and obese (class 2/3)

JAK inhibitor versus placebo

- Change in SF36 physical function score at 12 weeks. RoB: h
- Change in SF36 mental function score at 12 weeks. RoB: h
- ACR20 response at week 12. RoB: h
- ACR50 response at week 12. RoB: h
- ACR70 response at week 12. RoB: h
- Enthesitis absence at 12 weeks in people with enthesitis at baseline. RoB: vh
- Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline. RoB: vh
- Serious adverse events at 12 weeks RoB: h

Study	PALACE 1/2/3 Schett 2014(2)
Study type	Subgroup analysis using data from 3 double blind RCTs
Number of participants	n=1493
Countries and setting	Conducted in North America, Europe and Asia.
Line of therapy	Not applicable
Duration of study	Intervention: placebo controlled for 24 weeks with “early escape” at 16 weeks.
Method of assessment of guideline condition	CASPAR criteria
Stratum	Overall
Subgroup analysis within study	Outcomes in the subgroup of people who were overweight (BMI 25-30) or obese (>30). This was 1152 (77%) of the people in the 3 trials.
Inclusion criteria	Adults with a documented diagnosis of active PsA with duration ≥ 6 months. They were required to have had previous treatment with cDMARDs and/or bDMARDs.

Exclusion criteria	Failure of more than three agents for PsA (DMARDs or biologics) or >1 TNF inhibitor. People were also excluded if they had a history of or current (1) inflammatory, rheumatic or autoimmune joint disease other than PsA; (2) erythrodermic, guttate or generalised pustular psoriasis; (3) were functional class IV, defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis; (4) had used phototherapy or DMARDs other than methotrexate, leflunomide or sulfasalazine within 4 weeks of randomisation; (5) had used adalimumab, etanercept, golimumab, infliximab, certolizumab pegol or tocilizumab within 12 weeks of randomisation or alefacept or ustekinumab within 24 weeks of randomisation; or (6) had prior treatment with apremilast. Topical therapy for psoriasis within 2 weeks of randomisation was not permitted. Patients with active tuberculosis or a history of incompletely treated tuberculosis could not participate.
Age, gender and ethnicity	Age - Mean (SD): 51 (12) and 48 (11) and 51 (120). Gender (M:F): 249/255. Ethnicity: Not detailed
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=344 overweight and n=425 obese) Intervention 1: Apremilast – people were randomised to either 20 mg BID or 30 mg BID. Dose titrated over first week until target does reached. Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. Indirectness: No indirectness (n=152 overweight and n=231 obese) Intervention 2: Placebo – Concurrent medication/care: People taking concurrent csDMARD at baseline could continue stable doses of methotrexate (MTX; ≤ 25 mg/week), leflunomide (≤ 20 mg/day), sulfasalazine (≤ 2 g/day), or in combination. Nonsteroidal anti-inflammatory drugs were allowed if they were stable for ≥ 2 weeks before screening, and oral glucocorticoids (prednisone ≤ 10 mg or equivalent) if they were stable for ≥ 1 month before screening. Indirectness: No indirectness Early escape: People whose swollen and tender joint counts had not improved by ≥20% were considered non-responders at week 16 and were required to enter the protocol defined early escape. People receiving placebo were re-randomised (1:1) to apremilast 20 mg BID or 30 mg BID, while those on apremilast remained on their initial apremilast dose.

Funding	Trials were sponsored by Celgene Corp. However funding not stated for this analysis.

Apremilast versus placebo in people who were overweight or obese (class 1, 2 or 3). Each class of weight reported separately.

- ACR20 response at week 16. RoB: vh

Study	SPIRIT-P1/P2: Eder 2019(3)
Study type	Subgroup analysis using data from 2 double blind RCTs
Number of participants	n=453
Countries and setting	Conducted in North/Central America, Europe, Asia
Line of therapy	Not applicable
Duration of study	Intervention: 24 week double blind period of treatment
Method of assessment of guideline condition	Fulfilled the Classification Criteria for Psoriatic Arthritis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with active PsA who for one study were naïve to biologic DMARD treatment and in the other had inadequate response or intolerance to TNF inhibitors.
Exclusion criteria	None detailed
Age, gender and ethnicity	Age - Mean (SD): not stated Gender (M:F): 302/333. Ethnicity: not stated
Further population details	Numbers in intervention group and placebo group Overweight: 67 and 90 Obese (class 1, 2): 84 and 74 Obese (class 3): 24 and 20
Indirectness of population	No indirectness
Interventions	(n=175) Intervention 1: IL-17 inhibitor : Ixekizumab 80 mg every 4 weeks. Administered via subcutaneous injection. People were administered a starting dose of 160 mg given as two injections at week 0. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness

	(n=184) Intervention 2: Placebo: Administered via subcutaneous injection. Concurrent medication: people already on stable doses of allowed cDMARDs, oral corticosteroids, opiates and/or non-steroidal anti-inflammatory drugs/cyclo-oxygenase-2 inhibitors continued these during the study. Indirectness: No indirectness
Funding	The trials were funded and sponsored by Eli Lilly and Company. However funding not stated for this analysis

IL-17 inhibitor versus placebo

- ACR20 response at 24 weeks. RoB: h
- ACR50 response at 24weeks. RoB: h
- ACR70 response at 24 weeks. RoB: h
- Minimal disease activity at 24 weeks. RoB: h

Missing data were imputed using nonresponder imputation (NRI)

A)

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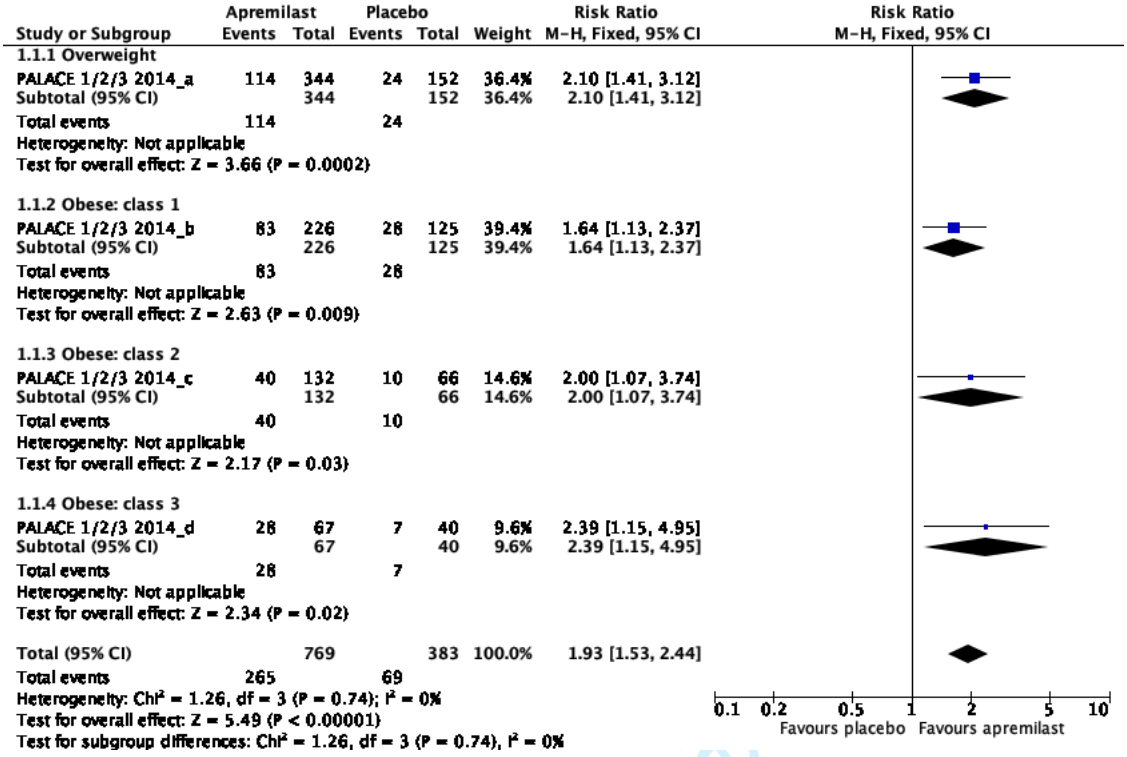
Appendix E: **Forest plots**

