Recommendations for the diagnosis and management of early rheumatoid arthritis

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INTRODUCTION

This supporting document provides a summary and grading of the evidence underpinning the recommendations outlined in the *Clinical guideline for the diagnosis and management of early rheumatoid arthritis* (www.racgp.org.au/guidelines/rheumatoidarthritis) and is intended to be read in conjunction with the guideline. The process used to develop these recommendations is outlined in full in the Process Report (*Appendix A*). Further information on the evidence presented in this report is available in the *Early rheumatoid arthritis: a literature review of recent evidence* (www.racgp.org.au/guidelines/rheumatoidarthritis/literaturereview) and in the guideline.

The recommendations are intended for adult patients aged over 16 years with early stage rheumatoid arthritis (RA) (disease duration of less than 2 years). Good practice points follow the evidence summary. These provide essential tips on how to effectively implement the recommendations. Unless otherwise referenced, the source for information presented in the good practice points is The Royal Australian College of General Practitioners (RACGP) Rheumatoid Arthritis Working Group (*Appendix B*). The Working Group supports all 30 recommendations and intends that they be used in conjunction with clinical judgement and patient preferences.

This project was supported by the RACGP and the Australian Department of Health and Aging (DoHA). The following experts were involved in the development of the guideline as part of the RACGP Rheumatoid Arthritis Working Group:

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The guideline has been endorsed by the National Health and Medical Research Council (NHMRC).

The RACGP Working Group recommends consulting the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information, including adverse effects.

NOTE: All website references were current at the time of publication.

Evidence sources

The evidence for the recommendations is based on:

1. A review of the literature through a systematic search for Level I evidence published from January 2000 to December 2006 (post-publication of the four primary guidelines).
2. Four existing international guidelines[1-4] that were identified from seven guidelines as being the most appropriate, recently published, high quality guideline to use as primary references. The guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.[5]
3. Additional manual literature searches.
4. The Working Group's expert opinion.

Primary reference guidelines

The Working Group assessed seven existing RA guidelines using the AGREE assessment tool[5] to select primary reference guidelines. Four international guidelines[1-4] were selected as the primary sources of information for the RA guideline. The AGREE scores for these guidelines are presented in *Table 1*. Reasons for selection were are follows:

- European League Against Rheumatism (EULAR). EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT).[1]
  The EULAR guideline was elected as a primary resource due to its high rigour of development and overall clarity.

- British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology. Guideline for the management of rheumatoid arthritis (the first 2 years).[3]
  The BSR guideline was selected because of overall high scoring on the AGREE tool, and specifically for its strong general practitioner focus, making this guideline particularly applicable to the project.

- Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis.[4]
  The SIGN guideline was selected because of its high rigour of development, high scores, and overall clarity based on research published up to mid 2000.

- Emery P, Suarez-Almazor M. Rheumatoid arthritis. Clinical Evidence 2003;(9):1349-71.[2]
  Rheumatoid arthritis was selected as a primary source on medications as it provided a comprehensive review of the pharmacological management of RA based on research published up to 2002.

Table 1. AGREE scores for identified guidelines (Shaded guidelines were selected as primary sources)

Guideline	AGREE domain scores					
	Domain 1. Scope and purpose	**Domain 2. Stakeholder involvement**	**Domain 3. Rigour of development**	**Domain 4. Clarity and presentation**	**Domain 5. Applicability**	**Domain 6. Editorial independence**
SIGN, 2000	**61%**	**58%**	**40%**	**75%**	**17%**	**8%**
Clinical Evidence, 2003	**64%**	**8%**	**86%**	**58%**	**33%**	**66%**
South African guidelines, 2003	44%	58%	24%	17%	0%	67%
Indian guidelines, 2002	11%	0%	4%	33%	0%	0%
ACR guidelines, 2002	8%	0%	4%	0%	22%	33%
EULAR, 2006	**72%**	**25%**	**52%**	**71%**	**0%**	**0%**
BSR, 2006	**72%**	**67%**	**52%**	**75%**	**83%**	**92%**

Literature review

The method used to conduct the evidence based literature review is outlined in full in the Process Report (*Appendix A*) and in *Early rheumatoid arthritis: a literature review of recent evidence* (www.racgp.org.au/guidelines/rheumatoidarthritis/literaturereview).

The literature review comprised a systematic search of MEDLINE, EMBASE, CINAHL and the Cochrane Library for English language publications. An additional manual search was used to identify evidence for interventions not represented in the initial search or not covered by the primary guidelines. Articles were also identified through review of reference lists of retrieved papers and research known to Working Group members. Papers were initially selected for inclusion based on reading the title and/or the abstract. Included literature relating to diagnosis of RA was limited to Level I to III evidence graded according to the *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*.[6] Included literature relating to management of RA was limited to Level I evidence. Papers that met the inclusion criteria were critically appraised using checklists developed by SIGN[7] and given an overall quality grade of high, moderate or low. Findings from the literature were reported descriptively and in a tabulated format presented in *Early rheumatoid arthritis: a literature review of recent evidence* (www.racgp.org.au/guidelines/rheumatoidarthritis/literaturereview).

Grading of the recommendations

Each recommendation has been graded from A to D according to the *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*[6] as outlined in *Table 2*. The grade reflects the degree of 'trust' that the clinician can place on the clinical application of the recommendation. Overall gradings were reached through consensus consideration of the grading for each component and each recommendation is supported by an evidence statement.

Table 2. Recommendation grades

A. Excellent evidence – body of evidence can be trusted to guide practice **B.** Good evidence – body of evidence can be trusted to guide practice in most situations **C.** Some evidence – body of evidence provides some support for recommendation(s) but care should be taken in its application **D.** Weak evidence – body of evidence is weak and recommendation must be applied with caution

The overall grade of each recommendation is based on a summation of an appraisal of individual components of the body of evidence on which the recommendation is based, including volume and consistency of the evidence. *Table 3* shows the body of evidence assessment matrix. It also lists all the components that were considered when assessing the evidence, together with the grades used.[6] The volume of evidence was defined to reflect the levels of evidence considered for this project (only Levels I and II evidence).

The overall grade of recommendation is based on a summation of the grading of individual components of the body of evidence assessment. In reaching an overall grade, recommendations did not receive a grading of A or B unless the volume and consistency of evidence components were both graded either A or B. Overall grades were reached through consensus consideration of the grading for each component listed below.

Table 3. NHMRC Body of evidence assessment matrix[6]

Component	**A**	**B**	**C**	**D**
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	Several Level I or Level II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review(SR)/multiple Level III studies with low risk of bias	Level III studies with low risk of bias or Level II studies with moderate risk of bias	Level IV studies or Level I–III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistencies may be explained	Some inconsistency reflecting genuine uncertainty around the clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalis-ability	Population(s) studied in body of evidence are the same as the target population for the guideline	Population(s) studied in the body of evidence are similar to the target population for the guideline	Population(s) studied in the body of evidence different to the target population for the guideline but it is clinically sensible to apply this evidence to the target population (eg. results obtained in adults that are clinically sensible to apply to children)	Population(s) studied in the body of evidence different to the target population for the guideline and hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to Australian health care context	Applicable to Australian health care context with few caveats	Probably applicable to Australian health care context with some caveats	Not applicable to Australian health care context

Limitations of the recommendations

Medication information

The literature search was not designed to retrieve safety trials for pharmacological interventions. The recommendations do not seek to provide full safety and usage information on pharmacological interventions. The pharmacological interventions outlined in the guideline should not be applied without consideration to the patient's clinical profile and personal preferences. The Working Group recommends consulting the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information including:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics.

Search date

The guideline is based on the best evidence available up to December 2006. Evidence published after this date has not been reviewed for the recommendations.

Interventions included

The search strategy was limited to include only papers graded as NHMRC Level I–III evidence for diagnosis of RA, and Level I evidence for management of RA. Other interventions, for example 'dietician referral' and 'complex multifaceted interventions' that may have been investigated using different study designs, are not represented in the guideline. The guideline is not intended to confirm or refute the effectiveness, nor provide guidance on the use of interventions that have not been included, as the evidence has not been reviewed.

Lack of evidence

For some interventions included in the recommendations there was limited evidence from which to draw conclusions on the intervention's effectiveness. The Working Group acknowledges that lack of evidence is not evidence of lack of effect, and has attempted to reflect this in the strength of the grading given to recommendations on interventions that are not supported. In addition, some interventions were not supported in the recommendations due to lack of evidence of effect. The Working Group acknowledges that this refers to lack of evidence of effect over placebo; that is, patients may receive some beneficial outcomes from the intervention but these do not exceed the beneficial effects that can be expected from a placebo therapy.

Commonly used abbreviations

ANA	antinuclear antibody
anti-CCP	anti-cyclic citrullinated peptide (antibody)
BMI	body mass index
BSR	British Society of Rheumatology
CI	confidence interval
COX-2	cyclo-oxygenase-2 selective inhibitors
CRP	C-reactive protein
DMARD	Disease modifying antirheumatic drug
EORA	Elderly onset rheumatoid arthritis
EPC	Enhanced Primary Care
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
GIT	gastrointestinal tract
GLA	gamma-linolenic acid
GP	general practitioner
HR	hazard ratio
LFT	liver function tests
MA	meta-analysis
MTX	methotrexate
NNH	number needed to harm
NNT	number needed to treat
NHMRC	National Health and Medical Research Council
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
OT	occupational therapy
PMR	polymyalgia rheumatica
RA	rheumatoid arthritis
RCT	randomised controlled trial
RhF	rheumatoid factor
RACGP	[The] Royal Australian College of General Practitioners
SMD	standardised mean difference
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TENS	transcutaneous electrical nerve stimulation
TNF	tumour necrosis factor
WMD	weighted mean difference

Additional resources

The *Clinical guideline for the diagnosis and management of early rheumatoid arthritis* (www.racgp.org.au/guidelines/rheumatoidarthritis) presents these recommendations, together with further information on implementation. Additional resources, as well as contact details for organisations providing services and support to people with RA, are included in the guideline.

Full details of the evidence presented in these recommendations is available in *Early rheumatoid arthritis: a literature review of recent evidence* (www.racgp.org.au/guidelines/rheumatoidarthritis/literaturereview).

The Process Report (*Appendix A*) outlines the full method used to develop these recommendations.

The RACGP Working Group recommends consulting the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information including:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics.

SUMMARY OF RECOMMENDATIONS

There is one recommendation indicating extreme caution: Recommendation 22 *Tripterygium wilfordii* (Chinese herb) (highlighted in **RED**).

Note: Most of the recommendations below have specific good practice points in the body of the guideline.

RECOMMENDATION 1 – EARLY DIAGNOSIS (Grade A)
General practitioners should diagnose RA as early as possible in order to optimise outcomes for patients.

RECOMMENDATION 2 – REFERRAL (Grade A)
General practitioners should refer patients to a rheumatologist if there is persistent swelling beyond 6 weeks, even if RA is not confirmed. Early referral enables aggressive intervention with disease modifying drugs, reducing long term joint damage and disability.

RECOMMENDATION 3 – CLINICAL EXAMINATION (Grade B)
General practitioners should base a diagnosis of RA (and differential diagnosis) on clinical examination in the first instance. A strong suspicion of RA is indicated by:

- the presence of persistent joint pain and swelling affecting at least three joint areas, and/or
- symmetrical involvement of the metacarpophalangeal or metatarsophalangeal joints, and/or
- morning stiffness lasting more than 30 minutes.

RECOMMENDATION 4 – DIAGNOSTIC INVESTIGATIONS (Grade A)
For patients presenting with painful and swollen joints, GPs should support clinical examination with appropriate tests to exclude other forms of arthritis and other differential diagnoses, and to predict patients likely to progress to erosive disease. Base investigations should include:

- erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)
- rheumatoid factor (RhF) and anti-cyclic citrullinated peptide (anti-CCP) antibody levels.

RECOMMENDATION 5 – MULTIDISCIPLINARY CARE (Grade B)
General practitioners should encourage and support a management approach that is based on individual patient need and involvement of a multidisciplinary team of health professionals.

RECOMMENDATION 6 – CARE PLANS (Grade B)
General practitioners should aim to engage patients with RA in individualised care plans that include treatment goals and objective measures of disease.

RECOMMENDATION 7– PATIENT INFORMATION (Grade B)
General practitioners should provide ongoing, tailored information to support patient understanding of their disease, treatment options, possible outcomes and their role in self management.

RECOMMENDATION 8 – PATIENT INFORMATION (Grade B)
General practitioners should encourage patients to seek appropriate information from relevant support agencies and encourage their participation in appropriate formal education opportunities according to their individual needs.

RECOMMENDATION 9 – PSYCHOSOCIAL SUPPORT (Grade C)
General practitioners should ensure access to appropriate psychosocial support for patients with RA, including support in managing relationship and sexuality issues.

RECOMMENDATION 10 – SLEEP (Grade D)
General practitioners should assess and manage sleep quality for patients with RA.

RECOMMENDATION 11 – SLEEP DISTURBANCES (Grade B)
General practitioners should consider the use of behavioural therapy, exercise, and tricyclic agents for early management of sleep disturbances.

RECOMMENDATION 12 – SIMPLE ANALGESICS (Grade B)
General practitioners should consider using simple analgesics (eg. paracetamol) where possible for pain relief in early arthritis.

