Literature search algorithm

" 'Polyarteritis nodosa tocilizumab' " OR "polyarteritis nodosa tocilizumab" OR "polyarteritis nodosa" AND "tocilizumab" OR " 'polyarteritis nodosa treatment' " OR "polyarteritis nodosa treatment" OR "polyarteritis nodosa" AND "treatment". Similarly, the search strategy for patients with adenosine deaminase 2 deficiency treated with tocilizumab was formulated as: " 'Adenosine deaminase 2 deficiency tocilizumab' " OR "adenosine deaminase 2 deficiency tocilizumab" OR "adenosine deaminase 2 deficiency" AND "tocilizumab" OR " 'adenosine deaminase 2 deficiency treatment' " OR "adenosine deaminase 2 deficiency treatment" OR "adenosine deaminase 2 deficiency" AND "treatment".

Supplementary Table S1. Features of polyarteritis nodosa patients that are treated with tocilizumab.

Case Number (Reference)	Age, sex	Disease duration until tocilizumab treatment (months)	Clinical findings, organs and systems involved, laboratory parameters	Previous treatments	Dose, mode of administration of tocilizumab, concomitant treatment	Duration of tocilizumab treatment	Response to tocilizumab	Side effects
Paediatric Patients								
1 (15)	3, male (M)	9 months	Atypical Kawasaki disease(KD) like initial presentation: dry cracked lips, extremity changes very mild ectasia of coronary arteries, right epididymoorchitis, stiff neck (torticollis), bilateral vertebral artery vasculitis and accompanying neck muscle myositis), right forearm hypertrophy, tenderness and warmth (due to diffuse periosteal thickening with myositis and marked soft tissue involvement), in bone scan increased uptake in both forearms and right mid-tibia, C-reactive protein(CRP) between 51 and 90 mg/l, erythrocyte sedimentation rate (ESR) between 90-100 mm/hour(hr)	Intravenous immunoglobulin (IVIG), aspirin (ASA), nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoid (GC), infliximab (IFX)	Intravenous (IV) monthly tocilizumab (TOC), concomitant cyclophosphamide (CYC) and GC	7 months	Complete response- clinical improvement in arthritis, myositis, osteitis, epididymoorchitis, improvement in inflammatory markers and radiographic improvement in vasculitis	Not stated
2 (16)	8, female (F)	43 months	Constitutional symptoms (fever), painful erythematous nodules on extremities, skin biopsy of the nodule revealing necrotizing vasculitis, arthritis in ankles and knees bilaterally, positron emission tomography-computed tomography (PET/CT) revealed disseminated hot spots throughout the muscles and subcutaneous tissue of extremities, digital ischemia, peripheral neuropathy	GC, azathioprine (AZA), cyclosporine A (CSA), tacrolimus (TAC), IVIG, etanercept (ETA), adalimumab (ADA), IFX	8 mg/kg/2 weeks IV	7 months	Complete response- clinical improvement, disappearance of hot spots in extremity in the PET/CT scan at the 5th month of TOC, prednisolone stopped	No serious side effects
3 (17)	4, F	4 months	Fever, polyarthralgia, swelling of hands and feet, palpable nodules in legs, skin biopsy from a leg nodule showing a vasculitis of the medium-sized vessels suggestive for polyarteritis nodosa (PAN), cyanosis and progressive ischemia of the second to fifth right fingers and the second right toe, PET/CT revealed muscular, synovial and diffuse bone involvement, with hyper-fixation also of lymph nodes and subcutaneous nodules, panniculitis CRP:100 mg/L, ESR: 120 mm/hr,	GC, IVIG, methotrexate (MTX), CYC, AZA, IV alprostadil	8 mg/kg/2 weeks, IV (which was later changed to every 3 weeks, concomitant GC and AZA	21 months	Second and fifth fingers of right hand amputated, (before TOC was initiated) patient in complete response, AZA and GC discontinued	No serious side effects
4 (18)	15, M	Not stated	Skin, retina, lung, kidney, inner ear, brain, heart, gastrointestinal tract, biopsy demonstrated severe acute respiratory syndrome caused by coronavirus-2(SARS-CoV-2) positivity, CRP: 153 mg/L	GC, low molecular weight heparin (LMWH), hydroxychloroquine (HCQ), IVIG	Not stated	Not stated	Complete response	Not stated