Apremilast versus placebo

Figure 2: ACR20 response at week 16



JAK inhibitor versus placebo

Figure 3: Change in SF36 physical component summary at 12 weeks

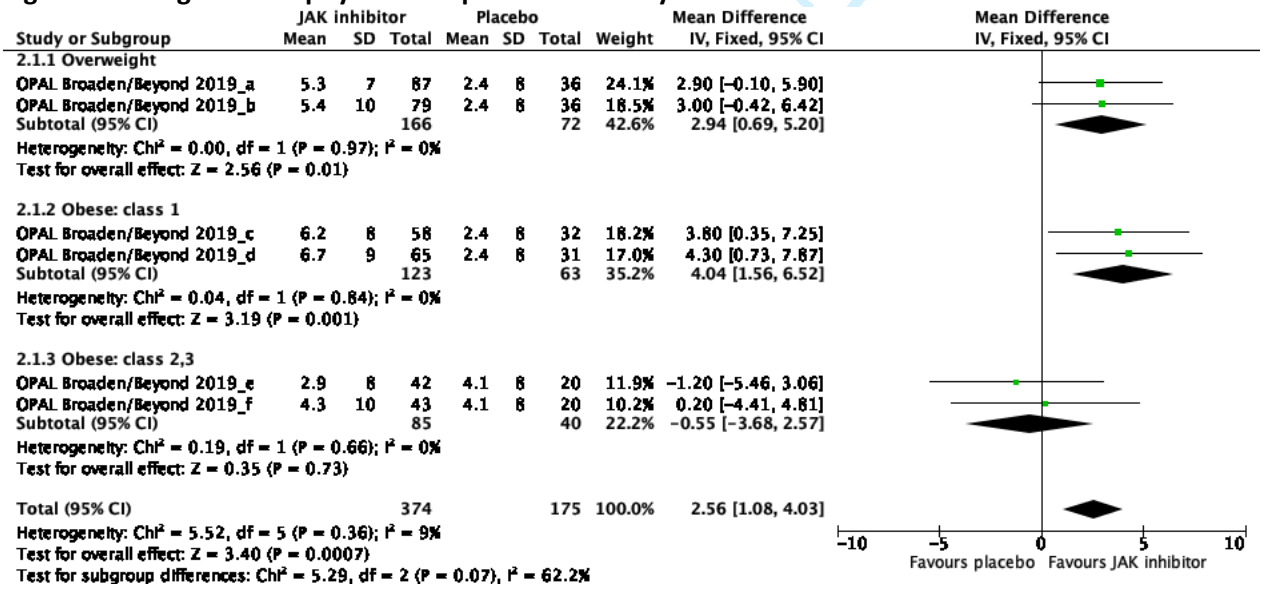


Figure 4: Change in SF36 mental component summary at 12 weeks

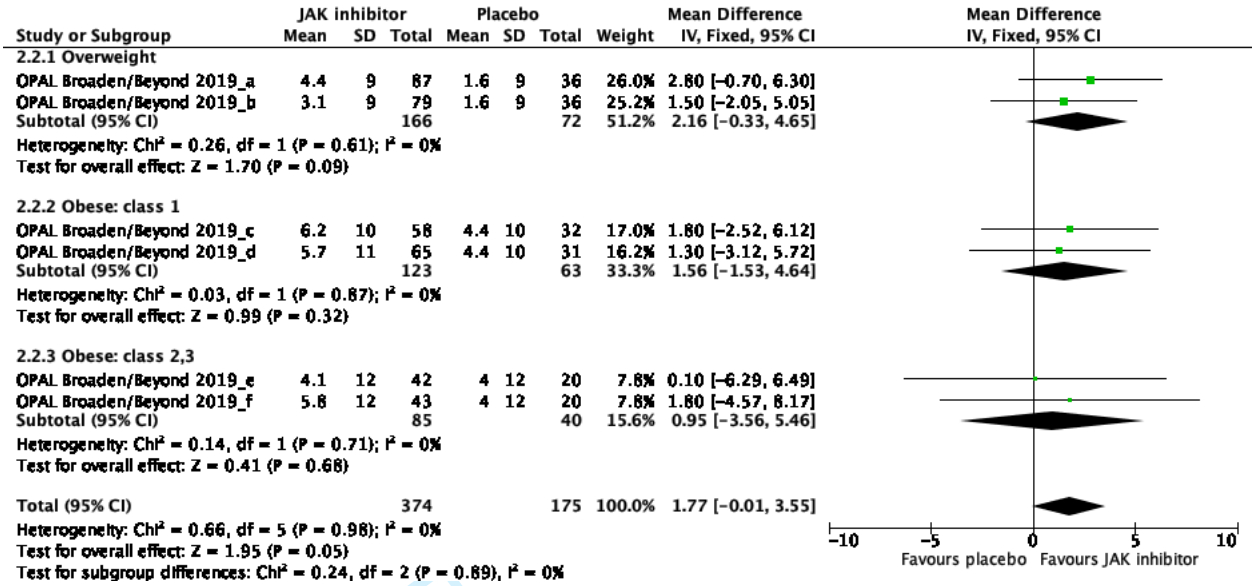


Figure 5: ACR20 response at week 12

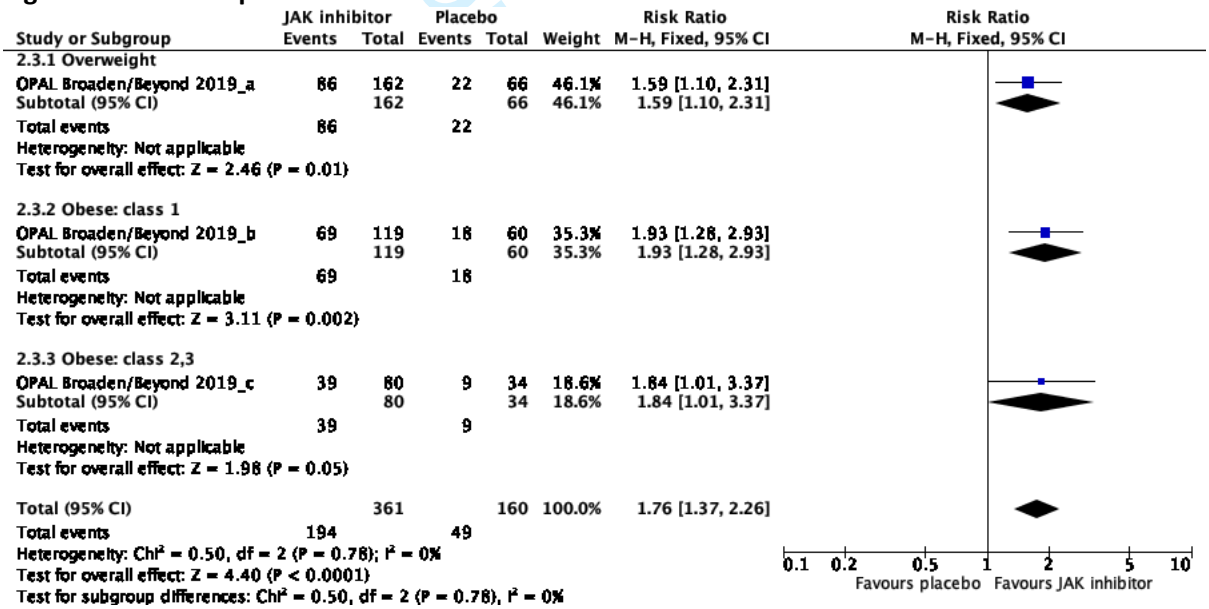


Figure 6: ACR50 response at week 12

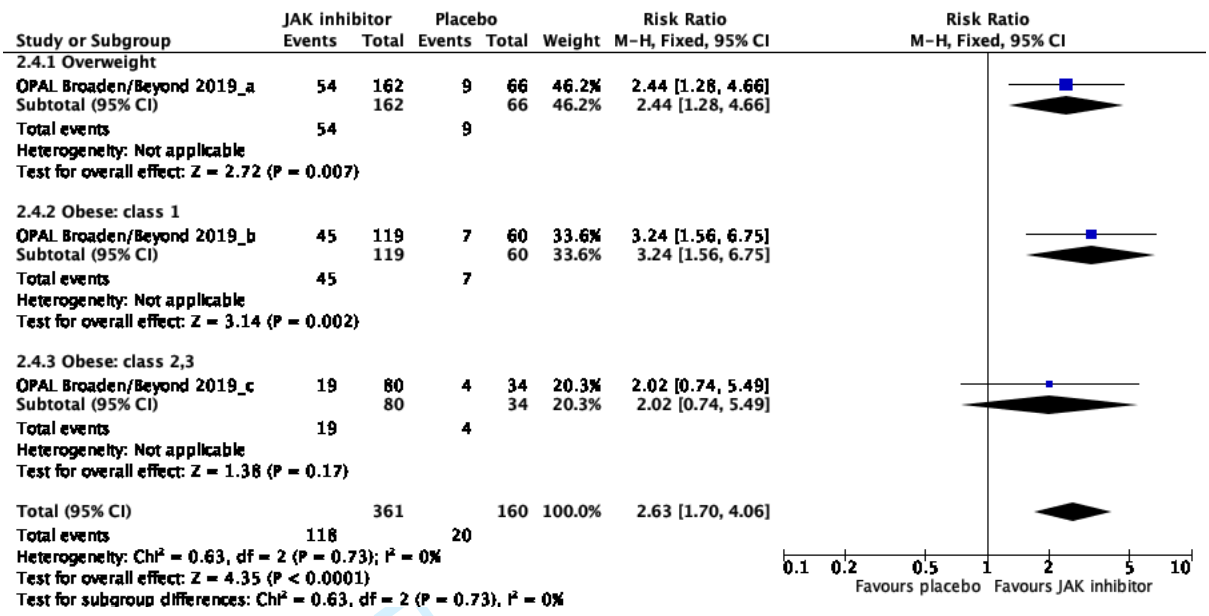


Figure 7: ACR70 response at week 12

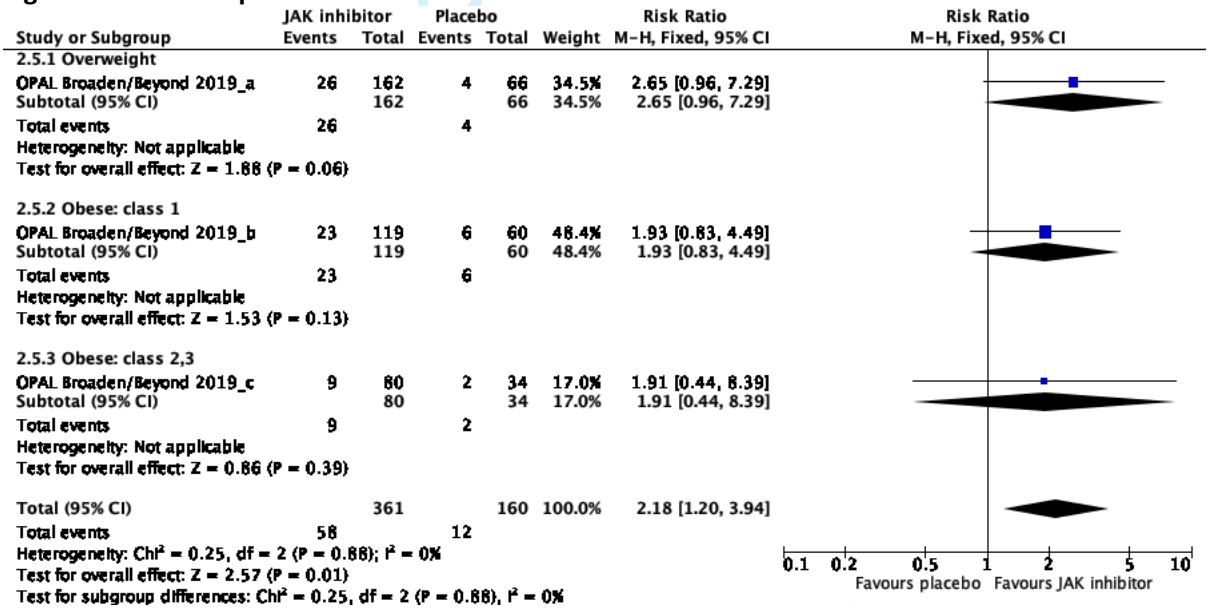