RECOMMENDATION 13 – OMEGA-3 SUPPLEMENTATION (Grade A)
General practitioners should recommend omega-3 supplementation as an adjunct for management of pain and stiffness in patients with RA.

RECOMMENDATION 14 – GAMMA-LINOLENIC ACID SUPPLEMENTATION (Grade C)
General practitioners might recommend gamma-linolenic acid for potential relief of pain, morning stiffness and joint tenderness in RA patients.

RECOMMENDATION 15 – NSAIDS AND COX-2 INHIBITORS (Grade A)
General practitioners should consider using conventional non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 selective (COX-2) inhibitors for reducing pain and stiffness in the short term treatment of RA where simple analgesia and omega-3 fatty acids are ineffective.

RECOMMENDATION 16 – NSAIDS AND COX-2 INHIBITORS (Grade A)
General practitioners should apply caution when using traditional NSAIDs and COX-2 inhibitors. Choice of NSAIDs or COX-2 inhibitors should be based on consideration of the patient's specific needs, baseline risk profile and concomitant medication. The potential benefits need to be measured in relation to potential harms. Caution is particularly required in those at risk, such as the elderly or patients who have gastrointestinal, renal or cardiovascular comorbidities.

RECOMMENDATION 17 – DMARD THERAPY (Grade A)
General practitioners must facilitate early treatment with disease modifying antirheumatic drugs (DMARDs) for patients diagnosed with RA as well as for those with undifferentiated inflammatory arthritis who are judged to be at risk of developing persistent and/or erosive arthritis. Ideally, DMARD therapy should be initiated by a rheumatologist in light of the potential toxicity of these agents.

RECOMMENDATION 18 – DMARD THERAPY (Grade A)
If initiating DMARD therapy, GPs should use methotrexate as the first line choice, particularly when the disease is judged to be moderate to severe, or when there is a high risk of erosive disease.

RECOMMENDATION 19 – CORTICOSTEROIDS (Grade A)
General practitioners should consider short term, low dose, oral corticosteroid treatment when simple analgesics, omega-3 fatty acids, and NSAIDs or COX-2 inhibitors have failed to achieve symptomatic relief. This should be undertaken in consultation with a rheumatologist and with consideration of the patient's comorbidities and individual risk factors.

RECOMMENDATION 20 – CORTICOSTEROIDS (Grade B)
General practitioners should consider intra-articular corticosteroid injections for rapid symptomatic relief of inflammation in target joints, but no more than three injections per year for a specific joint.

RECOMMENDATION 21 – COMPLEMENTARY MEDICINES (Grade B)
General practitioners should inform patients about complementary medicines and the insufficient volume of evidence available on treating RA with these medicines. General practitioners should also inform patients of the potential adverse effects and interactions of these medicines.

RECOMMENDATION 22 – COMPLEMENTARY MEDICINES (TRIPTERYGIUM WILFORDII) (Grade B)
General practitioners should not recommend *Tripterygium wilfordii* (Chinese herb). While it may have beneficial effects on the symptoms of RA, it is associated with serious adverse effects (impaired renal function, haematotoxic and immunosuppressive effects, hair loss, diarrhoea and nausea).

RECOMMENDATION 23 – WEIGHT CONTROL (Grade B)
General practitioners should encourage dietary modification and weight control for all RA patients.

RECOMMENDATION 24 – EXERCISE (Grade C)
General practitioners should encourage patients with RA to engage in regular dynamic physical activity compatible with their general abilities in order to maintain strength and physical functioning.

RECOMMENDATION 25 – OCCUPATIONAL THERAPY (Grade B)
General practitioners should refer patients with RA experiencing limitations in function to a skilled occupational therapist for advice.

RECOMMENDATION 26 – OCCUPATIONAL THERAPY (Grade C)
Occupational therapy should be directed at assisting activities of daily living, including activities associated with work and leisure.

RECOMMENDATION 27 – FOOT CARE (Grade C)
General practitioners should support access to appropriate foot care for patients with RA.

RECOMMENDATION 28 – ALTERNATIVE PHYSICAL THERAPIES (Grade D)
General practitioners should inform patients about complementary and alternative physical therapies, particularly highlighting the insufficient volume of evidence that is available on treating RA with these therapies. General practitioners should also inform patients of the potential for adverse effects.

RECOMMENDATION 29 – DISEASE MONITORING AND COMORBIDITIES (Grade B)
General practitioners should be involved in monitoring disease progression, response to treatment, and comorbidities in conjunction with the treating rheumatologist and other members of the multidisciplinary team.

RECOMMENDATION 30 – DISEASE MONITORING AND COMORBIDITIES (Grade B)
Patients with RA should be assessed and treated for cardiovascular risk factors such as smoking, obesity, physical inactivity, hypercholesterolaemia, hypertension and diabetes.

FULL RECOMMENDATIONS

Diagnosis of rheumatoid arthritis

Early diagnosis and referral

EVIDENCE STATEMENT

There is substantial evidence that in RA, joint destruction begins within a few weeks of symptom onset and that early treatment decreases the rate of disease progression. The evidence points to a 'window of opportunity' to initiate treatment that will change the course of the disease. Recent evidence indicates that this window may be as little as 3–4 months.[1] Therefore, it is important to diagnose the disease and initiate disease modifying therapy as soon as possible.

The EULAR guideline[1] stresses the importance of early referral (grade of recommendation B). The SIGN guideline[4] also supports early referral and early DMARD therapy (grade of recommendation B).

The BSR[3] and EULAR[1] guidelines[1] stress that a lack of precise diagnostic criteria means that patients with undifferentiated inflammatory arthritis and strong predictors of persistence would be candidates for receiving DMARD therapy.

It is the consensus of the RACGP Working Group to recommend that patients with symptoms indicative of RA that persist beyond 6 weeks be referred to a rheumatologist to enable early initiation of DMARD therapy.

A recent article, identified after the search timeframe and not subjected to critical appraisal, reported on a validation study of a prediction rule for development of RA among patients presenting with recent onset undifferentiated arthritis. A weighted score was generated for the following factors (ie. predictive power): positive anti-CCP antibody (2 pts); involvement of joints in both upper and lower extremities (1.5 pts); CRP ≥51 mg/L (1.5 pts), ≥11 tender or swollen joints (1 pt each); ≥60 minutes of morning stiffness (1 pt); positive RhF (1 pt); and female gender (1 pt). A score of ≥8 accurately predicted the risk of developing RA in 97% of individuals when tested in independent data collections. A score of ≤6 meant that it was possible to accurately reassure 83% of patients that they would not develop RA.[8]

	Component	Descriptor	Grade
Three international guidelines[1,3,4] with high AGREE scores that include a hierarchy of evidence, in descending order by study design, from meta-analyses (MAs) of randomised controlled trials (RCTs) to expert opinions	Volume of evidence	Excellent	A
The consistency of evidence is excellent and there is Working Group consensus	Consistency	Excellent	A
Potentially significant impact on disease progression and long term outcome if RA can be promptly diagnosed in primary care and appropriate referrals made to enable early commencement of DMARD therapy. Untreated, 20–30% of persons with RA become permanently work disabled within 2–3 years of diagnosis	Clinical impact	Excellent	A
The studies are directly generalisable to the Australian population with few caveats. Because access to GPs and RA management is not widely available in rural and remote areas, Aboriginal and Torres Strait Islander populations may be disadvantaged	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATIONS	GRADE
General practitioners should diagnose RA as early as possible in order to optimise outcomes for patients.	**A**
General practitioners should refer patients to a rheumatologist if there is persistent swelling beyond 6 weeks, even if RA is not confirmed. Early referral enables aggressive intervention with disease modifying drugs, reducing long term joint damage and disability.	**A**

Good practice points

- Refer to a rheumatologist immediately when there are many swollen joints, particularly if tests for RhF and/or anti-CCP antibody are positive.
- If access to a rheumatologist is not possible, contact one by telephone to discuss appropriate treatment.

History and clinical examination

EVIDENCE STATEMENT

Guidelines[1,3,4] and the RACGP Working Group concur that diagnosis of RA should be based primarily on careful history taking and clinical examination. Patients commonly present with pain and stiffness in multiple joints. RA should be particularly suspected in patients who present with: persistent joint pain and swelling affecting at least three joint areas; symmetrical involvement of the metacarpo-phalangeal or metatarso-phalangeal joints; and/or morning stiffness lasting more than 30 minutes (grade of recommendation C,[3] grade of recommendation B[1,4]). Systemic flu-like symptoms are also common.[4] In most patients, symptoms emerge over weeks to months.

The BSR guideline[3] stresses that a lack of precise diagnostic criteria means that patients with undifferentiated inflammatory arthritis and strong predictors of persistence would be candidates for early referral to a rheumatologist and commencement of DMARD therapy.[3]

The number of swollen/tender joints is an indicator of potentially serious progressive disease.[1,3,4] The number of swollen joints correlates better with radiographic progression than the number of tender joints.[1]

Rheumatoid arthritis can resemble any disorder causing acute or chronic polyarthritis. Elimination of other diseases is therefore a necessary step in RA diagnosis.[1,3,4]

	Component	Descriptor	Grade
Three international guidelines[1,3,4] with high AGREE scores that include a hierarchy of evidence, in descending order by study design, from MAs of RCTs to expert opinions	Volume of evidence	Good	B
The consistency of evidence is excellent and there is Working Group consensus	Consistency	Excellent	A
Potentially significant impact on long term outcome and adverse events if history taking and clinical examination result in proper early diagnosis and treatment of RA	Clinical impact	Excellent	A
Although directly generalisable to the Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATION	GRADE
General practitioners should base a diagnosis of RA (and differential diagnosis) on clinical examination in the first instance. A strong suspicion of RA is indicated by: • the presence of persistent joint pain and swelling affecting at least three joint areas, and/or • symmetrical involvement of the metacarpo-phalangeal or metatarso-phalangeal joints, and/or • morning stiffness lasting more than 30 minutes.	**B**

Diagnostic investigations

EVIDENCE STATEMENT

The diagnosis of RA requires a number of tests. The following tests are useful in increasing diagnostic certainty, excluding other forms of arthritis, predicting patients likely to progress to erosive disease, and monitoring disease progression. However, no single test accurately diagnoses RA.

Erythrocyte sedimentation rate and CRP indicate an inflammatory process but have low specificity for RA. One or other of these tests is usually performed (grade of recommendation C[1]).These markers are usually elevated in RA, but may be normal. A high ESR or CRP level independently predicts long term radiographic progression. They may be useful in monitoring disease activity and response to treatment.[4]

The RhF test is not conclusive and may indicate other chronic inflammatory diseases (false positive). It may not show as seropositive in some RA cases (false negative). RhF is positive in 60–70% of RA patients. However, when present in combination with other factors, especially anti-CCP antibodies, the level of RhF indicates the severity of the disease.[1] The anti-CCP antibody test is a relatively new and useful test, especially in early diagnosis of early RA. Recent research indicates that the test has similar sensitivity to RhF but considerably higher specificity, and is a strong predictor of progression to erosive disease. The DerSimonian-Laird random effects method[9] summarises sensitivities, specificities, and positive and negative likelihood ratios from 37 studies of anti-CCP antibodies and 50 studies of RhF. The pooled sensitivity, specificity, and positive and negative likelihood ratios for anti-CCP antibodies were 67% (95% CI: 62–72%), 95% (95% CI: 94–97%), 12.46 (95% CI: 9.72–15.98), and 0.36 (95% CI: 0.31–0.42), respectively. For immunoglobulin M (IgM) RhF**,** the values were 69% (95% CI: 65–73%), 85% (95% CI: 82–88%), 4.86 (95% CI: 3.95–5.97) and 0.38 (95% CI: 0.33–0.44). Likelihood ratios among IgM RhF, IgG RhF and IgA RhF seemed to be similar. Results from studies of patients with early RA were similar to those from all studies. Three of four studies found that risk for radiographic progression was greater with anti-CCP antibody positivity than with IgM RhF positivity.

Anti-CCP antibody research implies a potential role for this test in identifying patients with a high risk of progressive disease who may benefit from early aggressive treatment and thus early referral to a rheumatologist. A good quality MA[9] of studies conducted between 1987 to 2006 that involved a total of 30 235 participants compared the accuracy of anti-CCP antibodies and RhF as markers in the diagnosis and prognosis of RA. The authors concluded that the presence of anti-CCP antibodies is more specific than RhF for diagnosing RA and early RA. They support inclusion of anti-CCP antibody positivity among the diagnostic criteria for these conditions. There is a role for anti-CCP antibody testing in the standard evaluation of early inflammatory polyarthritis, to achieve early accurate diagnosis of RA and in turn support early intervention with DMARD therapy. Both EULAR and the RACGP Working Group support measuring RhF and anti-CCP antibody levels in every patient presenting with early arthritis.

A full blood count (FBC) test is usually undertaken to provide general information relating to inflammation and anaemia and is useful as prognosis indicator. (Working Group)

Plain X-rays of hands and feet have been key investigations in identifying erosions and predicting disease; however, erosions are not often apparent in disease of less than 3 months duration. Serial

X-rays over years may show disease progression and therefore indicate need for change in treatment strategy. EULAR suggests that in very doubtful cases, ultrasound, power Doppler and magnetic resonance imaging (MRI) might be helpful to detect synovitis.[1]

The RACGP Working Group suggests using plain X-rays as prognosis indicators and for monitoring of disease progression.