5 (19)	8, M	1 month	Arthritis (initially monoarthritis then becomes migratory), fever, ischemic changes and blue discoloration of the pulp of second and fifth fingers on his right hand, skin biopsy confirmed the diagnosis of PAN, revealing active leukocytoclastic vasculitis with fibrinoid necrosis of medium- sized deep dermal and hypodermal vessels, antistreptolysin O: 2857 IU/mL, CRP: 57 mg/L	ASA, penicillin G benzathine for infectious trigger	Not stated, concomitant GC, MTX, LMWH	Not stated	Dramatic clinical response: initial discoloration threatened necrosis of the fingers and subcutaneous nodules but it resolved completely, a significant reduction in fever episodes and a marked improvement in joint pain and arthritis.	Not stated
Adult Patients								
6 (20, 21)	33, M	77 months	Multiple crural ulcers, intestinal perforation, hypertension, myalgia, weight loss (15 kg), AA amyloidosis in intestinal and renal biopsies, clinical suspicion of cardiac amyloidosis, Birmingham Vasculitis Activity Score (BVAS): 4, Vasculitis Damage Index (VDI):8	GC, CYC	8 mg/kg/ month, IV, concomitant GC	50 months	A relapse of myalgia and tender skin nodules at 4th month but treatment continued after GC dose is increased, at the end of 10th month clinical remission, stable renal and cardiac function, decrease in proteinuria, increase in albumin, final BVAS score: 3, final CRP: 1 mg/L, GC stopped	Hyperlipidaemia after 3rd month, which was successfully treated with rosuvastatin
7 (22)	28, M	Not stated	Arthritis, livedo reticularis, skin nodules with arteritis/fibrinoid necrosis, necrotic skin lesions of scrotum and calves, CRP: 160-300 mg/L	GC, MTX, AZA, IFX, ADA, rituximab (RIT), ETA, potassium iodide	Not stated	Not stated	Patient failed to respond to TOC. Then plasma exchange was performed for 3 weeks which was stopped due to central line sepsis. Patient was treated with GC and tofacitinib 2*10 mg to which he responded well, final GC dose was 10 mg/day of prednisolone.	Not stated
8 (23)	39, F	120 months	Necrotic purpura with small and medium vessel vasculitis on the deep skin biopsy, renal artery aneurysm, constitutional symptoms, myalgia, elevated CRP (between 59 and 126 mg/L)	GC, MTX, mycophenolate mofetil (MMF), CYC, IFX	8 mg/kg/4 weeks, IV, concomitant GC	12 months	Clinical remission, CRP decreased to 1 mg/L, final prednisolone dose is 5 mg/day	Not stated
9 (23)	52, F	96 months	Necrotic purpura, skin necrosis, bullous skin lesions, livedo, oral ulcers, arthritis. Deep skin biopsy demonstrating vasculitis of small and medium vessels. Multiple aneurysms in angiography of the right arm.	GC, colchicine, dapsone, MTX, CYC, AZA	8 mg/kg/4 weeks, IV, concomitant GC	12 months	Clinical remission, prednisolone dose tapered to 5 mg/day	Not stated

Case Number (Reference)	Age, sex	Disease duration until tocilizumab treatment (months)	Clinical findings, organs and systems involved, laboratory parameters	Previous treatments	Dose, mode of administration of tocilizumab, concomitant treatment	Duration of tocilizumab treatment	Response to tocilizumab	Side effects
10 (23)	35, M	3 months	Arthritis, myalgia, tenosynovitis, subcutaneous nodules, paraesthesia in the dominant hand, weight loss, PET/CT revealed multiple subcutaneous and intramuscular nodules, deep skin biopsy showed necrosis and inflammation of small and medium sized vessels, CRP was 393 mg/L	GC, IVIG	8 mg/kg/4 weeks, IV, concomitant GC	10 months	Clinical remission, prednisolone completely stopped. Tocilizumab dose spaced out to every 6 weeks	Not stated
11 (24)	67, M	6 months	Constitutional symptoms (fever, fatigue, loss of appetite, loss of 18 kg), myalgia, arthralgia, dysphagia, pain in upper and lower limbs, polyneuropathy, abdominal pain, nausea, vomiting, headache, diplopia, MR angiography of brain revealed typical vasculitis like lesions, tinnitus, dizziness, CRP: 20.3 mg/L	GC, CYC	162 mg/week, subcutaneous (SC), concomitant MTX 15 mg/week SC, GC	12 months	Clinical remission except residual dizziness, acute phase reactants normalised	Not stated