Figure 8: Enthesitis absence at 12 weeks in people with enthesitis at baseline

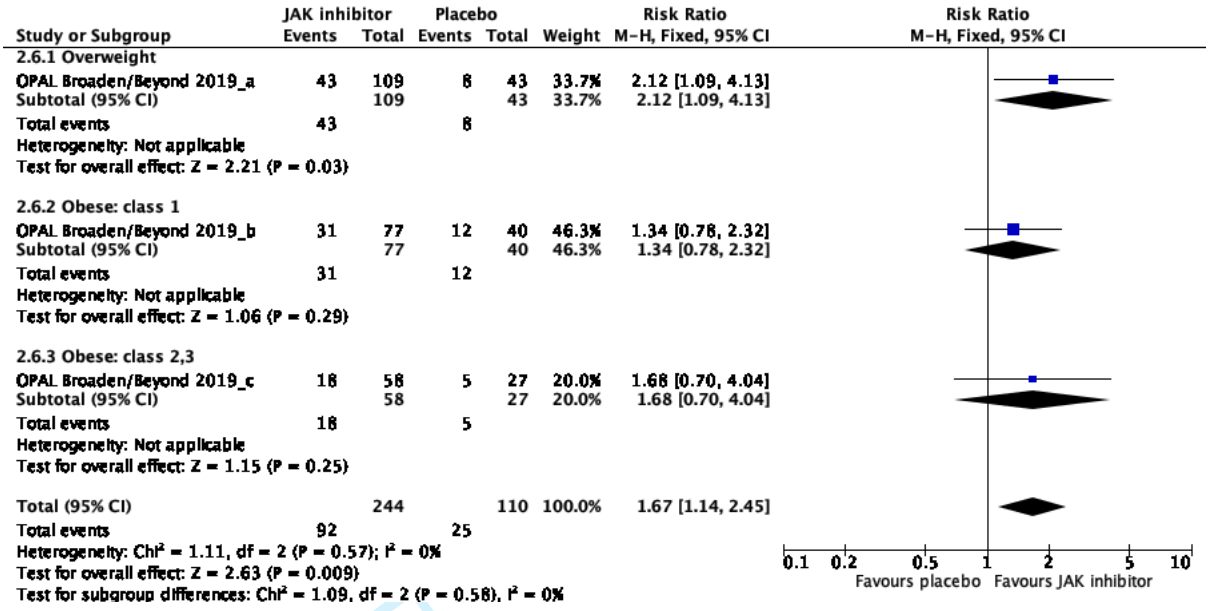
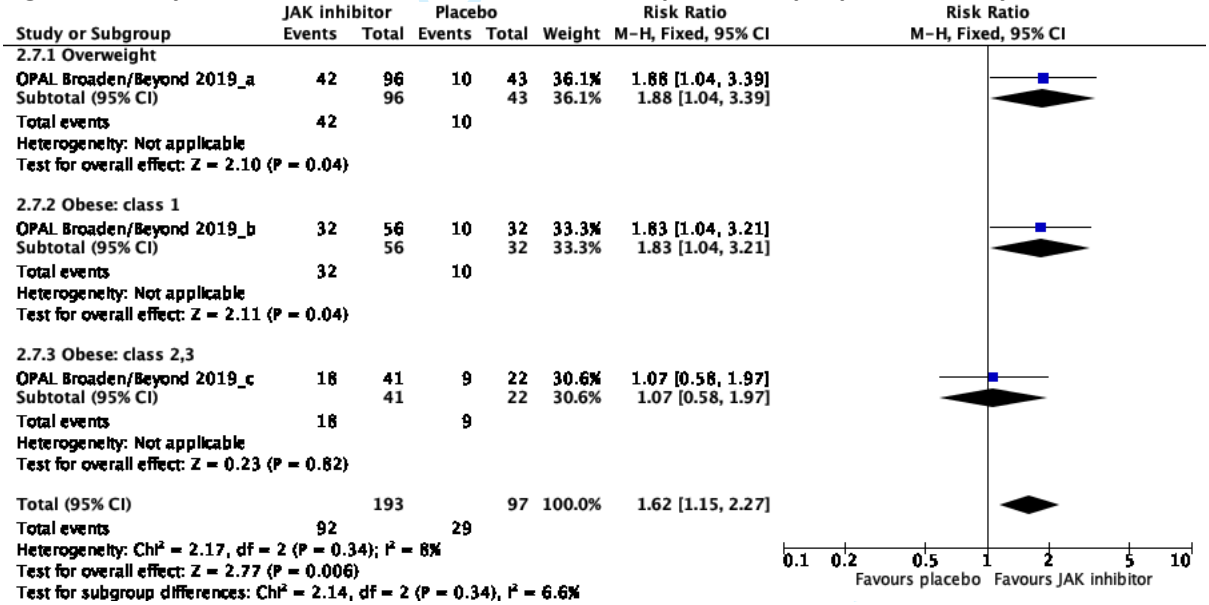


Figure 9: Dactylitis resolution at 12 weeks. Data are reported for people with dactylitis at baseline



IL-17 inhibitor versus placebo

Figure 10: MDA: Minimal disease activity (≥ 5 of 7 criteria) at week 24

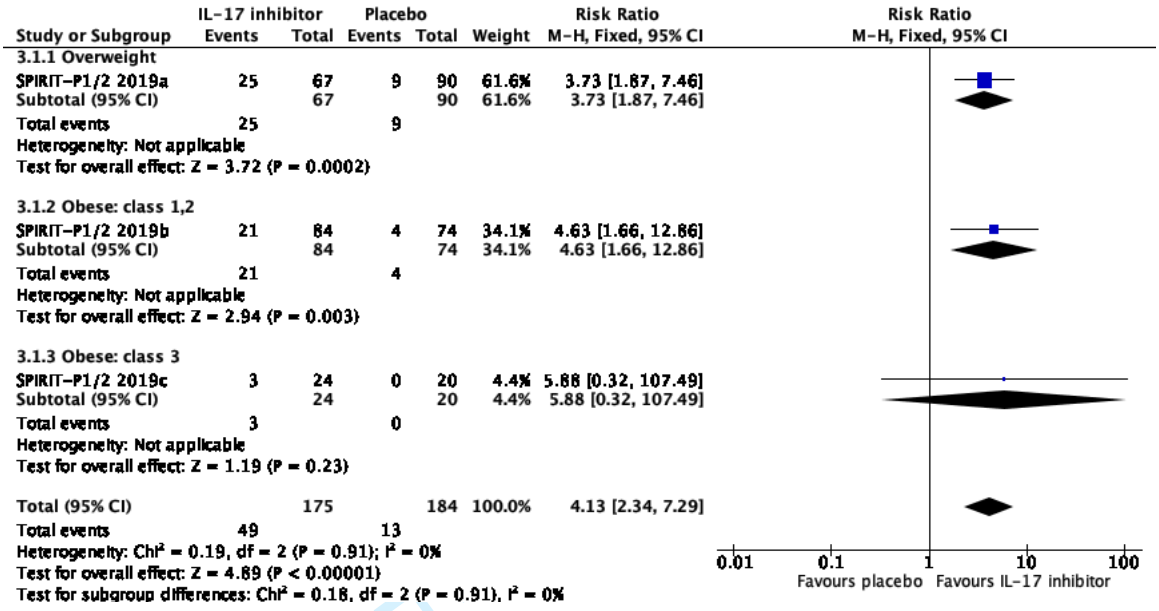


Figure 11: ACR20 response at 24 weeks

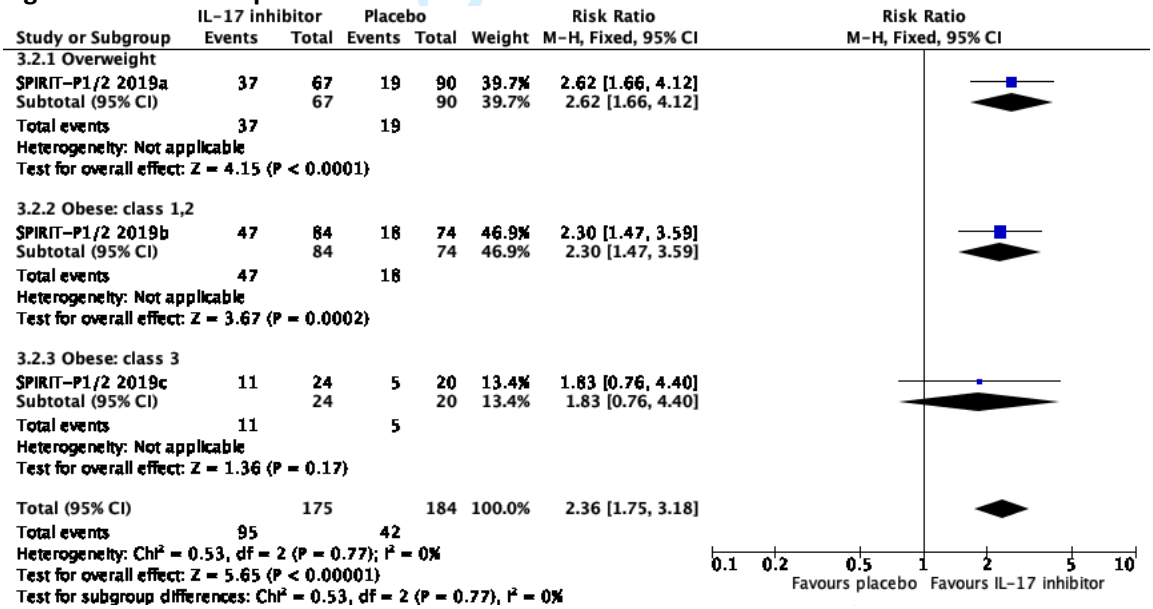


Figure 12: ACR50 response at week 24

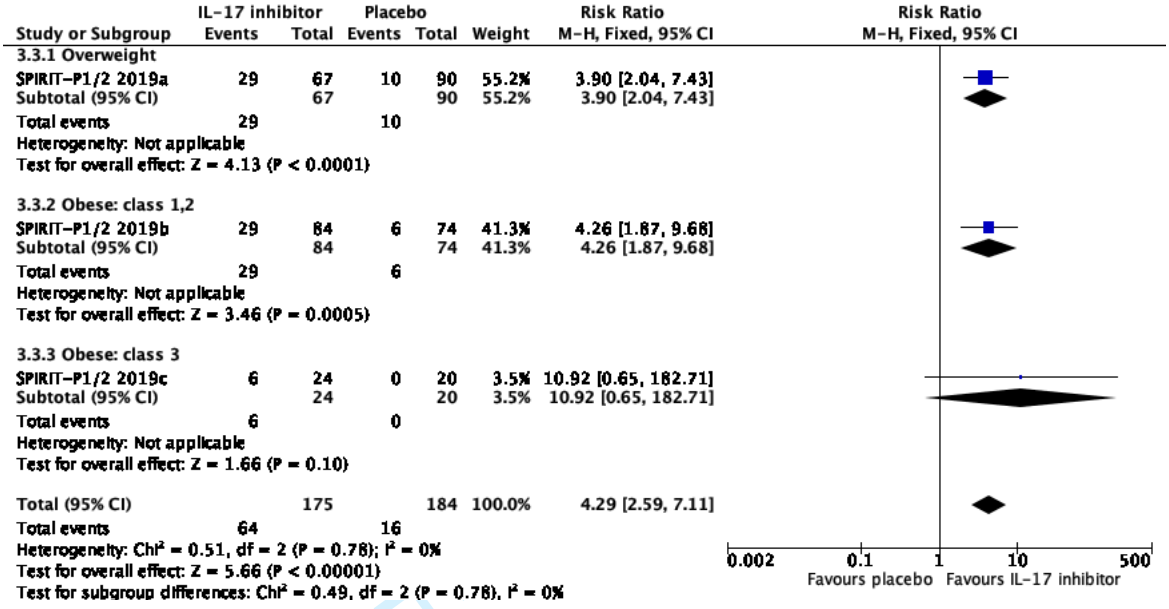
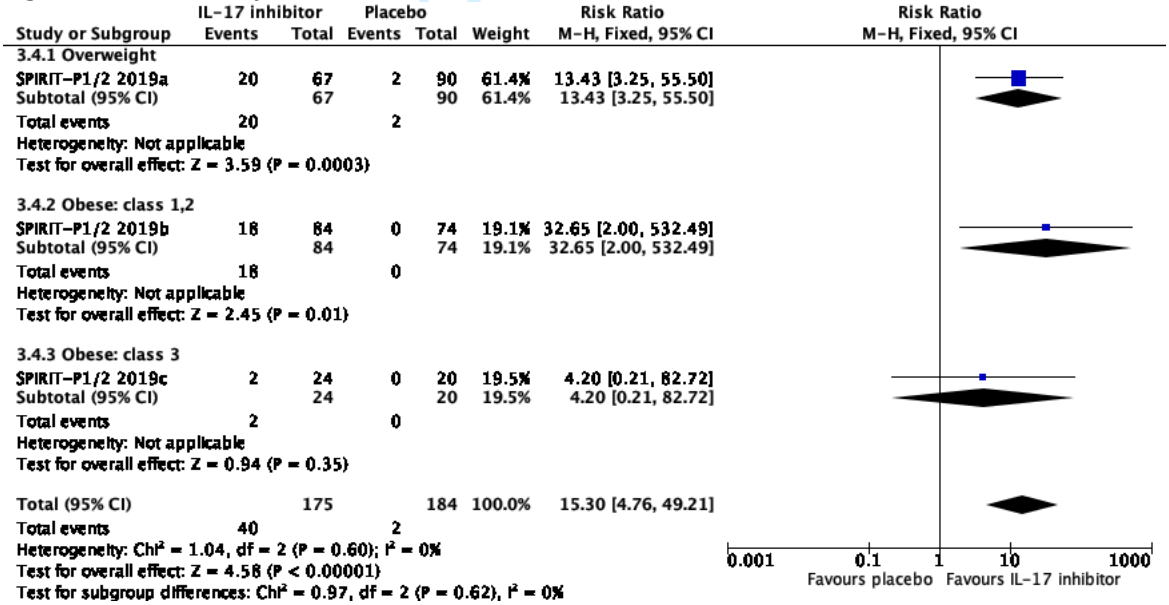