The antinuclear antibody (ANA) test may be useful in distinguishing between RA and lupus and should be used for differential diagnosis. Some RA patients with severe disease do test positive for ANA, so other criteria should be applied to determine an accurate diagnosis of RA.

The EULAR guideline[1] (grade of recommendation C) recommends that in every patient presenting with early arthritis, the following factors predicting persistent and erosive disease should be measured: number of swollen and tender joints; ESR or CRP; levels of RhF and anti-CCP antibodies; and radiographic damage. It further suggests that the diagnostic procedure to differentiate RA from other diseases may also include tests for uric acid and Lyme disease, parvovirus infection, urethral or cervical swab cultures, antibacterial serology, tests for hepatitis B or C, or chest X-ray, according to the context and the country.

The RACGP Working Group also suggests the use of synovial fluid analysis, including cell count, differential count, multiple chemical sensitivity, and crystal deposition.

	Component	**Descriptor**	**Grade**
Two international guidelines[1,4] with high AGREE scores and a good quality MA[9] of 37 studies supporting the use of anti-CCP antibody tests	Volume of evidence	Excellent	A
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially large clinical impact with reduction in adverse effects if appropriate diagnostic investigations are used to diagnose RA	Clinical impact	Excellent	A
Although directly generalisable to the target population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATION	**GRADE**
For patients presenting with painful and swollen joints, GPs should support clinical examination with appropriate tests to exclude other forms of arthritis and other differential diagnoses, and to predict patients likely to progress to erosive disease. Base investigations should include: • ESR and/or CRP • RhF and anti-CCP antibody levels.	**A**

Good practice points

- Absence of any key symptoms, signs or test results does not necessarily rule out RA.
- Depending on the clinical picture, additional investigations may be required to eliminate other causes of presenting symptoms. These may include FBC, urinalysis, plain X-rays of hands and feet, ANA and others according to the context and patient history.

General management of rheumatoid arthritis

Multidisciplinary care and care planning

EVIDENCE STATEMENT

There is strong support from the existing guidelines[3,4] that the successful, timely management of patients with RA depends on the involvement of a range of health care professionals, according to the individual patient's needs. These health care professionals include, but are not limited to, GPs, rheumatologists, physiotherapists, occupational therapists, pharmacists, psychologists, dieticians, and social workers. National strategic health policy has given increased recognition to the importance of chronic disease management (CDM). There are a number of recent Federal Government initiatives for the prevention or delay in onset, early detection, and evidence based management of chronic disease, including RA. The role of multidisciplinary input in the management of chronic disease is highlighted throughout CDM policy, with focus on improving capacity, effectiveness and efficiency of multidisciplinary collaboration.[10]

The BSR guideline[3] emphasises the importance of ongoing involvement of both primary and secondary care in the long term management of patients with RA, particularly in view of the multisystem involvement of RA as the disease progresses. The guideline recommends primary care physicians remain closely involved in the care of these patients and be responsible for their general health, particularly with regard to cardiovascular risk. The role of the primary care physician also includes encouraging patients to exert more control over their disease and disease management.

The RACGP Working Group agrees that the GP, rheumatologist and multidisciplinary team should aim to engage the patient in an individualised care plan, agreeing on treatment goals that include an objective measure of disease.

	Component	**Descriptor**	**Grade**
Two international guidelines[1,4] with high AGREE scores	Volume of evidence	Good	B
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Satisfactory clinical impact with reduction in adverse effects if patients receive multidisciplinary input from appropriately trained health care providers according to individual need	Clinical impact	Satisfactory	C
Although directly generalisable to the target population with few caveats, multidisciplinary teams trained in RA management are not widely available in Australia, particularly in rural and remote areas. In addition, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the interventions	Generalisability	Satisfactory	C
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATIONS	GRADE
General practitioners should encourage and support a management approach that is based on individual patient need and involvement of a multidisciplinary team of health professionals.	**B**
General practitioners should aim to engage patients with RA in individualised care plans that include treatment goals and objective measures of disease.	**B**

Good practice points

- Each person with RA should be cared for by more than one health professional.
- GPs may utilise Enhanced Primary Care (EPC) items to facilitate access to appropriate services (www.health.gov.au/epc). Eligible services include, but are not limited to, those provided by occupational therapists, physiotherapists, hand therapists, nurses, podiatrists, psychologists, mental health workers, Aboriginal health workers, chiropodists and exercise physiologists.
- Consider referral to a consultant pharmacist for a Home Medicine Review (Item 900).

Patient information and education

EVIDENCE STATEMENT

While evidence of the impact of patient information and education remains limited, all guidelines[1,3,4] and the RACGP Working Group agree that they represent important aspects of the general management of RA. Providing patient information and education should be encouraged among all members of the multidisciplinary team.

The EULAR[1] guideline cites evidence that education programs, aimed at helping patients to cope with pain and disability and to maintain work ability and general functionality, may be employed successfully as an adjunct intervention (grade of recommendation B). The BSR[3] guideline stresses that patient education needs to be individually tailored in terms of content and format and should be delivered at various times during the course of the disease[3] (grade of recommendation A).[3] This guideline also recommends a cognitive behavioural approach to patient education in order to promote long term adherence to management strategies (grade of recommendation C).[3] It further identifies psychological issues as likely to be important in determining how receptive patients are to education opportunities to learn about their disease.[3]

The EULAR[1] guideline cites three RCTs which demonstrate that written information may increase knowledge about disease.

Self management programs are designed to give patients more control over their chronic condition and make more efficient use of the primary and secondary care services in place to support them. Evidence from EULAR[1] shows that self management education programs can result in improved clinical outcome in RA patients, producing short term effects on disability and joint count, as well as on patient global assessment, anxiety and depression, but without any evidence of long term benefit (grade of recommendation B).[1]

The BSR[3] guideline cites a Cochrane review[11] that assessed the effectiveness of patient education interventions on health status (pain, functional disability, psychological wellbeing and disease activity) in patients with RA. They included 31 RCT studies with relevant data and found significant effects of patient education at first follow up for scores on disability, joint counts, patient global assessment, psychological status and depression. A trend favouring patient education was found for scores on pain. Physician global assessment was not assessed in any of the included studies. The dimensions of anxiety and disease activity showed no significant effects. At final follow up (3–14 months), no significant effects of patient education were found, although there was a trend favouring patient education for scores on disability.

There is also evidence that RA patients should be helped to contact support organisations (grade of recommendation B).[3] Patients with RA should be provided with a plan of care from diagnosis that outlines the principles of management, including a commitment to training patients to self manage

some aspects of their disease (grade of recommendation B).[3]

Overall, patient education seems to have only small short term effects on disability, joint counts, patient global assessment, psychological status and depression; there is no evidence of long term benefits in adults with RA. However, education plays a role in terms of patient knowledge gain, improved self confidence, desirable behaviour and improved functional status.

	Component	Descriptor	Grade
Three international guidelines[1,3,4] with high AGREE scores and a Cochrane review[11] with 31 RCTs	Volume of evidence	Excellent	A
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially a good clinical impact directly associated with the use of patient education for RA patients. There may also be a small psychological benefit that may translate to larger population effect	Clinical impact	Good	B
The RA population is relevant to the Australian context; however, the treatment may not be widely available. Also, the quality of patient education cannot be guaranteed. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Satisfactory	C
Although the guidelines used as primary sources for this guideline were not produced in Australia, it is probably applicable to the Australian health care context with some caveats	Applicability	Satisfactory	C

RECOMMENDATIONS	GRADE
General practitioners should provide ongoing, tailored information to support patient understanding of their disease, treatment options, possible outcomes and their role in self management.	**B**
General practitioners should encourage patients to seek appropriate information from support agencies and encourage their participation in appropriate formal education opportunities according to their individual needs.	**B**

Good practice points

- Joint protection, energy conservation and problem solving skills training should be taught early on in the disease course.
- GPs can access medication information for patients from the Australian Rheumatology Association's website (www.rheumatology.org.au) or refer patients to the website.
- Referral to Arthritis Australia is recommended for general disease and treatment information, as well as support services (www.arthritisaustralia.com.au).
- Lifestyle advice should be given to all RA patients to encourage smoking cessation, dietary modification, weight control and exercise.

Psychosocial support

EVIDENCE STATEMENT

Given the potential for disability and reduction in quality of life, psychological and social support is considered an important aspect of the assessment and management of RA. Such support is required early in the disease, in terms of coping with the diagnosis, and throughout disease progression as the impact of the disease becomes more evident.

Among the four primary guidelines, this aspect is only well addressed by the BSR.[3] The BSR[3] guideline identifies a shared role for all members of the multidisciplinary team in providing guidance on coping with the disease and encouraging positive attitudes toward self management and adjustment to the diagnosis of RA. It recommends that individuals should have social and psychological support to help them to stay at work and participate in normal activities of living. This may be accessed through a range of means, including via patient based support agencies. The BSR guideline[3] identifies evidence (though not high levels of evidence) for the effectiveness of support initiatives such as telephone help lines and the involvement of rheumatology nurses.

The BSR guideline[3] also makes a specific recommendation regarding the need to address sexuality and relationship issues with RA patients, identifying that health care professionals should provide opportunities to discuss these issues and refer patients for appropriate support (grade of recommendation C).[3] Health care professionals should be alert to issues such as the impact of pain, dysfunction and dependence on relationships and self esteem.

A considerable body of literature relating to chronic disease in general is relevant to this area but has not been included in this literature review.

	Component	Descriptor	Grade
One international guideline[3] with high AGREE score	Volume of evidence	Satisfactory	C
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
There is potentially a good clinical impact on the ability of RA patients to cope with their disease if psychosocial issues can be appropriately assessed and managed	Clinical impact	Good	B
Although directly generalisable to the Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATION	GRADE
General practitioners should ensure access to appropriate psychosocial support for patients with RA, including support in managing relationship and sexuality issues.	**C**

Good practice points

- Utilise EPC items to facilitate access to appropriate services (www.health.gov.au/epc). Eligible services include psychologists and mental health workers.
- Utilise Mental Health Care items (www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pcd-gp-mental-health-care-medicare).
- Refer patients to Arthritis Australia for information and services relating to psychosocial support (www.arthritisaustralia.com.au).

Sleep patterns and fatigue

EVIDENCE STATEMENT

The BSR guideline[3] identifies sleep disturbance as a common feature of RA, particularly during disease flares. Fatigue is also found to be a significant problem. A full review of the literature relevant to this consensus recommendation was not undertaken.

BSR[3] recommends that health providers give consideration to the impact of fatigue on the quality of life in early RA. The guideline cites a survey in which 40% of patients reported severe fatigue. The BSR recommends that the sleep patterns of patients with RA be specifically assessed (grade of recommendation A) and that early management of sleep disturbance may include behavioural therapy and the use of exercise (grade of recommendation B).[3]

The BSR guideline[3] also recommends the consideration of tricyclic agents in sleep management for patients with RA. Antidepressants may be used to improve symptoms and quality of life in patients with chronic pain (particularly pain impacting upon sleep quality) in conjunction with other pharmacological management. Tricyclic agents are recommended as the first choice of antidepressants for use in pain management.[3,12] A good quality SR[12] of 77 RCTs and 12 MAs provided support for the use of tricyclics in managing pain impacting upon sleep in patients with RA. In an analysis of the general analgesic effects of antidepressants that included two previous SRs (98 RCTs), the authors reported that the analgesic effects of tricyclics are independent of antidepressant effects and superior to selective serotonin re-uptake inhibitors. Sub-analysis of results reported from eight good quality, placebo controlled RCTs specifically in populations with inflammatory rheumatic diseases including RA supported these findings. The authors of the SR provide a number of recommendations for using tricyclic agents, including initiating therapy at the lowest dose; increasing to the maximum tolerable dose or minimal effective dose (whichever is lower); maintaining therapy for at least 4 weeks before assessing efficacy; and gradually decreasing the dose after 3–6 months of symptom remission and regular pain assessment.[12]

It is the opinion of the RACGP Working Group that monitoring sleep patterns and fatigue is important in the management of RA. The Working Group recommends consulting the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information, including adverse effects.

	Component	Descriptor	Grade
One international guideline[3] with high AGREE score and one good quality SR[12] of 12 MAs and 77 RCTs	Volume of evidence	Good	B
The consistency of evidence is good and there is consensus among the expert group	Consistency	Good	B
There is potentially a significant clinical impact on RA disease symptoms if sleep is appropriately assessed and managed	Clinical impact	Good	B
Although directly generalisable to the general Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Island populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATIONS	GRADE
General practitioners should assess and manage sleep quality for patients with RA.	**D**
General practitioners should consider the use of behavioural therapy, exercise and tricyclic agents for early management of sleep disturbances.	**B**

Good practice points

- Refer patients to Arthritis Australia for information and services relating to sleep (www.arthritisaustralia.com.au) or to Sleep Disorders Australia (www.sleepoz.org.au).
- Initiate tricyclic therapy at the lowest dose and gradually increase to the maximum tolerable dose or minimal effective dose (whichever is lower).
- Maintain tricyclic therapy for at least 4 weeks before assessing efficacy of treatment.
- After 3–6 months of symptom remission, gradually decrease the dose with regular pain assessment.