12 (25)	21, M	12 months,	Constitutional symptoms (fever, loss of 14 kg), myalgia, weakness of upper and lower limbs, CRP>300 mg/L, magnetic resonance imaging (MRI) revealed fasciitis of the forearm, arthritis and tenosynovitis of the wrist, PET/CT revealed inhomogeneous metabolic activity of the muscles, especially of the upper limbs, suspicious for myositis, livedo racemosa of the arms and legs with skin biopsy revealing panniculitis with vasculitis of the small- and medium-sized vessels, sensorimotor neuropathy demonstrated by electroneurography, severe calf pain with MRI demonstrating myositis of both lower legs, biopsy of the gastrocnemius muscle revealed a necrotizing vasculitis of the epimysial arteries and arterioles with ischemic damages of the muscle tissue. Patient initially had immunoglobulin A and mild immunoglobulin M deficiency but the workup for adenosine deaminase 2 deficiency was negative.	GC, MTX, ANA (anakinra), IVIG, CYC, RIT	-Initially 400 mg/4 weeks, IV, 1 month later increased to 800 mg/4 weeks, IV, then decreased to 680 mg/4 weeks IV, 2 months later increased to 800 mg/IV/4 weeks	25 months	Rapid and sustained clinical remission, electromyography (EMG) demonstrated significant improvement in sensorimotor neuropathy, prednisolone dose tapered to 5 mg/day	Upper respiratory tract infections
13 (10)	23, M	Not stated	Livedo racemosa, myalgias, fever, weight loss, sensorimotor polyneuropathy, subcutaneous nodules, CRP: 291 mg/L, initial BVAS:15	GC, MTX, RIT, CYC, ANA, IVIG	Initially: 8 mg/kg/4 weeks, IV, concomitant IVIG and GC, later 10 mg/kg/4 weeks IV and concomitant GC	37 months	Asymptomatic with sustained remission, prednisolone 4 mg/day, final CRP: 1 mg/L, final BVAS:0	No serious side effects
14 (10)	24, M	Not stated	Myalgias, fever, weight loss, arthritis, subcutaneous nodules, dropped hand (neuropathy), abdominal and flank pain, hypertension, increase of creatinine to 1.3 mg/dl, Renal angiography revealed renal artery aneurysms, MRI demonstrated generalised fasciitis CRP: 298 mg/L, initial BVAS: 27	GC, IVIG, CYC	Initially: 8 mg/kg/4 weeks IV, concomitant GC Later: 162 mg/week SC	11 months	Asymptomatic with sustained remission (normalised creatinine), final prednisolone dose 5 mg/day, final CRP:0.1 mg/L, final BVAS:0	No serious side effects
15 (10)	63, F	Not stated	Myalgia, fever, fatigue, weight loss, MRI revealed perivascular inflammation of the calves, PET/CT demonstrated vasculitis of medium and small vessels of the calves, initial CRP: 174 mg/L, initial BVAS: 3	GC	162 mg/week, SC, concomitant GC	6 months	Asymptomatic with sustained remission, final prednisolone dose:5 mg/day, final CRP: 0.3 mg/L, final BVAS:0	No serious side effects
16 (10)	70, F	Not stated	Myalgia, arthritis, livedo racemosa, sensorimotor polyneuropathy, MRI revealed myositis of both lower legs, initial CRP: 92.7 mg/L, initial BVAS:10	GC, MTX	8 mg/kg/4 week, IV, concomitant GC	13 months	Mild livedo racemosa but otherwise asymptomatic, final prednisolone dose: 5 mg/day, final CRP:0.3 mg/L, final BVAS:1	No serious side effects
17 (26)	70, F	56 months	Livedoid lesions and panniculitis in the lower extremities, skin biopsy demonstrated septal fibrosis in the subcutis and inflammatory changes compatible with PAN, myalgia, paraesthesia in the lower extremities with a neurophysiological study compatible with sensory axonal polyneuropathy, HbsAg negative, anti HBs and anti Hbc positive, CRP: 89.8 mg/L, BVAS score:5	GC, dapsone, AZA, MTX, mycophenolate mofetil (MPA)	8 mg/kg/month IV, concomitant GC, hepatitis B prophylaxis with tenofovir	14 months	Asymptomatic, without myalgia or neuropathic pain in lower extremities and without new skin lesions, final prednisolone dose:2.5 mg/day, final CRP: 1 mg/L, final BVAS:0	Neutropenia less than 1500 but more than 1000, TOC temporarily discontinued for 3 months
18 (27)	Not stated	Not stated	Cutaneous involvement	None	Not stated	Not stated	Complete response	Not stated
19 (28)	Not stated	Not stated	Coronary artery aneurysm with active inflammation demonstrated by PET/CT and deep skin involvement demonstrated by MRI	Not stated	Not stated	Not stated	Poor response, coronary aneurysm with increased inflammatory activity and deep skin involvement under tocilizumab	Not stated