Figure 13: ACR70 response at week 24



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Appendix F: **Excluded studies**

Table 8: studies excluded from the evidence review

Study	Exclusion reason
Elkayam 2015(4)	Conference paper looking at correlation between BMI and drug survival
Farisoğullari 2020(5)	Conference paper looking at correlation between BMI and drug survival
Højgaard 2016(6)	This study compares outcomes in obese people with non-obese people.
Højgaard 2016(7)	Conference paper comparing obese with non-obese people
Hoving 2014(8)	Systematic review not suitable for inclusion in this review and its included studies were checked for inclusion too.
Ko 2019(9)	Systematic review using a psoriasis population. Included studies were checked for inclusion in this review
Korsakova 2020(10)	Conference paper included people not using varying classes of b/tsDMARDs or no b/tsDMARD at all
McInnes 2018(11)	Outcomes presented as a comparison of people's weights rather than a comparison of treatments within weight categories
McInnes 2019(12)	Outcomes presented as a comparison of people's weights rather than a comparison of treatments within weight categories
Mease 2015(13)	Conference paper reporting effectiveness by weight quartile rather than BMI
Pantano 2020(14)	Conference paper comparing obese people to non-obese people
Siebert 2019(15)	Conference paper. Comparison of disease activity in people with PsA who have a high BMI to those who do not
Singh 2018(16)	Systematic review not suitable for inclusion in this review. and included studies were checked for inclusion too.

Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on the effect of weight loss on b/ts DMARD treatment

BSR Guideline

Intervention evidence review

December 2020

Contents

1 The effect of weight loss on b/ts DMARD treatment

1.1 In adults with active psoriatic arthritis who are overweight and using biologics, what is the clinical effectiveness of weight loss compared with no weight loss?

1.2 INTRODUCTION

Being overweight or obese places extra pressure on a person's joints, meaning it can contribute to the symptoms of psoriatic arthritis (PsA). It is also thought to contribute to inflammation and stops some PsA medications from working as well as they could. This review seeks to find out whether a weight loss strategy benefits people with PsA over no weight loss strategy.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis using b/tsDMARDS who are overweight or obese
Intervention	Weight loss strategy via diet and/or exercise
Comparison	No weight loss strategy
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: . • ACR20 (dichotomous) ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Radiological progression (continuous) Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous)

	• IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) • Adverse Events • Serious adverse events (dichotomous) **Important** **These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) Disease Assessment in PsA (continuous) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	• Randomised Controlled Trails (RCT's) • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

Included studies

A search was conducted for RCTs or observational studies comparing outcomes in people who are using b/tsDMARDs and following a weight loss strategy with those not following a weight loss strategy. No studies were included in this review.

Excluded studies

See **Table 4** in Excluded studies in the appendix.

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures to capture medication effects on other psoriatic disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA.

Benefits and harms

No studies were included for this questions. However there were studies excluded from the review referred to by the group. These were the Klingberg 2019 study {Klingberg, 2019 #553} and the Di Minno 2014 study {Di Minno, 2014 #556}. The former included a control group without PsA and the latter was a comparison of 2 diets. However in both cases they broadly indicated a benefit of weight loss in the population. The Di Minno 2014 study suggested weight loss was beneficial in terms of achieving minimal disease activity.

The group agreed weight loss is an issue that people should raise with patients where required. This is due to an understanding that being overweight or obese has a negative impact on disease severity and is thought to lessen the efficacy of treatment. It is also known to be linked to more general medical problems such as metabolic syndrome and depression

Therefore the group agreed that people who are overweight or obese should be offered weight loss advice and support. The support here is key and should be offered on top of advice. It is understood support structures exist within the NHS but some trusts do not offer this as standard to people with psoriatic arthritis. Also the PsA population may find some of the advice/support hard to follow as often exercise is recommended and this can be challenging to someone with peripheral arthritis symptoms.

A consultant rheumatologist on the group indicated that his department does not have access to dieticians or obesity services and they refer people back to primary care for this and it is unclear what happens from that point on. The support required for weight loss involves a multi-disciplinary team. However there are obesity clinics, weight loss surgery, access to dieticians provided by the NHS but the challenge is for people with PsA to access these services. They may be limited to people at the higher level of obesity, for example, a group member indicated that a BMI of 35 was required when they started 5 years ago and now a BMI of 45 is a requirement o access the services. However the group were certain that a benefit could be seen across the overweight/obese spectrum in people with PsA.

It was agreed that access to these services would benefit people with PsA. It was indicated that in one trust Lupus and Sjogren's syndrome services are more linked to these services and dermatologist on the group indicated she had access to a multi-disciplinary weight loss service. However PsA is not locked into these services as standard. One person indicated that there was access to services for people with inflammatory arthritis at lower levels of obesity. This was a recent change to policy but would be of benefit if seen UK wide.

A patient member commented that how the advice and support is provided is very important. It is better not to lecture people on this and also to offer ongoing support rather than a one stop shop. It was also indicated that healthcare professionals could benefit from training and support on offering a weight loss strategy. This training and support may be understanding how to enable people to access weight loss services that are already exist within the NHS.

Cost effectiveness and resource use

Other factors the committee took into account

References

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Appendices

Appendix A: **Review protocols**

Table 2: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020223048
1.	Review title	Weight loss and PsA
2.	Review question	In adults with active psoriatic arthritis who are overweight and using biologics, what is the clinical effectiveness of weight loss compared with no weight loss?
3.	Objective	To determine whether weight loss aids the effectiveness of biologics or targeted synthetic DMARDs in people who are overweight or obese.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Inclusion: Adults with psoriatic arthritis using b/tsDMARDS who are overweight or obese
7.	Intervention/Exposure/Test	Weight loss strategy via diet and/or exercise

8.	Comparator/Reference standard/Confounding factors	No weight loss strategy
9.	Types of study to be included	• Randomised Controlled Trails (RCT's) • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders including sex, smoking, alcohol consumption, change in medical therapy,
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Nil specific
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 <u>Dactylitis</u> • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score

		ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**<u>These outcomes are extracted if studies do not report ACR response criteria.</u>** <u>Arthritis</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous)

		PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) <u>Other outcomes</u> • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	BMI category: overweight or obese.
18.	Anticipated or actual start date	18/11/20
19.	Anticipated completion date	9/12/20

20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 25 November 2020	RCTs or observational studies
Embase (ProQuest)	1947 – 25 November 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 11 of 12, November 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4
6 S1 or S2 or S5
7 TI,AB("TNF inhibitor*" or "Tumor necrosis factor inhibitor*" or TNFi or Adalimumab or certolizumab or etanercept or golimumab or infliximab)
8 TI,AB("IL-12/23 inhibitor" or "IL12/23 inhibitor" or Ustekinumab or briankizumab)
9 TI,AB("IL23 inhibitor" or "IL-23 inhibitor" or guselkumab or tildrakizumab or risankizumab or mirikizumab)
10 TI,AB("IL17 inhibitor" or "IL-17 inhibitor" or Ixekizumab or secukinumab or brodalumab or Bimekizumab)
11 TI,AB(Abatacept or apremilast)
12 TI,AB("JAK inhibitors" or "Janus kinase inhibitor" or JAK1 or JAK2 or JAK3 or TYK2 or filgotinib or upadacitinib or filgotinib or upadacitinib or tofacitinib)
13 TI,AB(biologic* and DMARD)
14 TI,AB(targeted n/3 DMARD*)
15 TI,AB(tsDMARD*)
16 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
17 MESH.EXACT.EXPLODE("Overweight") OR MESH.EXACT.EXPLODE("Weight Reduction Programs") OR EMB.EXACT.EXPLODE("body weight management") OR EMB.EXACT.EXPLODE("obesity")
18 TI,AB(Overweight OR obese OR obesity OR fat OR diet OR exercise OR "high BMI")

19 TI,AB(loss OR reduc* OR lose)
20 TI,AB(weight OR BMI)
21 S19 AND S20
22 S17 OR S18 OR S21
23 TI(trial)
24 TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
25 TI,AB(doubl* n/1 blind*)
26 TI,AB(singl* n/1 blind*)
27 RTYPE(controlled clinical trial)
28 RTYPE(randomized controlled trial)
29 MESH.EXACT.EXPLODE("Clinical Trials as Topic")
30 EMB.EXACT.EXPLODE("crossover procedure")
31 EMB.EXACT.EXPLODE("single blind procedure")
32 EMB.EXACT.EXPLODE("randomized controlled trial")
33 EMB.EXACT.EXPLODE("double blind procedure")
34 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
35 S6 and S16 and S22 AND S34
36 MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
37 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
38 TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
39 TI,AB(before n/2 after n/2 stud*)
40 TI,AB(longitudinal or retrospective or prospective or cross sectional)
41 TI,AB(study or studies or review or analys* or cohort* or data)
42 S40 and S41
43 S36 OR S37 OR S38 OR S39 OR S42
44 S6 AND S16 AND S22 AND S43
45 S35 OR S44

Top up search completed on 28 November 2020

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4

6 S1 or S2 or S5
7 MESH.EXACT.EXPLODE("Weight Reduction Programs") OR EMB.EXACT.EXPLODE("body weight management")
8 TI,AB(loss OR reduc* OR lose)
9 TI,AB(weight OR BMI)
10 S8 AND S9
11 S7 OR S10
12 TI(trial)
13 TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
14 TI,AB(doubl* n/1 blind*)
15 TI,AB(singl* n/1 blind*)
16 RTYPE(controlled clinical trial)
17 RTYPE(randomized controlled trial)
18 MESH.EXACT.EXPLODE("Clinical Trials as Topic")
19 EMB.EXACT.EXPLODE("crossover procedure")
20 EMB.EXACT.EXPLODE("single blind procedure")
21 EMB.EXACT.EXPLODE("randomized controlled trial")
22 EMB.EXACT.EXPLODE("double blind procedure")
23 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
24 S6 and S11 and S23
25 MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR
26 EMB.EXACT("cross-sectional study")
27 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data) TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
28 TI,AB(before n/2 after n/2 stud*)
29 TI,AB(longitudinal or retrospective or prospective or cross sectional)
30 TI,AB(study or studies or review or analys* or cohort* or data)
31 S29 and S30
32 S25 OR S26 OR S27 OR S28 OR S31
33 S6 AND S11 AND S32
34 S24 OR S33