Pharmacological interventions for rheumatoid arthritis

Before commencing pharmacological interventions check drug sensitivities.

The RACGP Working Group recommends consulting the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information, including adverse effects.

Simple analgesics (eg. paracetamol)

EVIDENCE STATEMENT

The use of simple analgesia is accepted in managing pain in early RA; however, only a small number of patients receive sufficient pain relief from simple analgesia alone.[4] There is some evidence supporting the effectiveness of simple analgesia for RA;[4,13] however, much of the evidence is old and contains methodological weaknesses.[13] Paracetamol has an excellent safety profile and remains the analgesic of choice, particularly in mild to moderate pain. Around the clock pain control depends on taking adequate doses regularly.[14] The recommended dose for immediate release paracetamol is 500–1000 mg at 4–6 hourly intervals to a maximum of 4 g/day.[14]

In established RA, both conventional NSAIDs and COX-2 inhibitors are more effective than simple analgesics in relieving the signs and symptoms of active disease.[1,13] However, this must be balanced against potential gastrointestinal, renal and cardiovascular side effects of NSAIDs and COX-2 inhibitors. Simple analgesics can be added safely to more specific anti-inflammatory medication and may enable a reduction in the dose of NSAIDs required.[14]

The RACGP Working Group recommends that simple analgesics should be the first choice for pain management.

	Component	Descriptor	Grade
One international guideline[4] with high AGREE score	Volume of evidence	Satisfactory	C
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Satisfactory clinical impact with reduction of adverse effects if simple analgesics are used appropriately for pain relief in RA and NSAID use is minimised	Clinical impact	Satisfactory	C
Although directly generalisable to the target population with few caveats, the studies did not include, or did not report, data specific to early RA or to racial subgroups (eg. Aboriginal and Torres Strait Islanders). Paracetamol is readily available and there is no apparent reason why these groups would respond differently	Generalisability	Good	B

Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATION	GRADE
General practitioners should consider recommending the use of simple analgesics (eg. paracetamol) where possible for pain relief in early arthritis.	**B**

Good practice points

- Paracetamol should be prescribed in regular divided doses to a maximum of 4 g/day for treating persistent pain in people with RA.
- Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.
- Paracetamol is the analgesic of choice in the presence of pregnancy, peptic ulcer disease, or significant cardiac, renal and other comorbidities.
- Paracetamol has few side effects, but dosing is limited by possible hepatotoxicity.

Fatty acid supplements (omega-3 and gamma-linolenic acid)

EVIDENCE STATEMENT

The EULAR[1] and BSR[3] guidelines do not make specific reference to omega-3 supplements. The SIGN guideline[4] identifies a benefit in terms of a reduction in tender joints and duration of morning stiffness based on a MA.[15]

A recent, good quality MA of the analgesic effects of omega-3 polyunsaturated fatty acids[16] provides good evidence for a role of omega-3 in pain management in RA. Seventeen RCTs involving 823 patients were included. A MA of 16 of the studies at 3–4 months showed significant effects for four out of six pain outcomes: patient assessed pain (SMD -0.26; 95% CI: -0.49 to -0.03), morning stiffness (SMD -0.43; 95% CI: -0.72 to -0.15; p=0.003); number of painful and/or tender joints (SMD: -0.29; 95% CI: -0.48 to -0.10; p=0.003); and NSAID consumption (SMD -0.40; 95% CI: -0.72 to -0.08; p=0.01). In contrast, significant effects were not detected for physician assessed pain and the Ritchie articular index. Eleven of the 16 studies used high doses (above 2.7 g omega-3 per day). Significant improvements were noted in patient assessed pain and morning stiffness among studies providing high dose, but not low dose, omega-3. The results suggest a potential role for omega-3 supplements as adjunctive treatment for the pain and stiffness associated with RA.

The results differ from previous MAs, showing a stronger effect than reported by Fortin et al,[15] and a beneficial effect for patient assessed pain versus the lack of effect reported by Maclean et al.[17] The authors attribute the differences to the different outcomes measured, and to the inclusion of results from eight additional trials.

In a Cochrane review of RCTs of herbal interventions in RA compared to placebo, Little and Parsons[18] assessed the effectiveness of various herbal therapies in the treatment of RA. They found 11 suitable RCTs; seven of the studies compared gamma-linolenic acid (GLA) to placebo. All of the GLA studies found some improvement in clinical outcomes. However, drawing conclusive results from these studies proved to be difficult due to the varied methodologies used and the quality of the studies. However, the better quality studies suggest potential relief of pain, morning stiffness and joint tenderness. Further studies are required to establish optimum dosage and duration of treatment.

Studies of GLA in the treatment of RA are promising and suggest that GLA may provide a supplementary or alternative treatment to NSAIDs for some patients.

	Component	Descriptor	Grade
The volume of evidence consists of a MA[16] of 17 RCTs and a MA[15] reported in the SIGN guideline[4]	Volume of evidence	Excellent	A
The consistency of evidence for omega-3 is excellent and there is Working Group consensus. The consistency of evidence for GLA is satisfactory and there is Working Group consensus	Consistency	Excellent Satisfactory	A C
Potentially a good clinical impact associated with the use of high dose supplementary omega-3 for RA patients	Clinical impact	Good	B
Although directly generalisable to the general Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATIONS	GRADE
General practitioners should recommend omega-3 supplementation as an adjunct for management of pain and stiffness in patients with RA.	**A**
General practitioners might recommend gamma-linolenic acid for potential relief of pain, morning stiffness and joint tenderness in RA patients.	**C**

Good practice points

- GPs should ask their patients about their use of supplements/complementary medicines so that this can be considered in care planning. Recommendations 21 and 22 also refer to complementary/alternative medicines.
- Higher doses of omega-3 are likely to be of greatest benefit (up to 12 g/day).
- Fatty acid interventions may provide supplementary or alternative treatment to NSAIDs for some patients. They can also enable a reduction of NSAID doses.
- The recommended dosage for GLA is 1400 mg/day of GLA or 3000 mg/day of evening primrose oil.

Traditional NSAIDs and COX-2 inhibitors

EVIDENCE STATEMENT

There is substantial evidence that conventional NSAIDs and COX-2 inhibitors have both analgesic and anti-inflammatory effects in RA. However, there is no evidence that they prevent joint damage.[1,3,4] There is some evidence that NSAIDs and COX-2 inhibitors may be more effective than simple analgesics in relieving the signs and symptoms of active disease; however, the number and quality of trials is poor.[13] Substantial evidence also points to significant side effects for these groups of drugs, including gastrointestinal, renal and cardiovascular effects, as well as many potential drug interactions.[1,3,4] Studies suggest that the risk of cardiovascular and gastrointestinal events is associated with the dose and duration of NSAID use. Thus, the BSR guideline[3] advises the use of the lowest possible dose compatible with symptom relief. It further advises a reduction or cessation of the dose once a good response from DMARD therapy has been achieved (grade of recommendation A).

COX-2 inhibitors are equally effective analgesics when compared with conventional NSAIDs, but cause less gastrointestinal tract (GIT) side effects. A good quality SR of three RCTs involving 15 187 patients with RA or osteoarthritis identified that the selective COX-2 inhibitor, celecoxib, is associated

with significantly less gastrointestinal side effects compared to conventional NSAIDs.[19] The rate of withdrawals due to adverse GIT events was 46% lower (95% CI: 29–58%) in celecoxib patients compared with those taking NSAIDs. Moreover, the incidence of ulcers detected by endoscopy was 71% lower (95% CI: 59–79%) and the incidence of ulcers, perforations, bleeds and obstructions was 39% lower (95% CI: 4–61%). There was insufficient evidence on the safety and efficacy of this medication beyond 12 weeks.

Addition of gastro-protective drugs (eg. proton pump inhibitors) to conventional NSAIDs can significantly reduce complications such as the incidence of GIT bleeding.[1,3] The addition of gastro-protective medication is recommended for RA patients over 65 years of age as well as for those with a past history of peptic ulcer disease.[4]

The BSR[3] and EULAR[1] guidelines cite evidence that use of COX-2 inhibitors is associated with an increased risk of cardiac and cerebrovascular events. These guidelines suggest that COX-2 inhibitors should be used only after careful evaluation of cardiovascular status. The guidelines also identify that these effects are likely to extend to conventional NSAIDs. Concern over the potential cardiovascular toxicity of COX-2 inhibitors and NSAIDs generally suggests they should be avoided in high risk individuals. They should also be used with caution in those who cannot be managed with analgesia, steroid injections and one or more DMARDs.

A recent MA[20] estimates that taking a COX-2 selective NSAID is associated with a 42% increase in the relative risk of a first serious vascular event compared with placebo. This was chiefly attributable to an increased risk of myocardial infarction, with little apparent difference in other vascular outcomes. Overall, the incidence of serious vascular events was similar between a selective COX-2 inhibitor and any traditional NSAID; however, studies with naproxen showed it was not associated with increased vascular events.

All guidelines[1,3,4] recommend consideration of treatment with NSAIDs or COX-2 inhibitors for symptom relief in RA patients after evaluation of gastrointestinal, renal and cardiovascular status and recommend particular care with use in the elderly.[1,3,4]

There is strong evidence[1,4] that long term use of NSAIDs and COX-2 inhibitors should be at the lowest effective dose compatible with symptom relief and that they should be reduced and, if possible, withdrawn when a good response to DMARDs is achieved. Prescribers should be aware of the many potential drug interactions and side effects. There is evolving evidence as to their effectiveness and adverse effects; thus all anti-inflammatory drugs should be used only after considering the risks and benefits for the individual.

Compared to non-selective NSAIDs in Australia, COX-2 inhibitors have been demonstrated to be cost effective in arthritic patients at high risk of serious upper gastrointestinal events. In average risk patients, COX-2 inhibitors may not be cost effective, as higher costs relative to alternatives are not matched with commensurate benefits.[21]

The consensus of the RACGP Working Group is that the choice of NSAID and COX-2 inhibitor should be tailored to the patient's specific needs and baseline risk profile.

	Component	**Descriptor**	**Grade**
Three international guidelines[1,3,4] with high AGREE scores, one good quality SR[19] of three RCTs and one low quality SR[20]	Volume of evidence	Excellent	A
The consistency is excellent and there is Working Group consensus	Consistency	Excellent	A
Potentially good clinical impact improvement in quality of life if NSAIDs and COX-2 inhibitors are used appropriately	Clinical impact	Good	B
Directly generalisable to the target population with few caveats, the studies did not include, or did not report, data specific to early RA or to racial subgroups (eg. Aboriginal and Torres Strait Islanders). NSAIDs and COX-2 inhibitors are readily available and there is no apparent reason why these groups would respond differently	Generalisability	Good	B
Although the guidelines used as primary sources were not	Applicability	Excellent	A

Australian, the research is directly applicable to the Australian health care context			

RECOMMENDATIONS	GRADE
General practitioners should consider using conventional NSAIDs or COX-2 inhibitors for reducing pain and stiffness in the short term treatment of RA where simple analgesia and omega-3 fatty acids are ineffective.	**A**
General practitioners should apply caution when using traditional NSAIDs and COX-2 NSAIDs. Choice of NSAID or COX-2 inhibitor should be based on consideration of the patient's specific needs, baseline risk profile and concomitant medication. The potential benefits need to be measured in relation to potential harms. Caution is particularly required in those at higher risk, such as the elderly, or patients who have gastrointestinal, renal or cardiovascular comorbidities.	**A**

Good practice points

- Simple analgesics should be used in place of NSAIDs if possible, and DMARDs should be introduced early to suppress disease activity.
- NSAIDs and COX-2 inhibitors should be used for the shortest possible duration.
- Long term use of NSAIDs should be at the lowest effective dose.
- Only one NSAID or COX-2 inhibitor should be prescribed at a time.
- Avoid NSAIDs and COX-2 inhibitors in patients taking anticoagulants or corticosteroids.
- Avoid celecoxib in patients who are allergic to sulphonamides.
- Avoid COX-2 inhibitors in patients who have been asthmatic or have had an allergic reaction to NSAIDs.
- Blood pressure and renal function should be monitored, particularly in older people and others at higher risk.
- If NSAIDs and COX-2 inhibitors are not suitable and paracetamol, omega-3 and non-pharmacological interventions have failed to achieve symptomatic relief, consider use of low dose corticosteroid therapy in consultation with a rheumatologist.
- If NSAIDs or COX-2 inhibitors are required beyond 6 weeks, referral to a rheumatologist is strongly advised.
- NSAIDs and COX-2 inhibitors should be avoided during pregnancy and stopped in women planning to become pregnant. They can be continued until the second trimester if the woman becomes pregnant while taking them. However, they should be discontinued before the third trimester as they interfere with the onset of labour and ductus closure.
- NSAIDs and COX-2 inhibitors should be stopped at least 7–10 days before any major surgical procedure.
- Addition of gastro-protective drugs to conventional NSAIDs can significantly reduce complications, such as the incidence of gastrointestinal bleeding[1,3] and is recommended for RA patients over 65 years of age, as well as for those with a past history of peptic ulcer disease.[4]

Disease modifying antirheumatic drugs

EVIDENCE STATEMENT

Efficacy

It is well established that joint damage commences early in RA and that early treatment with disease modifying drugs is the foundation of best practice approach to disease management.[1,3,4] DMARDs suppress the inflammatory disease process and have been shown to reduce the rate of erosive change in patients with RA. They therefore have the potential to alter the disease course, reduce morbidity and mortality, and improve quality of life. All primary reference guidelines[1,3,4] recommend

that patients should be established on disease modifying therapy as soon as possible after a diagnosis of RA has been established. The EULAR guideline[1] supports the concept of a 'window of opportunity' for effective treatment, which may be as short as 3–4 months. The EULAR guideline[1] recommends that patients at risk of developing persistent and/or erosive arthritis should start DMARDs as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatologic diseases.