20-29 (29)	Median age: 57 (42-74), 5 F, 5 M	Not stated	Cutaneous involvement (7 patients), Constitutional symptoms (6 patients), arthralgia or arthritis (8 patients), myalgia (2 patients), peripheral nervous system involvement (4 patients), kidney involvement (5 patients), gastrointestinal involvement (2 patients), ocular involvement (4 patients), cardiac involvement (1 patient), pulmonary involvement (1 patients), median BVAS before TOC: 6 (2-8)	GC (10 patients), CYC (IV:6 patients, oral 2 patients), AZA (3 patients), MTX (6 patients), MMF (1 patient), IVIG (2 patients)	Mode of administration not stated, all 10 pts received concomitant GC, 1 pt received concomitant MTX	29 (8–50) months*	-7 pts received TOC for refractory disease and 3 pts received TOC for relapsing disease -Remission in 5 pts, treatment failure in 3 pts, treatment discontinuation due to early adverse events in 2 pts before TOC efficacy could be evaluated -Median BVAS dropped to 0 (0-1.5) at 3 months, 0 (0-1) at 6 months and 0 (0) at 12 months -Median prednisolone dose dropped from 27.5 (11.5–62.5) mg/day to 12.5 (8–27.5) mg/day at 3 months, 8.5 (5.5–14.5) mg/day at 6 months and 5 (2.5–10) mg/day at 12 months	-Three pts experienced severe adverse events, including one patient with zoster infection and two patients with cytopenia (neutropenia and thrombocytopenia in one case each) leading to reduction of the dose -2 pts discontinued for early adverse events (testicular abscess and worsening renal failure)

* Median follow up of the entire PAN cohort treated with biologic agents is stated, the follow up duration specific for tocilizumab group is not stated.

Supplementary Table S2. Features of adenosine deaminase 2 deficiency patients that are treated with tocilizumab.

Case Number (Reference)	Age, sex	Disease duration until tocilizumab treatment (months)	Clinical findings, organs and systems involved, laboratory parameters and CECR1 gene mutations	Previous treatments	Dose, mode of administration of tocilizumab, concomitant treatment	Duration of tocilizumab treatment	Response to tocilizumab	Side effects
Paediatric patients								
1 (30, 31)	5, male (M)	Not stated	Phenotype similar to Castleman's disease: Fever, malaise, arthralgia, one transient episode of erythematous maculae, splenomegaly, generalised lymphadenopathy, anaemia, thrombocytosis, elevated CRP: 105 mg/l, elevated ESR: 89 mm/hour, hypergammaglobulinemia, positron emission tomography-computed tomography (PET/CT) revealed increased uptake in lymph nodes and spleen. Lymph node biopsy revealed atrophic germinal centres with an expanded mantle zone with preserved architecture and no plasmacytosis, homozygous for c.139G>A mutation of the cat eye syndrome critical region candidate 1 gene (CECR1)	Glucocorticoid (GC)	8 mg/kg/month IV, concomitant GC	48 months	Complete response, rapid, complete, persistent suppression of clinical and laboratory features, 4 years later when the tocilizumab interval was increased to 6 weeks, patient developed erythema nodosum in lower legs	Not stated
2 (32)	12, M	Not stated	Livedo racemosa, intracerebral haemorrhage, lymphopenia, low immunoglobulin M levels, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), highest CRP: 15 mg/l, homozygous for c.506C>T mutation of the CECR1 gene	GC, cyclophosphamide (CYC)	Not stated	2 months	Patient has recurrent stroke under tocilizumab, switched to adalimumab and in remission with adalimumab	Not stated
3 (33)	11, M	Not stated	Livedo racemosa, basal ganglia stroke, lymphopenia, low immunoglobulin M levels, elevated CRP and ESR, highest CRP: 32 mg/l, homozygous for c.506C>T mutation of the CECR1 gene	GC, azathioprine (AZA), methotrexate (MTX)	Not stated	Not stated	Patient converted to adalimumab once the sibling (Patient 8) has recurrent stroke under tocilizumab, patient in remission under adalimumab	Not stated
4 (33)	6 months, female (F)	3 months	Fever, erythematous rash (biopsy: interface dermatitis with predominant infiltration by neutrophils, no evidence of vasculitis), nonspecific lymphadenopathy, elevated CRP, c.984G>C and c.706_708CTAdel mutations of the CECR1 gene.	GC	Not stated, concomitant GC	Not stated	Although tocilizumab achieved apparent clinical remission, patient was switched to infliximab to avoid possible vascular complications. Patient was symptom free except mild erythema under infliximab.	Not stated