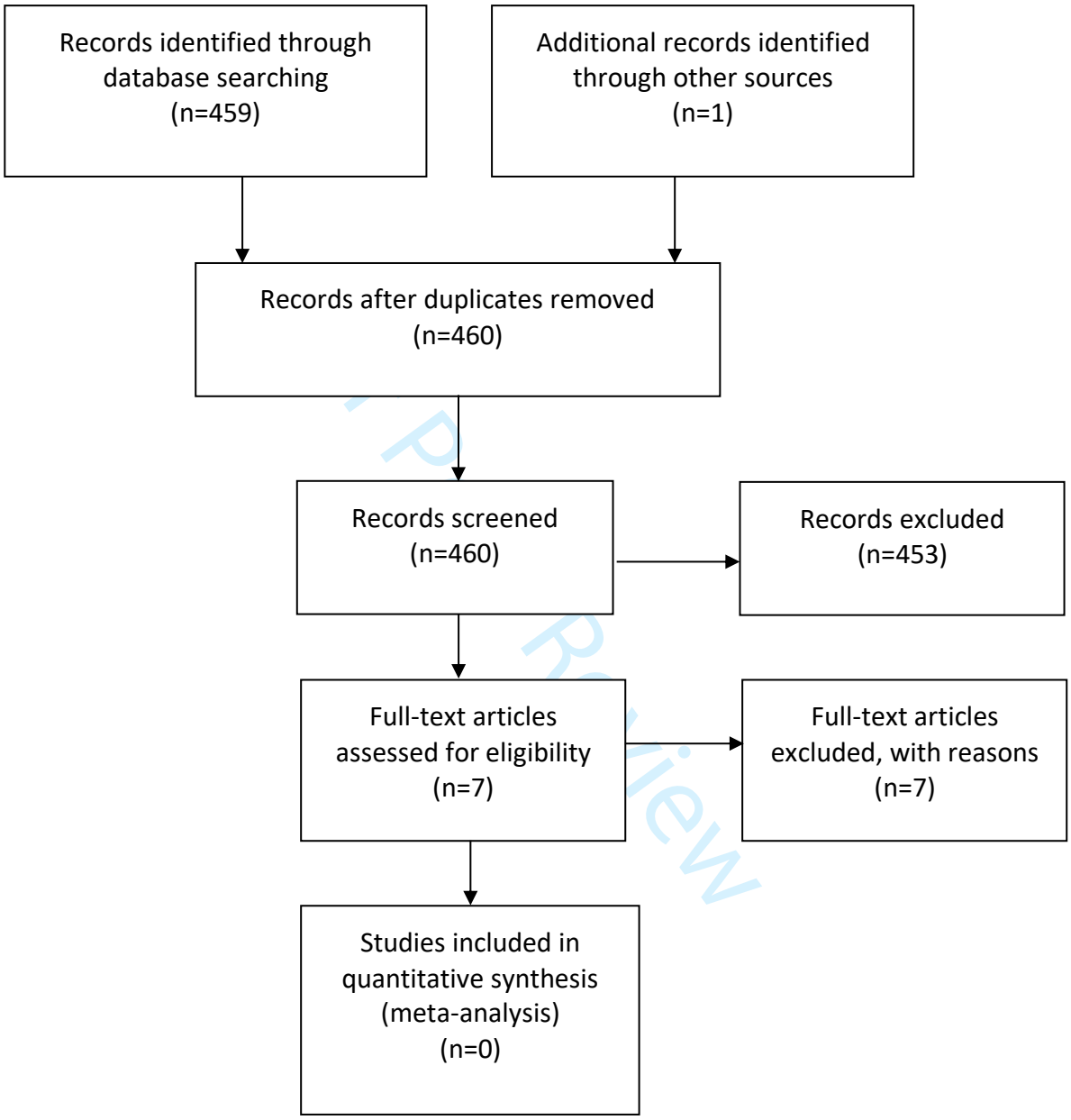
Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2	arthrosis or *arthritis
#3	Psoriasis or Psoriatic

#4	#2 and #3
#5	#1 or #4
#6	MeSH descriptor: [Weight Reduction Programs] explode all trees
#7	MeSH descriptor: [Overweight] explode all trees
#8	Overweight OR obese OR obesity OR fat OR diet OR exercise OR “high BMI”
#9	loss OR reduc* OR lose
#10	weight AND BMI
#11	#9 and #10
#12	#6 or #7 or #8 or #11
#13	#5 and #12

Appendix C: **Clinical evidence selection**

Figure 1: Flow chart of clinical study selection



British Society for Rheumatology

Appendix D: **Excluded studies**

Table 4: studies excluded from the evidence review

Study	Exclusion reason
Hsia 2013{#537}	Conference abstract for study including people with PsA and RA. Insufficient details and data were provided for inclusion in this review.
Klingberg 2020{#552}	Control group in this trial did not have PsA
Klingberg 2019{#553}	Uncontrolled study evaluating a VLED in people with PsA
Ford 2018{#554}	Systematic review of dietary interventions. Included studies checked for inclusion in this review.
Almodóvar 2018{#555}	Systematic review of weight change and disease activity in PsA. Included studies were checked for inclusion in this review.
Di Minno 2014{#556}	Comparison of hypocaloric diet to a self-managed diet
Abou-Raya 2014{#558}	Conference abstract with insufficient details and data provided for inclusion in this review.

British Society for Rheumatology

Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on b/ts DMARDs in people with PsA who are smokers

BSR Guideline

Intervention evidence review

January 2021

Contents

1 b/ts DMARDs in people with PsA who smoke

1.1 In adults with active psoriatic arthritis who are smokers, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, apremilast or JAK inhibitors, in comparison to each other or placebo?

1.2 INTRODUCTION

It is thought that smoking can adversely affect the efficacy of b/tsDMARD treatment and it is unclear which b/tsDMARD treatment is best for smokers. This review seeks to assess the efficacy of b/tsDMARDs in people who smoke.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis who are smokers
Intervention	• TNF inhibitors • IL12/23 inhibitors • IL23 inhibitors • IL17 inhibitors • Abatacept • Apremilast • JAK inhibitors
Comparison	Comparison of interventions or versus placebo
	Critical Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: . • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) • Radiological progression (continuous) Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) Psoriasis

	• Psoriasis score (PASI / IGA / BSA) (continuous) Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Adverse Events • Serious adverse events (dichotomous) **Important** **These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • Disease Assessment in PsA (continuous) Other outcomes • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
Study design	Randomised Controlled Trials (RCT's)- inclusion and exclusion criteria as stated above If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

Included studies

A literature search was conducted for RCTs or observational studies comparing biologic or targeted synthetic DMARDs in people with psoriatic arthritis. 1 conference abstract(1) detailing results from smokers and ex-smokers in 2 RCTs comparing a JAK inhibitor to placebo.

Excluded studies

See **Table 5** in Excluded studies in the appendix.

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Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
OPAL Broaden/Beyond: Behrens 2018(1)	5/10mg oral Tofacitinib twice per day versus placebo People were required to take a stable dose of a csDMARD	N=701. Study dependent inclusion criteria. Adults with psoriatic arthritis with an inadequate response to a csDMARD +/- a TNF inhibitor. This analysis concentrates on people who were smokers (17%) or ex-smokers (21%).	ACR20 response at week 12. Results were reported separately for people who were current smokers and those who were ex-smokers.	Conducted in North America, Europe, and Asia Trial funded by Pfizer Inc. and medical writing support funded by Pfizer Inc.

1.4.1 Quality assessment of clinical studies included in the evidence review

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR20 response: smokers/ex-smokers (follow up: 12 weeks)												
2	randomised trials	serious [a]	serious [b]	serious [c]	very serious [d]	publication bias strongly suspected [e]	97/195 (49.7%)	27/78 (34.6%)	**RR 1.43** (0.50 to 4.12)	**149 more per 1,000** (from 173 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
ACR20 response in ex-smokers (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAK inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [c]	not serious	publication bias strongly suspected [e]	64/113 (56.6%)	9/39 (23.1%)	**RR 2.45** (1.35 to 4.45)	**335 more per 1,000** (from 81 more to 796 more)	⨁◯◯◯ VERY LOW	CRITICAL

ACR20 response at week 12 - Smoker

1	randomised trials	serious [a]	not serious	not serious	very serious [d]	publication bias strongly suspected [e]	33/82 (40.2%)	18/39 (46.2%)	**RR 0.87** (0.57 to 1.34)	**60 fewer per 1,000** (from 198 fewer to 157 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 or 2 increments because the point estimate varies widely across studies. Random effects model used.
c. Population includes ex-smokers and is considered indirect
d. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
e. Data on smoker's results in most PsA b/tsDMARD RCTs is not available

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures to capture medication effects on other psoriatic disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA.

Benefits and harms

A single conference abstract detailing outcomes in smokers and ex-smokers in trial of a JAK inhibitor (tofacitinib) versus placebo. In total this was over 250 people. Only a single outcome was reported and this was ACR20 at 12 weeks. A clinically benefit was seen for JAK inhibitor in the combined group of smokers and ex-smokers and a similar benefit was seen when looking at ex-smokers alone. However, the subgroup of current smokers did not indicated no clinical difference between JAK inhibitor and placebo.

The group did not feel that this single outcome in a small number of people who were a subgroup of a subgroup in 2 RCTs was valid evidence upon which a recommendation against JAK inhibitors could be formulated. In addition the group did not take it as a general trend for the treatment effect of other b/tsDMARDs. In addition the group is aware of registry data that indicates smokers can respond to b/tsDMARD treatment.

Cost effectiveness and resource use

Other factors the committee took into account

References

1. Behrens F, Gomez-Reino J, Nash P, Gladman DD, FitzGerald O, Ritchlin C, et al. Impact of baseline demographics, disease activity and concomitant medication on american college of rheumatology 20 response rate and health assessment questionnaire-disability index score with tofacitinib in active psoriatic arthritis: A pooled subgroup analysis of 2 phase 3 studies. Annals of the Rheumatic Diseases. 2018;77:1585-6.
2. Campos Esteban J, Conesa Mateos A, Fernandez-Prada M, Expósito-Molinero R, Rubio Muñoz P, Lamua-Riazuelo JR, et al. Effectiveness of certolizumab pegol in psoriatic arthritis. Relationship with smoking status and BMI. Annals of the Rheumatic Diseases. 2018;77:1588.
3. Dos Santos Sobrín R, Vilas AS, Fernández JRM, Varela AM, Gómez-Reino JJ. Effect of smoking on the efficacy of TNF inhibitors in the treatment of chronic inflammatory immune-mediated diseases: Systematic review and meta-analysis. Annals of the Rheumatic Diseases. 2019;78:1576.
4. Højgaard P, Glintborg B, Hetland ML, Hansen TH, Lage-Hansen PR, Petersen MH, et al. Association between tobacco smoking and response to tumour necrosis factor α inhibitor treatment in psoriatic arthritis: Results from the DANBIO registry. Annals of the Rheumatic Diseases. 2015;74(12):2130-6.
5. Kinahan CE, Mazloom S, Fernandez AP. Impact of smoking on response to systemic treatment in patients with psoriasis: A retrospective case-control study. British Journal of Dermatology. 2015;172(2):428-36.
6. Ko SH, Chi CC, Yeh ML, Wang SH, Tsai YS, Hsu MY. Lifestyle changes for treating psoriasis. Cochrane Database of Systematic Reviews. 2019(7).
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8. Riechers E, Kiltz U, Brandt-Juergens J, Kastner P, Peterlik D, Tony HP. Does smoking affect secukinumab treatment outcomes and safety in patients with psoriatic arthritis?-real world data from the german aquila study. Annals of the Rheumatic Diseases. 2020;79(SUPPL 1):1711.
9. Villaverde-Garcia V, Cobo-Ibáñez T, Seoane-Mato D, Díaz Del Campo-Fontecha P, Guerra M, Candelas-Rodríguez G, et al. The effect of smoking on clinical and structural damage in patients with ankylosing spondylitis and axial spondyloarthritis: A systematic literature review. Annals of the Rheumatic Diseases. 2016;75:339.
10. Yarkan H, Kenar G, Capar S, Can G, Zengin B, Akar S, et al. The effect of smoking on response to tumour necrosis factor-alpha inhibitor treatment in psoriatic arthritis patients: Results from the Turkbio registry. Arthritis and Rheumatology. 2018;70:2927-8.