There is further recent evidence for commencement of DMARDs before confirmation of diagnosis in some patients. Results of a good quality RCT provided evidence for a potential role of DMARDs in undifferentiated arthritis, in terms of postponing progression to RA and retarding radiographic joint damage.[22] The delay in development of RA was seen particularly in anti-CCP antibody positive patients. This suggests a possible role of early DMARD therapy in this group of patients who are considered to be at high risk of developing RA and in whom the risk of side effects may outweigh the benefits of treatment.

There is evidence that treatment with methotrexate (MTX) can reverse the cardiovascular risk associated with active RA.[3] The recognition that the RA patient is at high risk of cardiovascular disease should encourage screening and treatment of risk factors in these patients.

Choice of DMARD

The basis for first agent selection is the risk-benefit ratio. One MA of placebo controlled trials suggests that sulphasalazine, MTX, leflunomide, intramuscular gold and pencillamine are equally effective in reducing radiological progression in RA. Existing guidelines[1-4] identify clear evidence for the disease modifying effects of MTX, sulfasalazine, leflunomide and intramuscular gold. They point to less compelling evidence, in terms of effect on reduction of erosions, for hydroxychloroquine, pencillamine, oral gold, cyclosporin and azathioprine. MTX has become the most popular first line DMARD agent because of its early onset of action (4–6 weeks), good efficacy, favourable toxicity profile, ease of administration, and relatively low cost. One SR and subsequent RCTs have found no consistent differences in efficacy between MTX versus leflunomide, parenteral gold, or etanercept.[23]

The guidelines[1,3,4] support MTX as a first line choice, particularly when the disease is judged to be moderate to severe or where there is a high risk of erosive disease. Leflunomide or sulphasalazine are identified as alternatives where MTX may be contraindicated.[1,3,4] Hydroxychloroquine is considered an appropriate choice for mild disease.[3] In Australia, leflunomide only attracts a Pharmaceutical Benefits Scheme (PBS) subsidy when MTX is ineffective or contraindicated. A recent SR and subsequent RCTs have found no consistent differences in efficacy between MTX, leflunomide, parenteral gold and etanercept.[24]

Combined therapies

There is increasing evidence that combination therapy is more effective than monotherapy for many patients. The Clinical Evidence guideline[2] cites evidence that low dose, once weekly MTX combined with most other DMARDs is more beneficial than treatment with a single drug. One SR and subsequent RCTs have found that combining certain DMARDs is more effective than using individual drugs alone. However, the balance between benefit and harm varies among combinations.[25] This has been backed up by a good quality MA of 36 RCTs. This MA found that combination DMARD therapy was more effective in reducing disease severity than monotherapy, both in patients with an early diagnosis of RA and in those with established RA.[26] Combination therapy appears to have no greater toxicity than monotherapy, although individual combinations vary in terms of toxicity.

The RACGP Working Group would consider monotherapy appropriate in mild to moderate RA.

Adverse effects

The adverse effects of conventional DMARDs are well established, as is the need for careful monitoring to identify and manage these effects. Adverse effects may include severe anaemia, liver damage, lung disease and even death. Combination therapy appears to have a similar risk profile to monotherapy. Alcohol use during MTX therapy may increase the risk of liver cirrhosis.

While the newer biological agents can only be prescribed by rheumatologists, their toxicity profile is of relevance to primary care physicians involved in patient care. Concerns about toxicity are reflected

in a recent, good quality SR[27] of nine RCTs investigating the safety of the tumour necrosis factor (TNF) inhibitors, infliximab or adalimumab, used for at least 12 weeks. The review sought to assess the extent to which anti-TNF therapies may increase the risk of serious infections and malignancies. The pooled odds ratio for malignancy was 3.3 (95% CI: 1.2–9.1) and for serious infection was 2.0 (95% CI: 1.3–3.1). This review provides good quality evidence that anti-TNF antibody therapy for 6–12 months is related to an increased risk of serious infections and malignancies in patients with active RA. Malignancies were significantly more common in patients treated with higher doses. However, the review did not show an accumulation of malignancies with longer study duration. The authors concluded that these risks should be considered alongside the efficacy of anti-TNF therapy in patients with RA and the limited therapeutic alternatives available for patients with active disease that is irresponsive to traditional DMARD therapy. Risks and benefits of this treatment must be considered for each individual.

All DMARD therapy should be reviewed in women planning to conceive and in pregnant and lactating women. There is evidence that sulfasalazine and hydroxychloroquine can be used safely during pregnancy. However, according to the Australian Rheumatology Association, MTX and leflunomide should not be used in pregnancy.[28] There is also evidence that potential fathers should stop using leflunomide or MTX at least 3 months before planning a pregnancy.[28]

Monitoring

All patients should have their disease and its impact assessed and documented at onset, before starting DMARD therapy. Once established on DMARD therapy, all patients should have a formal assessment of treatment response, or lack of it, in order to justify continuing therapy or changing it. DMARD therapy also involves a regular rigorous monitoring program to screen for drug toxicity and to reduce adverse effects on the liver, kidney or other organs. Annual assessment of potential complications of disease should also include long term screening for osteoporosis, evidence of joint failure, atherosclerosis and hyperlipidaemia.

	Component	**Descriptor**	**Grade**
Four international guidelines;[1-4] one good quality MA[26] of nine RCTs in early RA and 27 RCTs of DMARD therapy in established RA; one good quality SR[27] and one good quality RCT[22]	Volume of evidence	Excellent	A
The consistency of evidence is excellent and there is Working Group consensus	Consistency	Excellent	A
Potentially a very large clinical impact for reduced morbidity and mortality if DMARDs are used appropriately in early RA	Clinical impact	Excellent	A
Although directly generalisable to the target population with few caveats, studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations; however, there is no reason to believe that they would respond differently	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATIONS	**GRADE**
General practitioners must facilitate early treatment with disease modifying drugs (DMARDs) for patients diagnosed with RA as well as for those with undifferentiated inflammatory arthritis who are judged to be at risk of developing persistent and/or erosive arthritis. Ideally, DMARD therapy should be initiated by a rheumatologist in light of the potential toxicity of these agents.	**A**
If initiating DMARD therapy, GPs should use MTX as the first line choice, particularly when the disease is judged to be moderate to severe, or where there is a high risk of erosive disease.	**A**

Good practice points

- If access to a rheumatologist is not possible, consider commencing single drug therapy with methotrexate or sulphasalazine, based on a consideration of individual patient preference and comorbidities. Consult with a rheumatologist as soon as possible.
- Before commencing DMARDs, organise baseline chest X-ray, FBC, renal tests and liver function tests (LFTs), CRP, and hepatitis B and C status.
- Be aware of the dosage and monitoring schedules. For example, MTX is given as a weekly oral dosage, usually with a folic acid supplement throughout the week and blood tests for monitoring FBC and LFTs at least monthly.
- Physicians and patients must monitor for signs and symptoms of toxicity through regular clinical and laboratory review as treatment may cause serious adverse effects.
- All DMARD therapy should be reviewed in women planning to conceive and in pregnant and lactating women. For example, there is evidence that sulfasalazine and hydroxychloroquine can be used safely during pregnancy. However, MTX and leflunomide should not be used in pregnancy. There is some evidence that potential fathers should stop using MTX at least 3 months before planning a pregnancy.
- Monitor for continuing efficacy (ESR/CRP, number of tender and swollen joints, duration of morning stiffness and activities of daily living).
- Alcohol use should be reviewed for people being prescribed MTX as the danger of liver cirrhosis rises significantly with high alcohol intake. Smoking cessation should be highly recommended.

Corticosteroids

EVIDENCE STATEMENT

Corticosteroids are used in RA both for their effects on symptom control (reducing pain and swelling) and for their potential disease modifying action. Two SRs and one subsequent RCT have found benefit from both short and long term treatment (longer than 3 months) with low dose, oral corticosteroids. Short term treatment reduces disease activity and joint inflammation. Long term treatment may reduce radiological progression while treatment continues. However, long term use is associated with considerable adverse effects.[22] All four primary guidelines[1-4] recommend that systemic corticosteroids should be considered as short term therapy as part of a DMARD strategy. Systemic glucocorticoids, either alone or as part of a DMARD combination strategy, are effective in the short term relief of signs and symptoms, and are probably effective in retarding radiographic progression in early and established RA (grade of recommendation A).[1]

Symptom control

A Cochrane review[29] reviewed 10 studies involving 320 patients, comparing short term, oral, low dose corticosteroids (equivalent to 15 mg or less of prednisolone per day) with placebo or NSAIDs in RA. Prednisolone had a marked effect over placebo on joint tenderness and also a greater effect than NSAIDs. There was a low risk of adverse events with low doses, even when used long term. The authors concluded that prednisolone (less than 15 mg/day) may be used intermittently in patients with RA, particularly if the disease cannot be controlled by other means.

'Bridge' corticosteroids (usually intramuscular or intravenous) can be used to provide symptomatic relief while awaiting the effects of DMARDs. Rebound flare of symptoms following cessation is experienced in some patients.[4]

Disease modification

A Cochrane review[30] assessed the efficacy of corticosteroids in inhibiting the progression of radiological damage in adults with RA. The review included 15 RCTs using various daily and cumulative doses of oral corticosteroids, with treatment duration ranging from 6 months to 2 years. Most participants were also prescribed DMARDs. Patients treated with corticosteroids had

substantially less joint damage at 1 and 2 years follow up. The proportion of benefit gained in reducing the progression of erosions from an average of all studies was 67.2% over a 1 year period and 61.3% over 2 years. This benefit was over and above any benefit from DMARDs. The radiological benefit was demonstrated with all treatment combinations. Harmful events were not reported. However, the adverse effects of ongoing corticosteroid treatment (doses of 10 mg or less of prednisolone or equivalent) were reported in another paper.[30] The major risks appeared to be a doubling of the already increased risk of osteoporosis; an increase in blood glucose, which is dependent on the dose and type of corticosteroid used; fat redistribution; and an increase in body weight.

In a commentary[31] on the Cochrane review, the authors identify that there are still many unanswered questions about the use of low dose corticosteroids in RA, including the optimal dose, duration of treatment and the true risks of adverse effects over the long term. People with RA are already at an increased risk of cardiovascular disease and osteoporosis as a result of their disease. If oral corticosteroids are used, other drugs that increase steroid induced GIT and cardiovascular toxicity (eg. NSAIDs) should be avoided.

The difficulties in being able to withdraw even low dose corticosteroids in routine clinical practice, and the concomitant risks associated with longer than planned use, should not be underestimated. Furthermore, their value in long standing RA is unknown and the benefits need to be carefully weighed against the potential for harm in patients with, or at risk of, obesity, osteoporosis, diabetes, hypertension, glaucoma and heart disease. In view of the many unresolved issues, the use of low dose oral corticosteroids should be reserved for patients with severe active RA and restricted to short term use. The authors strongly advise consultation with a rheumatologist before commencement of oral corticosteroids for the treatment of RA.