5 (12)	1, F	10 months	Fever, lower extremity rash (biopsy: fibrous hypertrophy accompanied with lymphocyte infiltration, digital necrosis of the fingers, anaemia, bone marrow aspiration: hyperactive myeloproliferation, with inverted ratio of granulocytes/erythrocytes, initial CRP: 49.98 mg/l, compound heterozygote for c.1211T>C and c.1114 G>A mutations of the CECR1 gene.	GC, intravenous immunoglobulin, (IVIG)	Not stated, concomitant GC	7 months	No response, patient developed right thalamic infarct and right central retinal artery occlusion, later treated with hematopoietic stem cell transplantation and is in remission.	Not stated
6 (34)	5, F	Not stated	Fever, oral aphthous lesions, erythema nodosum and livedo reticularis on lower limbs, arthritis, haemorrhagic stroke at left basal ganglia, right eye external oblique, abnormal gait, elevated CRP. 115 mg/l, elevated ESR: 74 mm/hour, compound heterozygote for c.254A>T and c.851G>T mutations of the CECR1 gene.	GC, colchicine, IVIG	Not stated	6 months	Disease relapsed under tocilizumab, patient switched to etanercept, in remission under etanercept	Not stated
7 (35)	17, M	Not stated	Fever, rash (livedo racemosa), renal infarction, intracranial haemorrhage, compound heterozygote for c.680A>G and c.1072G>A mutations of the CECR1 gene.	Fresh frozen plasma (FFP), CYC	Not stated	Not stated	Partial response, recurrent cerebral infarcts, patient later switched to adalimumab, complete response to adalimumab	Not stated
8 (36)	11, not stated	Not stated	Livedo racemosa, Castleman's disease phenotype, patient later developed central nervous system microbleed and testicular thrombosis, homozygous for c.139G>A mutation of the CECR1 gene.	Not stated	Not stated	Not stated	Not stated, the text only states that patient later developed central nervous system microbleed and testicular thrombosis, it is not clear whether these manifestations occurred under tocilizumab treatment.	Not stated
9 (37)	8, M	2 months	Fever, abdominal and limb pain, polyarthritis, erythema nodosum, right side peripheral facial palsy, bilateral thalamic infarcts, right side hemiparesis due to haemorrhagic left side stroke, elevated CRP and ESR, hypogammaglobulinemia, homozygous mutation c.1358A>G in exon 9 of CECR1 gene	None	Not stated, concomitant GC	Few months	Minimal response, patient later responded favourably to etanercept with disease activity stabilised and inflammatory markers decreased	Not stated
10 (38)	3, M	1 month	Fever, arthralgia, cervical lymphadenopathy, elevated CRP: 88.5 mg/l, ESR: 33 mm/hour, intermittent fever, abdominal pain responsive to elevated dose of GC, intractable hypertension and intestinal perforation (initially perceived as adverse effects of tocilizumab but later induced the clinicians to search for alternative diagnosis), compound heterozygote for c.737 G>C and c.827 T>C mutations of the CECR1 gene.	IVIG, nonsteroidal anti-inflammatory drug (NSAID), GC, MTX	8 mg/kg/ every 2-4 weeks, IV, concomitant GC, MTX, NSAID	14 months	Once GC dose is tapered, fever, arthralgia and elevated CRP levels occurred before each tocilizumab dose, later tocilizumab was discontinued and patient received a combination of thalidomide and adalimumab to which he responded favourably.	Severe asymptomatic hypertension but tocilizumab was continued with concomitant antihypertensives, later intestinal perforation occurred which led to discontinuation of TOC
11 (39)	1, F	Not stated	Fever, rash, gangrene of the fingers, anaemia, CRP:59.5 mg/l, ESR: 32 mm/hour, hypogammaglobulinemia, compound heterozygote for c.1337T>C and c.1240G>A mutations of CECR1 gene	GC	Not stated, concomitant GC	Not stated	No response, patient developed right central retinal artery occlusion, she later had a complete response to hematopoietic stem cell transplantation	Not stated
12 (39)	1, M	Not stated	Fever, rash, arthritis, ischemic stroke, intestinal haemorrhage and perforation, hypertension, hepatomegaly, hypogammaglobulinemia, anaemia, thrombocytosis, CRP: 33 mg/l, ESR: 44 mm/hr, compound heterozygote for c.916C>T, c.1069G>A mutations of CECR1 gene	NSAID, GC, MTX, cyclosporine A (CSA), IVIG	Not stated	Not stated	Partial remission, patient later received a combination of GC, tacrolimus and adalimumab and had a complete response	Not stated