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Appendices

Appendix A: **Review protocol**

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42021227539
1.	Review title	Smokers with psoriatic arthritis
2.	Review question	In adults with active psoriatic arthritis who are smokers, what is the clinical effectiveness of TNF inhibitors, IL12/23 inhibitors, IL23 inhibitors, IL17 inhibitors, apremilast or JAK inhibitors, in comparison to each other or placebo?
3.	Objective	To evaluate whether the act of smoking impacts the effectiveness of biologic or targeted synthetic DMARD treatment in people with psoriatic arthritis.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	Psoriatic arthritis, an inflammatory musculoskeletal disease associated with psoriasis
6.	Population	Adults with psoriatic arthritis who are smokers
7.	Intervention/Exposure/Test	TNF inhibitors IL12/23 inhibitors IL23 inhibitors IL17 inhibitors

		Abatacept apremilast JAK inhibitors
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions or versus placebo
9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders including sex, socioeconomic status, alcohol, line of therapy,
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	The impact of smoking status on clinical response or time to secondary inefficacy
12.	Primary outcomes (critical outcomes)	Generic • Mortality (dichotomous) • Quality of life (continuous) Arthritis: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) Enthesitis • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 Dactylitis • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous)

		Axial Spondylarthritis • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI). • ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • pinal Pain VAS- 0-100 (continuous) Psoriasis • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score Uveitis • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Adverse Events • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**These outcomes are extracted if studies do not report ACR response criteria.** Arthritis • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1.

		• Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) <u>Other outcomes</u> • Health Assessment Questionnaire (HAQ) 0-3 (continuous) • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Current / previous smoker
18.	Anticipated or actual start date	O6/12/20
19.	Anticipated completion date	16/01/20
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.

22.	Details of existing review of same topic by same authors	This is not an update
23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 10 December 2020	RCTs or observational studies
Embase (ProQuest)	1947 – 10 December 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Reviews: Issue 12 of 12, December 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1	MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2	EMB.EXACT.EXPLODE("psoriatic arthritis")
3	TI,AB(Psoriasis or Psoriatic)
4	TI,AB(arthrosis or *arthritis)
5	S3 n/3 S4
6	S1 or S2 or S5
7	MESH.EXACT("Smoking Cessation") OR MESH.EXACT.EXPLODE("Tobacco Smoking") OR EMB.EXACT.EXPLODE("smoking") OR EMB.EXACT("smoking cessation")
8	TI,AB(smoke or smokes or smoking)
9	TI,AB(cigar or cigars or cigarette* or tobacco)
10	S7 OR S8 OR S9
11	TI(trial)
12	TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
13	TI,AB(doubl* n/1 blind*)
14	TI,AB(singl* n/1 blind*)
15	RTYPE(controlled clinical trial)
16	RTYPE(randomized controlled trial)
17	MESH.EXACT.EXPLODE("Clinical Trials as Topic")
18	EMB.EXACT.EXPLODE("crossover procedure")
19	EMB.EXACT.EXPLODE("single blind procedure")
20	EMB.EXACT.EXPLODE("randomized controlled trial")
21	EMB.EXACT.EXPLODE("double blind procedure")
22	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

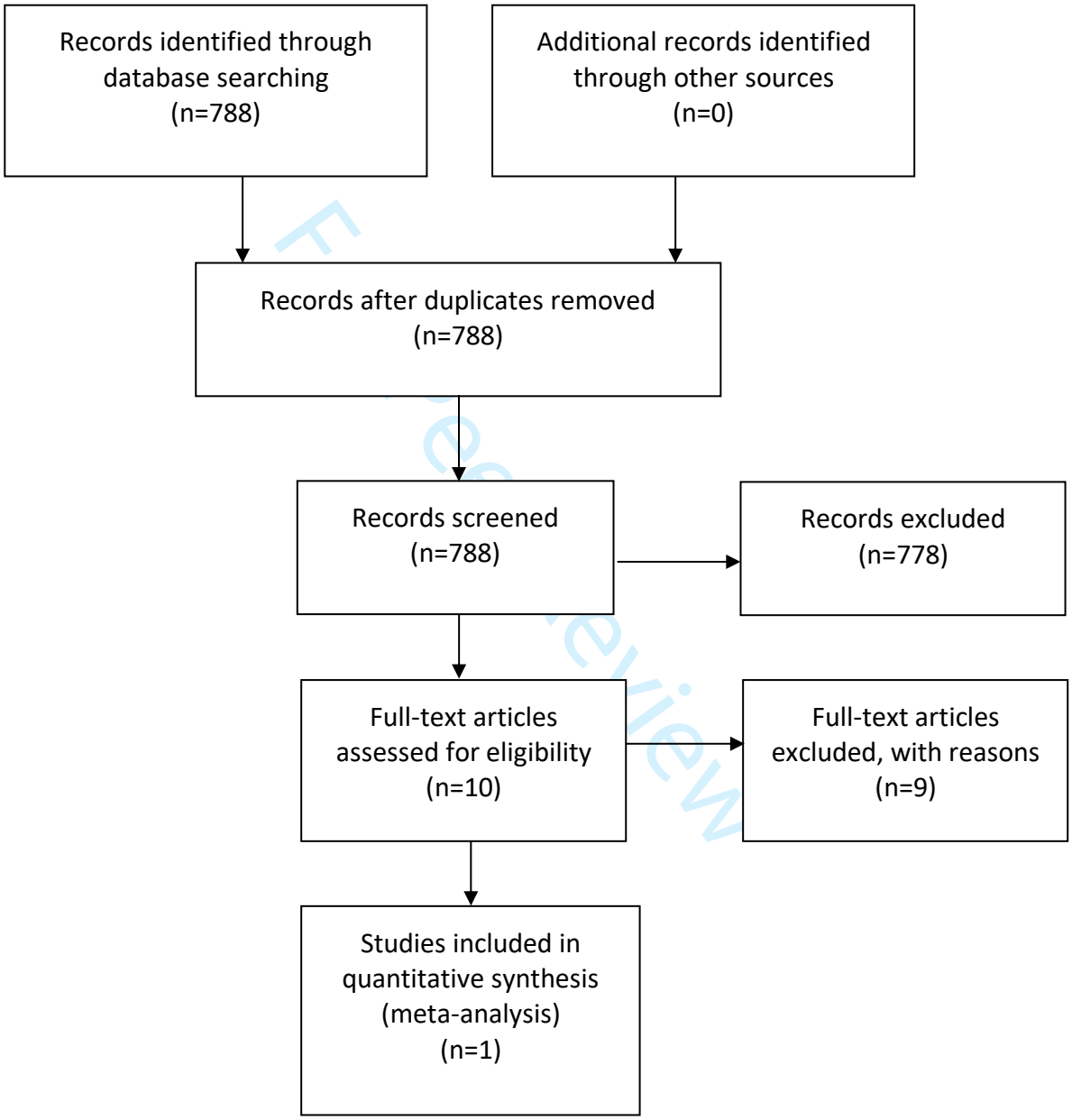
23	S6 and S10 and S22
24	MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")
25	TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)
26	TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)
27	TI,AB(before n/2 after n/2 stud*)
28	TI,AB(longitudinal or retrospective or prospective or cross sectional)
29	TI,AB(study or studies or review or analys* or cohort* or data)
30	S28 and S29
31	S24 OR 25 OR S26 OR S27 OR S30
32	S6 AND S10 AND S31
33	S23 OR S32

Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Arthritis, Psoriatic] this term only
#2	arthrosis or *arthritis
#3	Psoriasis or Psoriatic
#4	#2 and #3
#5	#1 or #4
#6	MeSH descriptor: [Tobacco Smoking] explode all trees
#7	MeSH descriptor: [Smoking Cessation] explode all trees
#8	smoke or smokes or smoking or cigar or cigars or cigarette* or tobacco
#9	#6 or #7 or #8
#10	#5 and #9

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D: Clinical evidence tables

Study	OPAL Broaden/Beyond: Behrens 2018(1)
Study type	Subgroup analysis using data from 2 double blind RCTs
Number of participants	n=710
Countries and setting	Conducted in North America, Europe, and Asia
Line of therapy	Not applicable
Duration of study	Intervention: Randomised treatment for 12 weeks
Method of assessment of guideline condition	CASPAR
Stratum	Overall
Subgroup analysis within study	This is an analysis of smokers (17%) and ex-smokers (21%) in the 2 RCTs
Inclusion criteria	This varies by study. Adults who had received a diagnosis of psoriatic arthritis at least 6 months previously. OPAL Broaden recruited people who previously had an inadequate response to at least one conventional synthetic DMARD. OPAL Beyond recruited people who had an inadequate response to at least 1 TNF inhibitor.
Exclusion criteria	Varies by study.
Age, gender and ethnicity	Not reported
Further population details	Intervention and placebo Smoker: 82 and 39 Ex-smoker: 113 and 39
Indirectness of population	No indirectness
Interventions	(n=195) Intervention 1: JAK inhibitor – Two tofacitinib groups where people either used a dose of 5 mg or 10 mg taken orally twice daily. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide Indirectness: No indirectness (n=78) Intervention 2: Placebo - placebo subcutaneously injected at week 0, week 4, and then every 8 weeks. Concurrent medication/care: People were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide. Indirectness: No indirectness
Funding	Trial funded by Pfizer Inc. and medical writing support funded by Pfizer Inc.

Analysis of populations separated into smoker and ex-smoker

JAK inhibitor versus placebo

- ACR20 response at week 12. RoB: h

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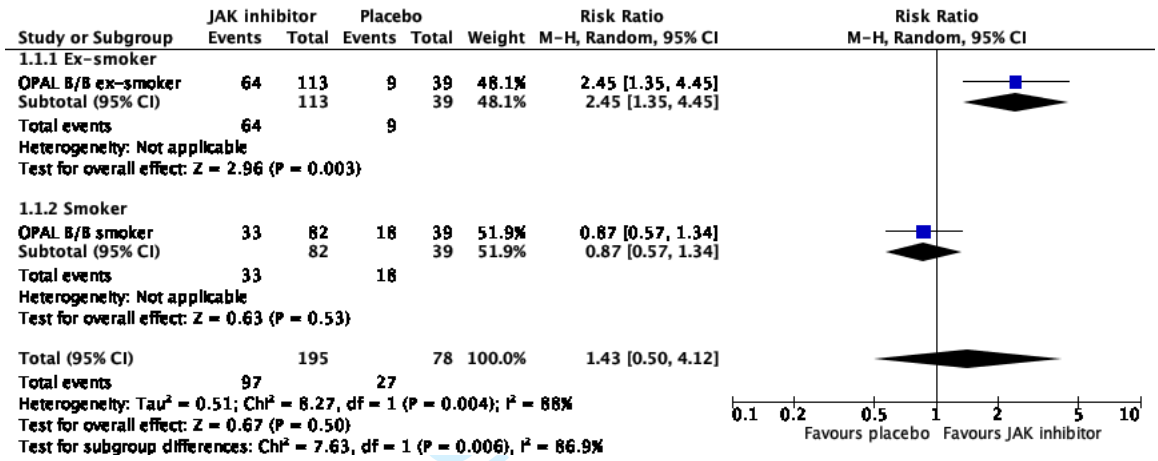
Appendix E: **Forest plots**

Figure 2: ACR20 response at week 12



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Appendix F: Excluded studies

Table 5: studies excluded from the evidence review

Study	Exclusion reason
Campos Esteban 2018(2)	Comparison of smokers and non-smokers
Dos Santos Sobrín 2019(3)	Comparison of smokers and non-smokers
Højgaard 2015(4)	Comparison of smokers and non-smokers
Kinahan 2015(5)	Comparison of smokers and non-smokers
Ko 2019(6)	Cochrane review that did not meet the inclusion criteria for this review. Included studies were checked for inclusion in this review.
Miller 2013(7)	Comparison of smokers and non-smokers
Riechers 2020(8)	Comparison of smokers and non-smokers
Villaverde-Garcia 2016(9)	Systematic review not suitable for inclusion in this review. Included studies were not stated in this conference abstract and could not be checked for inclusion in this review.
Yarkan 2018(10)	Comparison of smokers and non-smokers

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Guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

Evidence review on b/tsDMARDs treatment and smoking cessation

BSR Guideline

Intervention evidence review

December 2020

Contents

1 b/tsDMARDs treatment and smoking cessation

1.1 In adults with psoriatic arthritis who are smokers and using b/tsDMARDs, what is the clinical effectiveness of giving up smoking versus continuing to smoke

1.2 INTRODUCTION

Smoking is thought to lessen the effectiveness of b/tsDMARD treatment in people with psoriatic arthritis. There are smoking cessation services offered by the NHS and this review seeks to assess whether smoking cessation is an effective strategy to support disease control.