Intra-articular corticosteroids

There are few controlled trials on the use of intra-articular corticosteroids in RA, although it is widely accepted that they provide short term relief of pain and swelling. Large cohort trials suggest that complications such as joint sepsis are rare, and that aspiration of synovial fluid at the time of joint injection reduces the relapse rate. There is no evidence on the long term effect on radiological progression or disability for intra-articular steroids. Local injections of corticosteroids into joints can directly suppress synovitis and prevent the development of erosions in early RA.[3] All base guidelines[1-4] recommend that intra-articular corticosteroid injections should be considered for the relief of local symptoms of inflammation (grade of recommendation A).[1] Intra-articular corticosteroids and bridging therapy with intra-muscular and possibly intravenous corticosteroids are useful strategies to rapidly suppress inflammation when starting and increasing DMARDs.[3]

In Australia, corticosteroids (combined with DMARDs) have been shown to be cost saving relative to NSAIDs (combined with DMARDs).[21]

	Component	**Descriptor**	**Grade**
Four international guidelines[1-4] that scored highly on the AGREE tool	Volume of evidence	Excellent	A
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Good evidence for substantial clinical impact on symptoms of pain and inflammation, as well as disease modification for low dose, short term corticosteroids	Clinical impact	Excellent	A
Although directly generalisable to the target population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be more susceptible to corticosteroid side effects due to associated comorbidities	Generalisability	Excellent	A
The studies are directly applicable to the Australian health care context	Applicability	Excellent	A

RECOMMENDATIONS	GRADE
General practitioners should consider short term, low dose oral corticosteroid treatment when simple analgesics, omega-3 fatty acids, and NSAIDs or COX-2 inhibitors have failed to achieve symptomatic relief. This should be undertaken in consultation with a rheumatologist and with consideration of the patient's comorbidities and individual risk factors.	**A**
General practitioners should consider intra-articular corticosteroid injections for rapid symptomatic relief of inflammation in target joints, but no more than three injections per year for a specific joint.	**B**

Good practice points

- Oral corticosteroids are not recommended for routine use and should be withdrawn slowly to avoid rebound flare of symptoms.
- Inform patients of the risks of using corticosteroids before prescribing.
- Monitor bone density and ensure osteoporosis protection if there is prolonged use.
- Avoid NSAIDs in patients taking corticosteroids.
- When administering intra-articular injections, always consider possible septic arthritis in the differential diagnosis of mono/oligo flare in RA. Adverse reactions of intra-articular injection (eg. injury, infection, bruising) are minimised and clinical efficacy is increased by accuracy of needle placement and adherence to an appropriate sterile technique during the injection procedure.[32,33]

Complementary medicines

EVIDENCE STATEMENT

Complementary medicines are widely used by patients with RA to support control of symptoms and assist general wellbeing. With the exception of omega-3 fatty acids and, to a lesser extent, GLA, there is limited evidence of the effect of complementary or herbal medicines in RA. The studies are few and are generally of poor quality.[1,3,4]

In a Cochrane review[18] the effectiveness of various herbal therapies in RA compared to placebo was assessed. The review included 11 RCTs comparing complementary therapies to placebo. Drawing conclusive results proved to be difficult due to the small number of studies, the varied methodologies used, and the quality of the studies. Good tolerance of most of the herbal remedies was demonstrated, although caution is warranted in interpreting safety due to the small sample sizes in some of the studies. The review raised concerns about potential serious side effects of *Tripterygium wilfordii*, a Chinese herb with immunosuppressive effects and an established history of use in the treatment of RA. While it may have beneficial effects on the symptoms of RA, *T. wilfordii* is associated with serious adverse effects that include impaired renal function, haematotoxic and immunosuppressive effects, hair loss, diarrhoea and nausea.[18]

A good quality SR[34] investigated the efficacy and safety of *T. wilfordii*. Based on findings from two RCTs of moderate to good quality, the authors concluded *T. wilfordii* extract was effective in improving symptoms and functional outcomes in RA patients with active symptoms. However, it was associated with significantly higher rates of serious adverse events than placebo and its use could not be recommended.

Another good quality review[35] including 182 patients investigated the effect and tolerability of Ayurvedic medicines on symptoms including pain, morning stiffness and joint swelling, as well as effects on the general health questionnaire. Of the seven RCTs reviewed, only one was of good quality. Ayurvedic medicines had no effect above placebo in improving symptoms in patients who have had RA for at least 6 months. Minor adverse events were reported.

The RACGP Working Group highlights the need for vigilance with respect to potential toxicity and interactions of complementary and alternative medicines and the need for primary care physicians to be alert to such medicines that their patients may be taking.

Further supporting evidence identified after the search time frame and not subjected to critical appraisal was available from conference presentations of an update to this Cochrane review. One additional moderate to good quality RCT involving 30 participants investigated T. wilfordii - in two doses (360 mg/day and 180 mg/day) compared with placebo. The results showed that more participants in the high dose T. wilfordii group met ACR20 criteria than those in the low dose T. wilfordii group or the placebo group. (No placebo participants met ACR20 criteria.) However, the safety profile of T. wilfordii remained concerning and the product was not recommended.[36,37]

	Component	**Descriptor**	**Grade**
Three international guidelines[1,3,4] with high AGREE scores and three SRs[18,34,35] report there is a small volume of evidence for specific interventions	Volume of evidence	Good	B
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially only a minimal or restricted clinical impact associated with the use of complementary medicines for RA patients	Clinical impact	Satisfactory	C
Although directly generalisable to the target population with few caveats, studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations; however, there is no reason to believe that they would respond differently	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATIONS	**GRADE**
General practitioners should inform patients about complementary medicines and the insufficient volume of evidence in treating RA. General practitioners should also inform patients of the potential for adverse effects and interactions of these medicines.	**B**
General practitioners should not recommend *Tripterygium wilfordii* (Chinese herb). While it may have beneficial effects on the symptoms of RA, it is associated with serious adverse effects (impaired renal function, haematotoxic and immunosuppressive effect, hair loss, diarrhoea and nausea).	**B**

Good practice points

- GPs should ask their patients about use of complementary medicines when prescribing treatment for RA. Recommendations 13 and 14 also refer to complementary and alternative medicines.

Non-pharmacological interventions for rheumatoid arthritis

Weight control

EVIDENCE STATEMENT

A full review of the literature relevant to this consensus recommendation was not undertaken. While there is limited evidence of the effect of diet on RA, there is general acceptance of the need to encourage patients to adopt a healthy diet and maintain a healthy weight. The SIGN guideline[4] highlights the importance of maintaining a health weight and body mass index (BMI) in the general management of patients with RA. Weight reduction in RA patients who are over weight or obese reduces impact on weight bearing joints and reduces risk factors for cardiovascular disease. SIGN[4] also cites several studies that suggest RA patients with a BMI below healthy range have poorer functional status, highlighting the importance of maintaining BMI within the normal range. The EULAR and BSR[3] guidelines also identify weight control as an important aspect of general disease management.

There have been insufficient studies on the effectiveness of specific diets in managing RA and studies that have investigated diet have not reported BMI as an outcome measure. SIGN[4] and EULAR[1] guidelines reported that small RCTs investigating a range of diets including gluten free, vegetarian, vegan and fasting, found evidence of significant effect on ACR20 response and pain in patients with RA, however long term compliance and nutritional deficiencies reduced the acceptability and practicality of many dietary interventions.

It is the opinion of the RACGP Working Group that promotion of sound diet and weight control by GPs is important in the management of RA.

	Component	Descriptor	Grade
Two international guidelines[3,4] with high AGREE scores	Volume of evidence	Good	B
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially a restricted clinical impact associated with the use of diet for RA patients	Clinical impact	Satisfactory	C
Although directly generalisable to the target population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATION	GRADE
General practitioners should encourage healthy diet and weight control for all RA patients.	**B**

Good practice points

- Healthy diet and regular exercise are important in long term weight control.
- The diet recommended for arthritis is similar to that for good health generally, with special emphasis on cardiovascular risk prevention. This includes:
  - eating plenty of fruit, vegetables and wholegrain cereal foods
  - eating foods rich in fish oil (omega-3)
  - eating a diet low in fat
  - maintaining a healthy body weight
  - limiting alcohol intake
  - eating only a moderate amount of sugars and foods containing added sugars, and
  - choosing low salt foods and using salt sparingly.
- Appropriate exercise is discussed in Recommendation 24.

Exercise

EVIDENCE STATEMENT

Exercise therapy is well accepted as having a role in combating the adverse effects of RA on muscle strength, endurance and aerobic capacity. The effect of exercise has not been investigated in early RA or inflammatory RA and can only be extrapolated from results in established RA. In recommending that such interventions can be applied as treatment adjuncts in early arthritis, the EULAR guideline cites a number of RCTs and Cochrane reviews in support of dynamic exercise and hydrotherapy (grade of recommendation B).[1] The effect is generally on improved strength and physical functioning, but may have symptom relieving effects.

A Cochrane review[38] and the SIGN guideline[4] identify dynamic exercise therapy (ie. exercises of low to moderate aerobic intensity) as effective in increasing aerobic capacity and muscle strength, with no adverse effects on disease activity or pain observed. The BSR guideline[3] recommends aerobic exercise should be encouraged while being mindful of minimising or joint destruction. The guideline cites two recent studies[39,40] which show exercise can be undertaken without disease exacerbation in the short term. Long term effects are still unknown.

A Cochrane review[41] examined four trials involving 206 participants that investigated tai chi. The comparative studies measured improvements in adults with RA who participated in 8–10 week tai chi programs. In three studies, tai chi had no clinically important or statistically significant effect on most outcomes, including activities of daily living, tender and swollen joints, and patient global overall rating. In one small study, the most notable results were significantly increased range of motion in the ankle, hip and knee, and increased enjoyment of exercise. No detrimental effects were reported. Preserving range of motion in affected joints is particularly important to maintain functionality.

The RACGP Working Group reached consensus that general physical activity and exercise therapy should be encouraged in RA. Specifically, exercise should be tailored to the needs and preferences of the patient to combat the adverse effects of the disease on muscle strength, endurance and aerobic capacity.

	Component	Descriptor	Grade
Three international guidelines[1,3,4] and two good quality SRs[38,41]	Volume of evidence	Good	B
The consistency of evidence is satisfactory. There is also Working Group consensus	Consistency	Satisfactory	C
There is potentially a restricted clinical impact on RA disease symptoms. However, exercise supports general maintenance of strength, endurance and aerobic capacity and general welling	Clinical impact	Satisfactory	C
Although generalisable to the general Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalis-ability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATION	GRADE
General practitioners should encourage patients with RA to engage in regular dynamic physical activity compatible with their general abilities in order to maintain strength and physical functioning.	**C**

Good practice points

- GPs may utilise EPC items to facilitate access to appropriate services (www.health.gov.au/epc). Eligible services include, but are not limited to, those provided by physiotherapists, occupational therapists and exercise physiologists.

- GPs could refer patients to Arthritis Australia for information and services relating to exercise in RA (www.arthritisaustralia.com.au).
- Exercises such as tai chi may not show statistically significant improvement in body function but tend to be enjoyable and have a strong social component.

Occupational therapy

EVIDENCE STATEMENT

The international guidelines[1,3,4] support the role of occupational therapy (OT) interventions in maintaining function for RA patients, while accepting there is absence of evidence from RCTs. Occupational therapy interventions include training of motor function, skills training, instruction on joint protection and energy conservation, counselling, instruction about assistive devices and provision of splints.

The SIGN guideline[4] recommends that skilled OT should be available to those experiencing limitation in function (grade of recommendation C). The BSR guideline[3] also recommends that joint protection, energy conservation and problem solving skills should be taught early in the course of the disease (grade of recommendation B). It also specifically recommends a continuing OT role in maintaining hand function, utilising devices for assisting hand function, and in aiding alternative work methods (grade of recommendation C).[3]

A moderate quality SR[42] identified three SRs of OT interventions in RA and concluded that OT improved functional ability in RA patients. However, its effect on other outcome measures was unclear.

	Component	Descriptor	Grade
Three international guidelines[1,3,4] and a moderate quality SR[42] of three SRs	Volume of evidence	Good	B
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially a significant impact in terms of functionality and quality of life for RA patients receiving OT intervention	Clinical impact	Good	B
Although directly generalisable to the general Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATIONS	GRADE
General practitioners should refer patients with RA experiencing limitations in function to skilled occupational therapists for advice.	**B**
Occupational therapy should be directed at assisting activities of daily living, including activities associated with work and significant leisure activities.	**C**

Good practice points

- Splints (including hand/wrist resting splints and functional wrist splints) may be offered by an experienced health care professional when hands and wrists are painful and/or swollen; however, the role of splinting remains uncertain.
- Joint protection, energy conservation, and problem solving skills should be taught early in the disease course.
- GPs may utilise EPC items to facilitate access to appropriate services (www.health.gov.au/epc).

Foot care

EVIDENCE STATEMENT

The value of appropriate foot care for RA is well recognised in practice but there is little evidence based research to support recommendations in early arthritis. Both the SIGN[4] and BSR[3] guidelines identify podiatry input and appropriate foot orthoses as important and effective interventions in RA.

It is the opinion of the RACGP Working Group that access to appropriate foot care for patients with RA is important in the management of the disease.

	Component	Descriptor	Grade
Two international guidelines[1,4] with high AGREE scores	Volume of evidence	Satisfactory	C
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially significant clinical impact associated with the provision of appropriate foot care to patients with RA	Clinical impact	Good	C
Although the RA population is relevant to the Australian context, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, it is probably applicable to the Australian health care context with some caveats	Applicability	Good	B

RECOMMENDATION	GRADE
General practitioners should support access to appropriate foot care for patients with RA.	**C**

Good practice points

- An annual foot assessment and review is recommended for patients at risk of developing serious complications in order to detect problems early.
- GPs may utilise EPC items to facilitate access to appropriate services (www.health.gov.au/epc). Eligible services include podiatrists and chiropodists.

Alternative physical therapies

EVIDENCE STATEMENT

The BSR guideline[3] reports that the evidence for effectiveness of complementary therapy is conflicting and no firm recommendations can be made (grade of recommendation B). For many specific interventions there is insufficient evidence available regarding effectiveness. However, complementary therapies can play an important role in encouraging positive changes in lifestyle and outlook,[3] and the majority of these forms of therapy are not harmful.

In a good quality SR[43] of five RCTs, low level laser therapy (LLLT) for up to 4 weeks had a clinically relevant effect in reducing pain and morning stiffness in patients with RA of the hand; however it did not have long lasting effects. There was no significant difference between dosage, wavelength and method of delivery. The SIGN guideline[4] suggests that the evidence for use of LLLT is conflicting or insufficient to make conclusions on its use.