Case Number (Reference)	Age, sex	Disease duration until tocilizumab treatment (months)	Clinical findings, organs and systems involved, laboratory parameters and CECR1 gene mutations	Previous treatments	Dose, mode of administration of tocilizumab, concomitant treatment	Duration of tocilizumab treatment	Response to tocilizumab	Side effects
13 (39)	1, F	Not stated	Fever, livedo racemosa, erythema nodosum, arthritis, haemorrhagic stroke and ischemic stroke, colitis, hepatomegaly, anaemia, CRP:44.3 mg/l, ESR: 74 mm/hour, hypogammaglobulinemia, compound heterozygote for c.380A>T and c.977G>T mutations of CECR1 gene.	GC, MTX, thalidomide, CSA, IVIG	Not stated	Not stated	No response, patient later received a combination of GC, MTX and adalimumab and had a complete response	Not stated
14 (39)	3.5, F	Not stated	Fever, rash (skin biopsy demonstrating vasculitis), arthralgia, haemorrhagic stroke, hepatosplenomegaly, anaemia, leukopenia, CRP: 15 mg/l, ESR: 99 mm/hour, hypogammaglobulinemia, c.143_144delinsT and c.97dupA mutations of CECR1 gene	NSAID, GC	Not stated	Not stated	No response, patient later treated with adalimumab and had a complete response	Not stated
Adult Patients								
15 (40)	22, M	Not stated	Fever, myalgia/arthralgia, livedo racemosa, erythema nodosum, necrotic ulcers, strabismus, myelofibrosis, AA amyloidosis (renal and intestinal), hepatosplenomegaly, pancreatitis, rheumatoid factor, antinuclear antibody, lupus anticoagulant positive, homozygous c.139G>A mutation in exon 2 of CECR1 gene	GC, CYC, FFP, IVIG	Not stated	Not stated	Failure, patient died due to necrotizing pneumonia, temporal relationship of pneumonia and tocilizumab is not stated.	Patient died due to necrotizing pneumonia but it is not clear whether he was under immunosuppressive effect of tocilizumab at that time

PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 2, "Search Strategy" section in Supplementary Materials section
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (*e.g.*, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 2
	10b	List and define all other variables for which data were sought (*e.g.*, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Not available
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2
Effect measures	12	Specify for each outcome the effect measure(s) (*e.g.*, risk ratio, mean difference) used in the synthesis or presentation of results.	Not available

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (*e.g.*, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not available
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not available
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not available
	13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not available
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (*e.g.*, subgroup analysis, meta-regression).	Not available
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results.	Not available
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not available
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 2-3 Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (*e.g.*, confidence/credible interval), ideally using structured tables or plots.	Supplementary Tables 1, 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 2, Table III
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (*e.g.*, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not available
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not available
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not available
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not available
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 5-7
	23b	Discuss any limitations of the evidence included in the review.	Page 6, Table IV
	23c	Discuss any limitations of the review processes used.	Page 6, Table IV
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not available
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	References section, Supplementary Tables 1, 2