1.3 PICO table

For full details, see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults with psoriatic arthritis who are smokers and using b/tsDMARDs
Intervention	Smoking cessation
Comparison	Continuing to smoke
Outcomes	**Critical** Generic • Mortality (dichotomous) • Quality of life including SF-36, PsAQoL (continuous) Arthritis • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) IBD • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) Psoriasis in those with psoriasis at baseline • Psoriasis score (PASI / IGA / BSA) (continuous) **Important** Arthritis • Radiological progression (continuous) Adverse Events • Serious adverse events (dichotomous) **The outcomes below are extracted if studies do not report ACR response.** • Psoriatic Arthritis Response Criteria (PSARC) (continuous) • PsARC score • Disease Assessment in PsA (continuous) • DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) • Health Assessment Questionnaire (HAQ) 0-3 (continuous), • Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)

Study design	Randomised Controlled Trials (RCT's)- inclusion and exclusion criteria as stated above If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders

1.4 Clinical evidence

1.4.1 Included studies

A literature search was conducted for studies comparing smoking cessation to continuing to smoke in people with psoriatic arthritis who are using biologic or targeted synthetic DMARDs. However no studies were found for inclusion in this evidence review.

1.4.2 Excluded studies

See **Table 4** in Excluded studies in the appendix.

1.5 The guideline working group's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The outcomes were assigned to cover the varied manifestations of psoriatic arthritis. Mortality, quality of life and disease activity outcomes, such as meeting the American College of Rheumatology 20/50/70 criteria and achieving minimal disease activity are critical outcomes. Furthermore, outcome measures to capture medication effects on other psoriatic disease domains, such as enthesitis, dactylitis, axial spondylarthritis, psoriasis, uveitis, and inflammatory bowel disease, which may not be present in all individuals with PsA.

Benefits and harms

No studies were included in the review. The group highlighted that there is registry data which indicates response rate and persistence of therapy appears to be improved by not smoking. Smoking is also known to exacerbate activity of co-morbidities. Therefore it made sense for the group to recommend people with PsA who are smokers should attempt to stop smoking.

There are specialist smoking cessation services available in the NHS that can provide expertise and ongoing support to people to stop smoking. The group agreed there was registry evidence while this benefits people specifically in terms of their PsA disease severity and treatment efficacy. In some trusts people can self-refer to these services.

The group discussed possible unintended consequences of recommending smoking cessation in smokers. It could lead to people being asked to stop smoking prior to starting b/tsDMARDs and is not what the group wish to recommend.

Cost effectiveness and resource use

Other factors the committee took into account

References

1. Kinahan CE, Mazloom S, Fernandez AP. Impact of smoking on response to systemic treatment in patients with psoriasis: A retrospective case-control study. British Journal of Dermatology. 2015;172(2):428-36.
2. Roelsgaard IK, Esbensen BA, Østergaard M, Rollefstad S, Semb AG, Christensen R, et al. Smoking cessation intervention for reducing disease activity in chronic autoimmune inflammatory joint diseases. Cochrane Database of Systematic Reviews. 2019;2019(9).
3. Schreiber K, Barnetche T, Combe BG, Morel J, Daien CI. Current and past smoking are associated with functional impairement and increased disease activity in axial spondyloarthritis: Systematic review and meta-analysis. Arthritis and Rheumatology. 2015;67.

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Appendix A: **Review protocols**

Table 2: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42021227541
1.	Review title	Smoking cessation and PsA
2.	Review question	In adults with psoriatic arthritis who are smokers and using b/tsDMARDs, what is the clinical effectiveness of giving up smoking versus continuing to smoke
3.	Objective	In adults with psoriatic arthritis who are smokers and using b/tsDMARDs, to determine clinical effectiveness of giving up smoking versus continuing to smoke
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	PsA is chronic, inflammatory, musculoskeletal disease associated with psoriasis.
6.	Population	Adults with psoriatic arthritis who are smokers and using b/tsDMARDs
7.	Intervention/Exposure/Test	Smoking cessation
8.	Comparator/Reference standard/Confounding factors	Continuing to smoke

9.	Types of study to be included	• Randomised Controlled Trails (RCT's)- inclusion and exclusion criteria as stated above • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders including sex, BMI, alcohol consumption, socioeconomic status, line of therapy
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Amongst adults with Psoriatic Arthritis what is the clinical impact on disease of smoking cessation. This may include clinical response amongst adults with active PsA who are commencing b/tsDMARDS or adults in remission established on b/tsDMARDS and the impact on developing secondary inefficacy/ time to flare
12.	Primary outcomes (critical outcomes)	<u>Generic</u> • Mortality (dichotomous) • Quality of life (continuous) <u>Arthritis</u>: American College of Rheumatology criteria (ACR). Achievement of 20%, 50%, 70% reduction in joint count, pain, global score and CRP. • ACR20 (dichotomous) • ACR50 (dichotomous) • ACR70 (dichotomous) • Minimal Disease Activity (MDA) (dichotomous) MDA (achievement of 5 of the following 7 criteria- tender joint count 1 or less, swollen joint count 1 or less, Body surface area 3% or less, patient pain VAS 15 or less, Patient global 20 or less, HAQ 0.5 or less, LEI 1 or less) <u>Enthesitis</u> • Presence/ absence of enthesitis (dichotomous) • Enthesitis score (LEI / (MASES / SPARCC) (continuous) Leeds Enthesitis Score- LEI- 0-6 Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES)- 0-13 Spondyloarthritis Research Consortium of Canada (SPARCC)- 0-16 <u>Dactylitis</u> • Dactylitis count 0-20 (continuous) • Presence or absence of dactylitis (dichotomous) <u>Axial Spondylarthritis</u> • Bath Ankylosing Spondylitis Disease activity Index (BASDAI)- 0-10 score ASAS 20/40/50/70 response (% of and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: Patient global assessment, Pain assessment, Function (BASFI), and Inflammation (last 2 questions of BASDAI).

		• ASAS20 (dichotomous) • ASAS40 (dichotomous) • ASAS50 (dichotomous) • ASAS70 (dichotomous) • Spinal Pain VAS- 0-100 (continuous) <u>Psoriasis</u> • Psoriasis score (PASI / IGA / BSA) (continuous) Psoriasis Area Severity Index (PASI)- 0-72 score Investigator Global Assessment (IGA)- (0-5) score Body Surface Area (BSA)- (0-100) score <u>Uveitis</u> • VRQol (continuous) • Visual acuity (continuous) • SUN scoring of inflammatory activity (continuous) • OCT scoring of macular oedema (continuous) • Topical or systemic steroid requirement (dichotomous) <u>IBD</u> • Induction of IBD remission (dichotomous) • Maintenance of IBD remission (dichotomous) • IBD clinical response (dichotomous) <u>Adverse Events</u> • Serious adverse events (dichotomous) Outcome timepoints are study defined.
13.	Secondary outcomes (important outcomes)	**<u>These outcomes are extracted if studies do not report ACR response criteria.</u>** <u>Arthritis</u> • Psoriatic Arthritis Response Criteria (PSARC) (continuous) PsARC score is composed of a joint count, the Patient Global Assessment (graded 0 to 5) and Physician Global Assessment (graded 0 to 5). PsARC requires improvement in at least two items with no worsening of any of them, improvement in joint counts defined as decrease by ≥30% and improvement in global assessment ≥1. • Disease Assessment in PsA (continuous) DAPSA score (0- no upper limit) (joint count, pain, global VAS and CRP) <u>Other outcomes</u> • Health Assessment Questionnaire (HAQ) 0-3 (continuous)

		• Pain VAS- 0-100 (continuous) • Global VAS 0-100 (continuous) • Physician VAS 0-100 (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form using MS Office software will be used to extract data from studies. Include if appropriate for your review: Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist. For Intervention reviews: • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	None
18.	Anticipated or actual start date	06/12/20
19.	Anticipated completion date	16/01/21
20.	Funding sources/sponsor	This systematic review is being completed by the British Society for Rheumatology. No private funding is sought or accepted for guideline work.
21.	Conflicts of interest	All guideline working group members must declare any potential conflicts of interest in line with the British Society for Rheumatology code of conduct and conflicts of interest policy prior to the guideline starting and new conflicts that arise during the development of the guideline.
22.	Details of existing review of same topic by same authors	This is not an update

23.	Details of final publication	https://www.rheumatology.org.uk/

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Appendix B: Literature search strategies

The literature searches for this review are detailed below.
For more detailed information, please see the Methodology.