The EULAR guideline[1] describes a number of therapies including acupuncture, laser therapy, compression gloves, transcutaneous electrical nerve stimulation (TENS), ultrasound, thermotherapy, splints and orthoses. The BSR guideline[3] refers to a range of alternative therapies including massage and the Alexander technique. While some studies report short term pain relief for some of interventions, there is no evidence for long lasting benefits and recommendations for use are only as adjuncts to pharmaceutical therapies.

A Cochrane review[44] sought to evaluate the effectiveness of thermotherapy on objective and subjective measures of disease activity in RA. Seven studies and 328 participants were included. The review found no significant effect on objective measures (joint swelling, pain, pain medication intake, range of motion, grip strength or hand function) for hot or cold pack application, cryotherapy or faradic baths. There was also no difference in patient preference and no harmful effects were reported. The review concludes that thermotherapy may be used as palliative therapy.

There is evidence from a Cochrane review[45] relating to the use of acupuncture and electro-acupuncture by rehabilitation specialists as an adjunct therapy for the symptomatic treatment of RA. Two studies involving 84 participants were included; one used acupuncture and the other used electro-acupuncture. In the acupuncture study, there were no statistically significant differences between groups for ESR, CRP, patient global assessment on visual analogue scale, number of swollen joints and tender joints, general health questionnaire, modified disease activity scale, or for decrease in analgesic intake. Pain improved more in the treatment group than in the placebo group but the difference was not statistically significant.

In the electro-acupuncture study, a significant decrease in knee pain compared with placebo was reported in the experimental group 24 hours post-treatment. This effect was sustained at 4 months post-treatment. Even though electro-acupuncture seems beneficial for reducing symptomatic knee pain, the reviewers precluded its recommendation due to the poor quality of the trial, including the small sample size. They concluded that acupuncture had no significant effect on any outcomes measures used in the trials. These conclusions are limited by methodological considerations such as the type of acupuncture (acupuncture vs. electro-acupuncture), the site of intervention, the low number of clinical trials and the small sample size of the included studies.[45]

The BSR guideline[3] states that acupuncture-like TENS (AL-TENS) is beneficial for reducing pain intensity and improving muscle power scores over placebo, while conversely, conventional TENS (C-TENS) resulted in no clinical benefit on pain intensity compared with placebo.

The SIGN guideline,[4] states that acupuncture showed no benefit based on low quality evidence.

According to the EULAR guideline,[1] acupuncture is among several non-pharmaceutical interventions of which controversial effects have been reported in RCTs. If positive, the RCTs demonstrated a short term relief of pain rather than an effect on disease activity.

Many other ‘natural’ therapies are used, such as capsaicin, wintergreen and magnet therapy. While they are generally harmless, benefit has not always been rigorously demonstrated and can often be costly.[21]

	Component	Descriptor	Grade
Three international guidelines[1,3,4] and three Cochrane reviews.[43-45] For individual interventions there is a low volume of evidence	Volume of evidence	Good	B
The consistency of evidence is variable as there are conflicting results	Consistency	Satisfactory	C
Potentially a minimal or restricted clinical impact associated with the use of complementary physical therapies. While evidence of benefit is limited, some may help alleviate symptoms, improve general sense of wellbeing, and play a role in encouraging positive changes in lifestyle and outlook	Clinical impact	Poor	D
Although generalisable to the Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATION	GRADE
General practitioners should inform patients about complementary and alternative physical therapies, particularly highlighting the insufficient volume of evidence that is available on treating RA with these therapies. General practitioners should also inform patients of the potential for adverse effects.	**D**

Good practice points

- GPs should be alert to alternative physical therapies used by their patients.
- Patient information about physical therapies is available from Arthritis Australia (www.arthritisaustralia.com.au).
- The choice of physical therapies should be guided by patient preference.

Disease monitoring and comorbidities

EVIDENCE STATEMENT

Ongoing monitoring, including disease activity, comorbidities and adverse effects of medication, is an important aspect of the management of RA.[46] Monitoring requirements vary depending on disease severity, disease activity and the drug regimen used. A full review of the literature relevant to this consensus recommendation was not undertaken. The GP has an ongoing role in monitoring for adverse events and toxicity associated with medication, which is discussed under relevant pharmacological management recommendations.

The EULAR[1] (recommendation A) and SIGN[4] guidelines include recommendations relating to disease activity monitoring including: tender and swollen joint count; patient and physician global assessments; ESR and CRP as well as X-rays to monitor structural damage; and functional assessment (eg. via the health assessment questionnaire). The BSR[3] guideline identifies a role for primary care in monitoring later complications of RA, but specific recommendations are not made in this regard. Such complications are beyond the scope of this guideline, which addresses management in the first 2 years. The EULAR recommendation[1] is based on a number of RCTs that showed significant improvement related to intensive treatment and monitoring strategy.

The BSR guideline[3] addresses the specific monitoring of cardiovascular risk for RA patients, and recommends that in light of the fact that RA is an independent risk factor for ischaemic heart disease, patients should be screened for cardiovascular risk factors. These factors should be actively addressed by primary care services. The guideline recommends that lifestyle advice should be given to all RA patients to encourage smoking cessation, dietary modification, weight control and exercise. In addition, regular blood pressure monitoring and treatment of hypertension, diabetes screening and treatment, and screening and treatment of hyperlipidaemia is advised.

If complete remission is not achieved, the management goals are to control disease activity, alleviate pain, maintain function for essential activities of daily living and work, maximise quality of life, and slow the rate of joint damage.[46]

It is the consensus of the RACGP Working Group to recommend that disease monitoring is essential and GPs should be involved in monitoring disease progression and comorbidities in conjunction with the treating rheumatologist.

The RACGP Working Group recommends that GPs review Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information, including ongoing monitoring requirements, toxicity and adverse effects.

	Component	Descriptor	Grade
Three international guidelines[1,3,4] with high AGREE scores	Volume of evidence	Good	B
The consistency of evidence is good and there is Working Group consensus	Consistency	Good	B
Potentially significant clinical impact on disease management and adverse effects, if appropriate monitoring is undertaken	Clinical impact	Good	B
Although directly generalisable to the Australian population with few caveats, the studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander populations. These populations may be disadvantaged because of lack of access to the intervention	Generalisability	Good	B
Although the guidelines used as primary sources for this guideline were not produced in Australia, the literature and research are directly applicable to the Australian health care context	Applicability	Good	B

RECOMMENDATIONS	GRADE
General practitioners should be involved in monitoring disease progression, response to treatment and comorbidities in conjunction with the treating rheumatologist and other members of the multidisciplinary team.	B
Patients with RA should be assessed and treated for cardiovascular risk factors such as smoking, obesity, physical inactivity, hypercholesterolaemia, hypertension and diabetes.	B

Good practice points

- Arthritis activity should be assessed at least three times per year. Treatment should be adjusted to keep the swollen and tender joint count, and the CRP levels, as low as possible.
- Patients should be monitored for potential toxicity of medications.
- Frequency and type of monitoring will depend on the DMARD prescribed, but most require FBC (to monitor for marrow suppression) and LFTs (to look for raised transaminases as a sign of hepatotoxicity) approximately monthly.
- Cardiovascular risk factors should be assessed at least three times per year.

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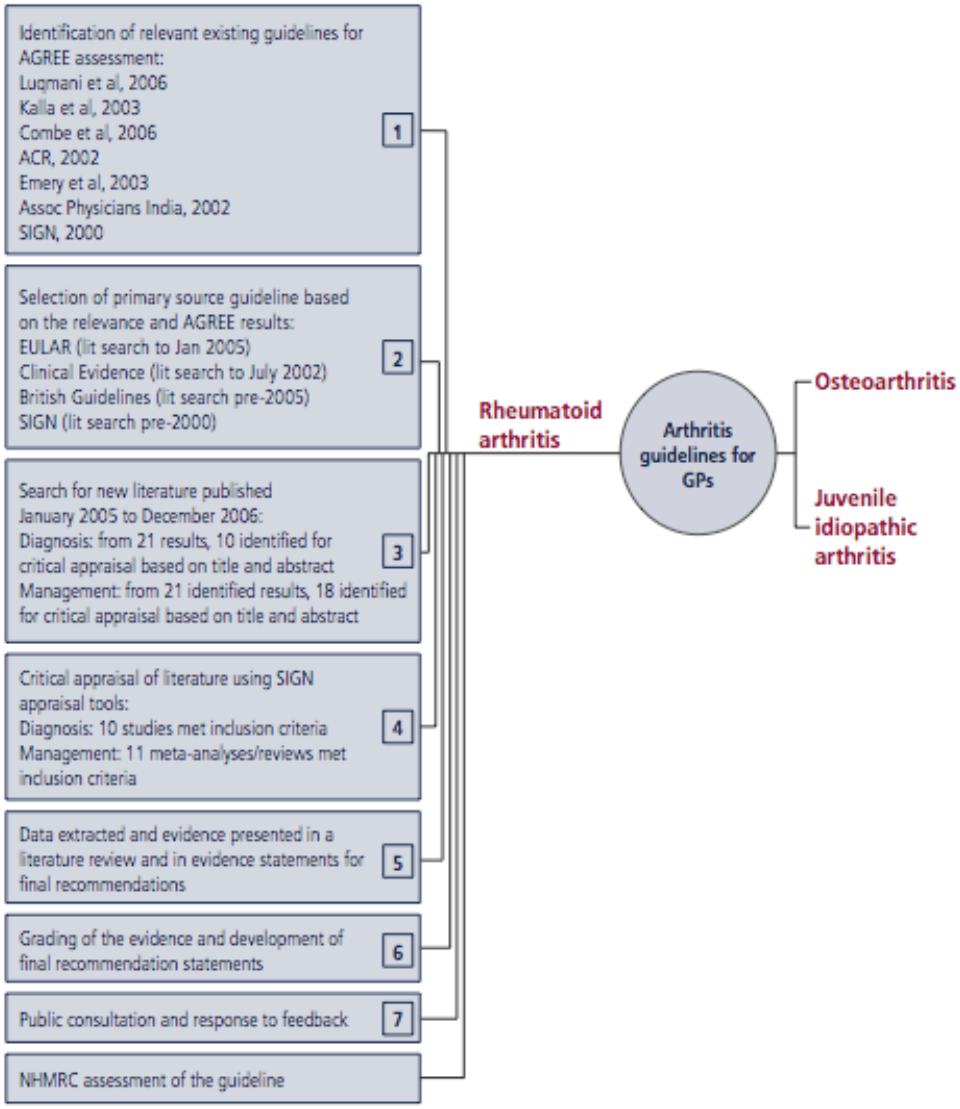
APPENDIX A. PROCESS REPORT

This report outlines the process used for the development of the evidence based *Clinical guideline for the diagnosis and management of early rheumatoid arthritis***.** The process consisted of the following major phases:

- Formation of a disease focused, multidisciplinary expert Working Group (see Appendix B)
- Development of a scoping document outlining the scope and objectives of the project, including the process to be used during guideline development
- Identification and appraisal of relevant existing clinical guidelines, leading to the selection of existing guidelines for use as the primary references
- Systematic literature searches to identify the most recent evidence
- Synthesis of new evidence and evidence from the primary reference guidelines into graded clinical recommendations and algorithms
- Peer review and appraisal through a public consultation process
- Response to feedback and completion of final guideline.



Identification of the guideline focus

A process model developed by The Royal Australian College of General Practitioners (RACGP) Steering Committee was used to identify the primary focus of the guideline (see Background). The Working Group reached consensus opinion on the primary focus of the guideline through discussion of the most important areas to cover for the primary audience (Australian GPs), with consideration to the feasibility of completing the guideline within the prescribed timeframe and budget. Clinical questions relevant to the scope of guideline were developed to focus the search for relevant literature.

Identification, appraisal and selection of existing clinical guidelines

Due to extensive research that has been published on rheumatoid arthritis (RA) and its management, it was not feasible for the Working Group to conduct appraisals and a review of all the relevant research within the time and budget constraints of the project. Because several guidelines were available on the management of RA, it was determined that the most feasible methodology would be to use appropriate existing guidelines as primary references and conduct literature searches limited to new research published after the selected primary guidelines.

Existing guidelines were identified through database searches and those known to the experts in the Working Group. Those considered to be the most relevant to the focus of this project were selected for broad appraisal of quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.[1] Developers of the AGREE tool propose its use to assess '…the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice'.[1]

The AGREE tool includes 21 questions organised into six quality domains:

- scope and purpose
- stakeholder involvement
- rigour of development
- clarity and presentation
- applicability
- editorial independence.

Reviewers score each question on a 4-point Likert scale (strongly agree, agree, disagree and strongly disagree). The scores from multiple reviewers are used to calculate an overall quality percentage for each domain.