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (ProQuest)	1946 – 10 December 2020	RCTs or observational studies
Embase (ProQuest)	1947 – 10 December 2020	RCTs or observational studies
The Cochrane Library (Wiley)	Cochrane Reviews: Issue 12 of 12, December 2020	None

Medline (ProQuest) and Embase (ProQuest) search terms

1 MESH.EXACT.EXPLODE("Arthritis, Psoriatic")
2 EMB.EXACT.EXPLODE("psoriatic arthritis")
3 TI,AB(Psoriasis or Psoriatic)
4 TI,AB(arthrosis or *arthritis)
5 S3 n/3 S4
6 S1 or S2 or S5
7 MESH.EXACT("Smoking Cessation") OR MESH.EXACT.EXPLODE("Tobacco Smoking") OR EMB.EXACT.EXPLODE("smoking") OR EMB.EXACT("smoking cessation")
8 TI,AB(smoke or smokes or smoking)
9 TI,AB(cigar or cigars or cigarette* or tobacco)
10 S7 OR S8 OR S9
11 TI(trial)
12 TI,AB(random* or factorial* or crossover* or cross over* or assign* or allocat* or volunteer* or placebo*)
13 TI,AB(doubl* n/1 blind*)
14 TI,AB(singl* n/1 blind*)
15 RTYPE(controlled clinical trial)
16 RTYPE(randomized controlled trial)
17 MESH.EXACT.EXPLODE("Clinical Trials as Topic")
18 EMB.EXACT.EXPLODE("crossover procedure")
19 EMB.EXACT.EXPLODE("single blind procedure")
20 EMB.EXACT.EXPLODE("randomized controlled trial")

21 EMB.EXACT.EXPLODE("double blind procedure")

22 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

23 S6 and S10 and S22

24 MESH.EXACT("Epidemiologic Studies") OR MESH.EXACT("Observational Study") OR MESH.EXACT.EXPLODE("Cohort Studies") OR MESH.EXACT("Controlled Before-After Studies") OR MESH.EXACT("Historically Controlled Study") OR MESH.EXACT("Interrupted Time Series Analysis") OR MESH.EXACT.EXPLODE("Case-Control Studies") OR MESH.EXACT("Cross-Sectional Studies") OR EMB.EXACT("clinical study") OR EMB.EXACT("observational study") OR EMB.EXACT("family study") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("prospective study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT("cross-sectional study")

25 TI,AB(cohort n/1 study or cohort n/1 studies or cohort n/1 analys* or cohort n/1 data)

26 TI,AB(follow up n/1 study or follow up n/1 studies or follow up n/1 data or observational n/1 study or observational n/1 studies or observational n/1 data or uncontrolled n/1 study or uncontrolled n/1 studies or uncontrolled n/1 data or non randomi?ed n/1 study or non randomi?ed n/1 studies or non randomi?ed n/1 data or epidemiologic* n/1 study or epidemiologic* n/1 studies or epidemiologic* n/1 data)

27 TI,AB(before n/2 after n/2 stud*)

28 TI,AB(longitudinal or retrospective or prospective or cross sectional)

29 TI,AB(study or studies or review or analys* or cohort* or data)

30 S28 and S29

31 S24 OR 25 OR S26 OR S27 OR S30

32 S6 AND S10 AND S31

33 S23 OR S32

Cochrane Library (Wiley) search terms

#1 MeSH descriptor: [Arthritis, Psoriatic] this term only

#2 arthrosis or *arthritis

#3 Psoriasis or Psoriatic

#4 #2 and #3

#5 #1 or #4

#6 MeSH descriptor: [Tobacco Smoking] explode all trees

#7 MeSH descriptor: [Smoking Cessation] explode all trees

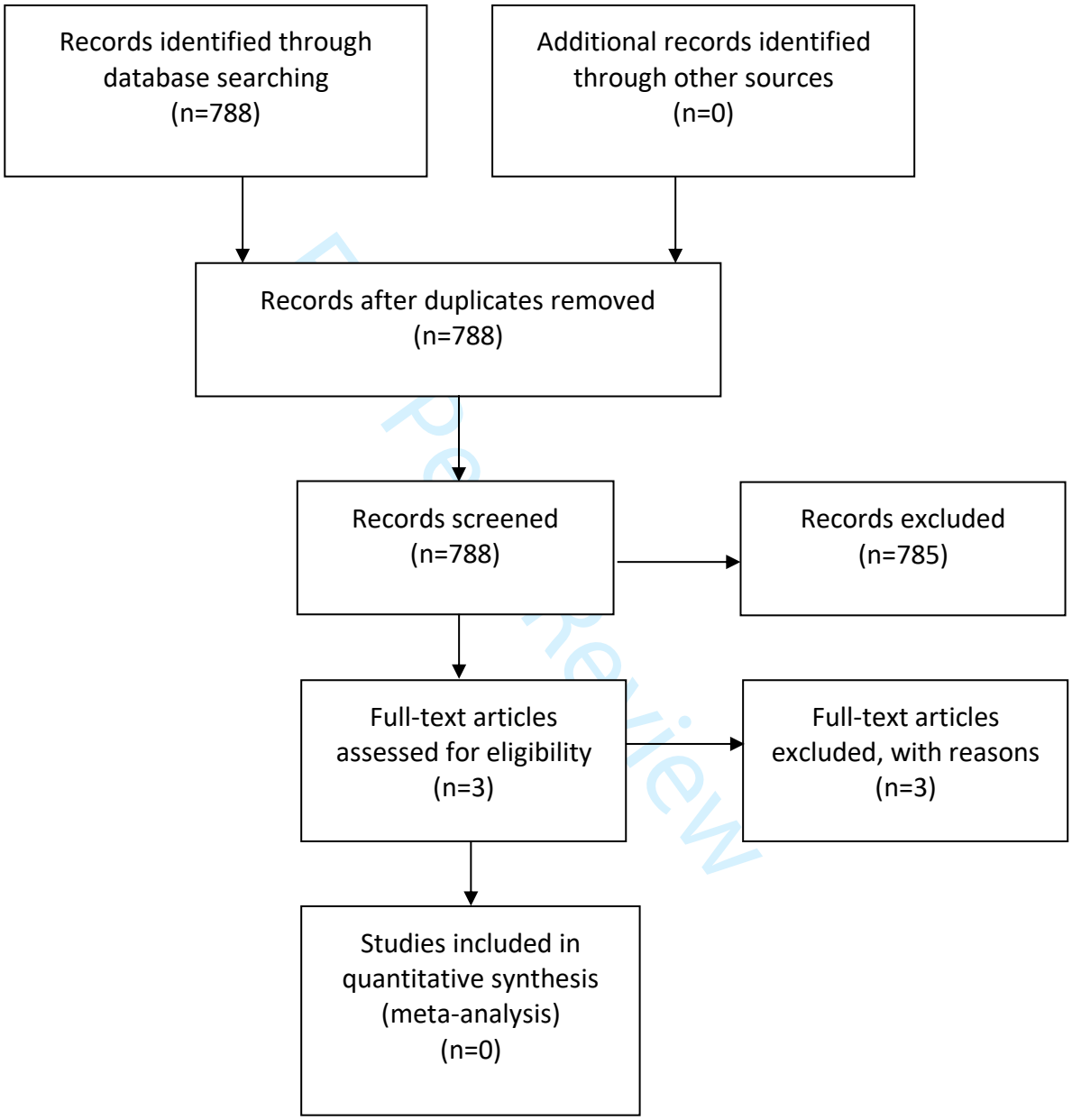
#8 smoke or smokes or smoking or cigar or cigars or cigarette* or tobacco

#9 #6 or #7 or #8

#10 #5 and #9

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection



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Appendix D: **Excluded studies**

Table 4: studies excluded from the evidence review

Study	Exclusion reason
Kinahan 2015(1)	Not a formal assessment of smoking cessation
Roelsgaard 2019(2)	Unable to access full text but the plain language summary indicated both included studies were in people with rheumatoid arthritis and would not be included in this review
Schreiber 2015(3)	Conference abstract detailing a systematic review not suitable for inclusion in this review. Included studies not stated and could not be checked for inclusion

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BSR guideline for psoriatic arthritis audit tool

The purpose of this audit tool is to ensure that the BSR psoriatic arthritis guideline criteria for biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARD) are being met. The tool is not intended to be an exhaustive representation of the guideline; the tool can be supplemented in order to address finer points of the guideline. The audit should be undertaken on a sample of all PsA patients attending clinic.

SECTION A		**YES**	**NO**	
1.	Does the patient have a diagnosis of PsA?			
2.	How long has the patient had PsA?			Number of years
3.	Does the patient have predominant/severe or high impact psoriasis?			If no, skip to Q5
4.	Has the patient been referred to/seen by dermatology?			
5.	Does the patient have peripheral arthritis?			
6.	Does the patient have dactylitis?			
7.	Does the patient have nail psoriasis?			
8.	Does the patient have predominantly axial disease?			If yes, please refer to BSR axSpA guideline audit tool
9.	Have comorbidities been assessed to address Practice Points?			
10.	If the patient smokes, have smoking cessation interventions been offered?			
11.	If the patient has an elevated BMI, have weight loss interventions been offered?			
SECTION B – peripheral disease		**YES**	**NO**	
1.	Has the patient been offered Treat to Target?			
2.	What was the first csDMARD prescribed?			
	• Methotrexate			
	• Leflunomide			
	• Sulfasalazine			
	• Ciclosporin			
	• Other			
3.	Was treatment target achieved?			If yes, go to Q24 If no, go to Q4
4.	What was the reason for failing the first DMARD?			
	• Inefficacy			
	• Raised LFTs			
	• Rash			
	• Other			
5.	Does the patient have any adverse prognostic indicators? Defined as at least three tender and three swollen joints or those with fewer joints and either poor prognostic markers or severe disease impact defined as ≥2 domains involved, extraarticular involvement or impaired quality of life.			If yes, go to Q9
6.	What was the second/other line of csDMARD prescribed?			
	• Methotrexate			
	• Leflunomide			
	• Sulfasalazine			
	• Ciclosporin			
	• Other			
7.	Was treatment target achieved?			If yes, go to Q24 If no, go to Q6
8.	What was the reason for failing the second DMARD?			
	• Inefficacy			

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	• Raised LFTs			
	• Rash			
	• Other			
9.	Has the patient been offered Treat to Target?			
10.	Was the patient eligible for b/tsDMARD therapy (≥3 Tender/ Swollen Joints)?			
11.	If active arthritis was (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i) offered?			
12.	If b/tsDMARD was TNFi, IL17i, or upadacitinib (UPA) considered ahead of IL12/23i or IL23i ahead of PDE4i ahead of CTLA4-Ig?			
13.	If active enthesitis was TNFi (IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i) offered?			
14.	If active dactylitis was (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i) offered?			
15.	If active axial disease and intolerance/ inadequate response to two NSAIDS, was TNFi or IL-17i offered or JAKi considered?			
16.	Was the patient prescribed a b/tsDMARD therapy?			If no, go to Q17 If yes, go to Q18
17.	Which b/tsDMARD therapy was prescribed?			
	• Adalimumab			
	• Etanercept			
	• Certolizumab			
	• Golimumab			
	• Secukinumab			
	• Ixekizumab			
	• Ustekinumab			
	• Guselkumab			
	• Tofacitinib			
	• Upadacitinib			
	• Apremilast			
	• Abatacept			
18.	Why was b/tsDMARD therapy not prescribed?			
	• Patient refused			
	• Previous cancer			
	• Infections			
	• Other			
19.	Was response to b/tsDMARD therapy assessed at 12/16 weeks?			
20.	Was PsARC assessment used?			
21.	Was treatment target achieved?			If no, go to Q23 If yes, go to Q24
22.	If partial response, was patient reassessed at 6 months?			
23	Have further lines of b/tsDMARD been offered without limit to previous lines of therapy and including those previously discontinued can be considered?			
24.	If the patient has achieved remission, has tapering/cessation of the csDMARDS been considered?			
25.	If the patient has achieved sustained remission, has dose optimisation/ tapering of b/tsDMARDS been considered?			

Abbreviations: PsA: Psoriatic Arthritis; Ps: Psoriasis; BSA: Body Surface Area; PASI: psoriasis area and severity index; PsARC: Psoriatic Arthritis Response Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: Visual analogue scale; b/tsDMARD: biologic and targeted synthetic disease-modifying anti-rheumatic drugs; CTLA4i: Cytotoxic T-lymphocyte-Associated antigen 4 inhibitor; IL12/ 23i, IL23i, IL17i: Interleukin 12/23, 23, 17 inhibitor; JAKi: Janus Kinase Inhibitor; PDE4i: Phosphodiesterase-4 inhibitor; Upa: Upadacitinib; TNFi: Tumour Necrosis Factor alpha Inhibitor.