Literature searches conducted in 2005 and 2006 by the Working Group identified a number of relevant existing guidelines. Seven identified guidelines were assessed by two independent reviewers using the AGREE tool. The following seven guidelines were assessed and the results are presented in *Table 1*:

- Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis: A national clinical guideline. December 2000[2]
- Emery P, Suarez-Almazor M. Rheumatoid arthritis. Clinical Evidence 2003[3]
- Kalla AA, Stanwix A, Gotlieb D, et al. Rheumatoid arthritis: Clinical guideline. South African Med J 2003[4]
- Combe B, Landewé R, Lukas C, et al. European League Against Rheumatism (EULAR) recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). 2006[5]
- Luqmani R, Hennell S, Estrach C, et al. British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology. Guideline for the management of rheumatoid arthritis (the first 2 years). 2006[6]
- The Association of Physicians of India. Indian guidelines for the management of rheumatoid arthritis. 2002[7]
- American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. 2002 update.[8]

Table 1. AGREE domain scores for identified guidelines (Shaded guidelines were selected as primary sources)

Guideline	AGREE domain scores					
	Domain 1. Scope and purpose	Domain 2. Stakeholder involvement	Domain 3. Rigour of development	Domain 4. Clarity and presentation	Domain 5. Applicability	Domain 6. Editorial independence
SIGN, 2000	**61%**	**58%**	**40%**	**75%**	**17%**	**8%**
Clinical Evidence, 2003	**64%**	**8%**	**86%**	**58%**	**33%**	**66%**
South African guidelines, 2003	44%	58%	24%	17%	0%	67%
Indian guidelines, 2002	11%	0%	4%	33%	0%	0%
ACR guidelines, 2002	8%	0%	4%	0%	22%	33%
EULAR, 2006	**72%**	**25%**	**52%**	**71%**	**0%**	**0%**
BSR, 2006	**72%**	**67%**	**52%**	**75%**	**83%**	**92%**

The following four international guidelines were selected as the primary sources of information for the RA guideline for the following reasons:

1. EULAR recommendations for the management of early arthritis.[5] This guideline was selected as a primary resource due to its high rigour of development and overall clarity.
2. BSR. Guideline for the management of rheumatoid arthritis (the first 2 years).[6] This guideline was elected because of its overall high scoring on the AGREE tool, and specifically for its strong GP focus, making this guideline particularly applicable to this project.
3. SIGN. Management of early rheumatoid arthritis.[2] This guideline was selected because of its high rigour of development, high scores, and overall clarity based on research published up to mid 2000.
4. Rheumatoid arthritis. Emery P, Suarez-Almazor M. Clinical evidence, 2003;(9):1349-71.[3] This guideline was selected as a primary source on medications as it provided a comprehensive review of the pharmacological management of RA based on research published up to 2002.

Identification, appraisal and synthesis of new evidence

Following the selection of existing guidelines, literature searches were conducted to identify new evidence published since the selected guidelines. The Working Group conducted extensive literature searches to identify the most recent available evidence under the guidance of experienced librarians, research consultants, and a National Health and Medical Research Council (NHMRC) consultant. The process used for the literature search is reported in more detail in *Early rheumatoid arthritis: a literature review of recent evidence* (www.racgp.org.au/guidelines/rheumatoidarthritis/literaturereview).

Search strategy

The MEDLINE, EMBASE and CINAHL databases and the Cochrane Library (including CENTRAL Cochrane Controlled Trial Register) were searched to identify studies for inclusion. As this literature review intended to update previous guidelines, only papers published between January 2005 and December 2006 were included, and inclusion was limited to English language literature. Reference lists in review articles and trials were also retrieved. An additional manual search was used to identify evidence for interventions not represented in the initial search or not covered by the primary guidelines. Further grey literature was also identified through personal contact with the authors. In specific areas where randomised controlled trials (RCTs) or systematic reviews (SRs) were not

available, lesser levels of evidence and expert opinion were sourced. The following search strategies were applied to the MEDLINE database and were adapted to apply to the other databases.

Search of evidence on diagnosis of RA

1. Arthritis, Rheumatoid/bl, cf, di, ra, ri, us [Blood, Synovial Fluid, Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography] (13155)
2. Early Diagnosis/ or Diagnosis/ or Diagnosis, Differential/ (301051)
3. (sensitivity and specificity).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (202073)
4. sensitivity.tw. (302016)
5. specificity.tw. (198517)
6. ((pre test or pre-test) adj probability).tw. (157)
7. ((pre-test or pretest) adj probability).tw. (576)
8. predictive value$.tw. (12)
9. predictive value$.tw. (36002)
10. likelihood ratio$.tw. (3573)
11. 3 or 4 or 5 or 7 or 9 or 10 (545298)
12. 1 and 2 and 11 (111)
13. limit 12 to (humans and English language and yr='2005 - 2006') (21).

Search for evidence on management of RA

1. Arthritis, Rheumatoid/di, dh, pc, dt, ra, ri, rt, rh, su, th, us [Diagnosis, Diet Therapy, Prevention & Control, Drug Therapy, Radiography, Radionuclide Imaging, Radiotherapy, Rehabilitation, Surgery, Therapy,] (10573)
2. 'Practice Guideline [Publication Type]'/ (8111)
3. 'Review Literature'/ or Meta-Analysis/ (6343)
4. 'Guideline [Publication Type]'/ (9399)
5. 2 or 3 or 4 (16730)
6. 1 and 5 (60)
7. limit 6 to (humans and English language and yr='2005 - 2006') (24)
8. from 7 keep 1-18 (18).

Diagnosis inclusion/exclusion criteria

Types of studies

Only studies considered to be of NHMRC Level I–III evidence (*Table 3*) that evaluated diagnostic strategies for RA were considered for inclusion. Studies reported in SRs already selected for inclusion were not subjected to individual critical appraisal to prevent replication of data.

Types of participants

Studies that included individuals aged 16 years or over with disease duration of 2–5 years.

Management inclusion/exclusion criteria

Types of studies

Only studies considered being of NHMRC Level I evidence (*Table 2*) that evaluated the effectiveness and/or safety of pharmacological and non-pharmacological interventions for RA were considered for inclusion.

Types of participants

Studies that included individuals aged 16 years or over with a diagnosis of RA.

Table 2. NHMRC levels of evidence[9]

Level	Intervention	Diagnosis
I	Evidence obtained from a SR of all relevant RCTs	A SR of Level II studies
II	Evidence obtained from at least one properly designed RCT	A study of test accuracy with independent blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III–1	Evidence obtained from well designed, pseudo-randomised, controlled trials (alternate allocation or some other method)	A study of test accuracy with independent blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III–2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group	A comparison with reference standard that does not meet the criteria for Level II or Level III-1 evidence
III–3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group	Diagnostic case control evidence
IV	Evidence obtained from case series, either post-test or pre-test and post-test	Study of diagnostic yield (no reference standard)

Critical appraisal

Critical appraisals were conducted for all studies that met the inclusion criteria, with the exception of Cochrane reviews, for which critical appraisal was not considered to be warranted (NHMRC advisor). One reviewer critically appraised all studies that met the inclusion criteria, with a second reviewer appraising 40% of the papers. There was a high level of consensus between reviewers, with minor discrepancies in SIGN scoring resolved by a third reviewer.

The following critical appraisal tools were used where appropriate by the appraisers:

- SIGN appraisal tool for SRs (www.sign.ac.uk/guidelines/fulltext/50/checklist1.html)
- SIGN appraisal tool for RCTs (www.sign.ac.uk/guidelines/fulltext/50/checklist2.html)
- NHMRC diagnostic study appraisal form (www.nhmrc.gov.au)
- Textual paper score designed for this project.

Studies were graded as being of good, moderate or low quality based on the results of appraisal using the SIGN tools. The appraisal tools and their use are described in detail in the methodology in *Early rheumatoid arthritis: a literature review of recent evidence* (www.racgp.org.au/guidelines/rheumatoidarthritis/literaturereview).

Data extraction

Data extraction tools and tables were used to systematically identify and extract evidence. The following data extraction tools were used where appropriate by the appraisers:

- SR data extraction form developed by the Joanna Briggs Institute (JBI) (available on request from JBI or NHMRC)
- NHMRC intervention data extraction form (www.nhmrc.gov.au)
- Textual paper data extraction form.

For diagnosis studies the primary and secondary reviewers used a tabulated format to extract the relevant data. On combining data from the two reviewers, no discrepancies were found. For

intervention studies the primary reviewer used the JBI data extraction tool for SRs to extract data from the included studies in a systematic manner.[10] The second reviewer checked and tabulated the data and no discrepancies were found. *Early rheumatoid arthritis: a literature review of recent evidence* presents the new evidence from included studies in a descriptive and tabulated format.

Special populations

The search strategy was designed to retrieve all available evidence meeting the inclusion criteria for the literature review, including research specific to the identified special populations – Indigenous Australians (Aboriginal and Torres Strait Islanders), rural and remote communities, Muslim Australians, and Vietnamese Australians. The literature searches identified minimal to no evidence directly related to these populations, thus a broader search was conducted to identify any research that addressed management of arthritis in these special population groups.

The following search was conducted in MEDLINE, CINAHL, EMBASE and Cochrane Library to identify relevant information:

1. Aboriginal.mp. OR Aborigine.mp. OR koori.mp. OR indigenous.mp. OR torres strait.mp. OR Vietnam/ OR Vietnamese.mp. OR rural health centers/ OR Hospitals, Rural/ OR Rural Health/ OR Rural Health Services/ OR Rural Areas/ OR Rural Health Nursing/ OR muslim.mp. OR Islam/
2. Arthritis, Rheumatoid/ OR Arthritis/ OR Arthritis.mp
3. 2 and 3.

Ten papers were identified for retrieval – five papers related to Indigenous Australians, three papers related to rural health and two focussed on Muslim populations. Nine papers were excluded as they did not directly relate to arthritis, or contained purely historical health information.

Development of the recommendations

Through group meetings, email circulation and feedback, the Working Group used the information from new evidence, together with recommendations from the primary source guidelines and expert opinion to develop recommendations relevant to general practice within Australia.

Evidence statements were developed that represented a summary of the most relevant research from the literature or, where there had been no newly published research, from the primary resource guidelines. The NHMRC body of evidence assessment matrix[9] (*Table 3*) was used to make an assessment of the volume and consistency of the literature on which the evidence statement was based. Additional assessments included clinical impact, generalisability, and applicability of the recommendation.

Each recommendation was given a final grading (*Table 4*) representing its overall strength. The gradings reflect implementability in terms of confidence practitioners can use in a clinical situation. The overall grade of each recommendation was reached through consensus and is based on a summation of the grading of individual components of the body of evidence assessment. In reaching an overall grade, recommendations did not receive a grading of A or B unless the volume and consistency of evidence components were both graded either A or B.

Where appropriate, recommendations are followed by good practice points. The good practice points are essential tips on how to effectively implement the recommendations.

Table 3. NHMRC body of evidence assessment matrix[9]

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	Several Level I or Level II studies with low risk of bias	One or two Level II studies with low risk of bias or a SR/multiple Level III studies with low risk of bias	Level III studies with low risk of bias or Level II studies with moderate risk of bias	Level IV studies or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistencies may be explained	Some inconsistency reflecting genuine uncertainty around the clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as the target population for the guideline	Population(s) studied in the body of evidence are similar to the target population for the guideline	Population(s) studied in the body of evidence different to the target population for the guideline, but it is clinically sensible to apply this evidence to the target population (eg. results obtained in adults that are clinically sensible to apply to children)	Population(s) studied in the body of evidence different to the target population for the guideline and hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to the Australian health care context	Applicable to the Australian health care context with few caveats	Probably applicable to the Australian health care context with some caveats	Not applicable to the Australian health care context

Table 4. NHMRC grade of recommendations[9]

Grade	Description
A	Excellent evidence – body of evidence can be trusted to guide practice
B	Good evidence – body of evidence can be trusted to guide practice in most situations
C	Some evidence – body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Weak evidence – body of evidence is weak and recommendation must be applied with caution
Note: A recommendation cannot be graded A or B unless the volume and consistency of evidence components are both graded either A or B.	

Consultation phase

Draft versions of the *Clinical guideline for the diagnosis and management of early rheumatoid arthritis; Recommendations for the diagnosis and management of early rheumatoid arthritis; and Early rheumatoid arthritis: a literature review of recent evidence,* were presented for public feedback via the RACGP website. An interactive survey was designed to collect comments from all potential stakeholders. The public consultation period was advertised in a major national newspaper, information was sent to almost 20 000 GPs, and over 200 known stakeholders (eg. members of RACGP musculoskeletal groups, arthritis foundations, departments of general practice, consumer groups) were sent personal invitations to review the material. Feedback collected from the survey and independent submissions were collated and addressed by the Working Group.

The Working Group would like to thank respondents who provided feedback during the consultation phase of the project. The Working Group acknowledges the contribution of Dr Melainie Cameron, who provided access to new evidence[11,12] relevant to this project via the consultation process.

Dissemination

Final versions following consultation of *Clinical guideline for the diagnosis and management of early rheumatoid arthritis; Recommendations for the diagnosis and management of early rheumatoid arthritis; and Rheumatoid arthritis: a literature review of recent evidence*, together with supporting resources, will be made available to Australian GPs, and the public, on the RACGP website.

Process report references

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APPENDIX B. MEMBERSHIP AND TERMS OF REFERENCE OF THE RACGP RHEUMATOID ARTHRITIS WORKING GROUP

Aim of the Working Group

The aim of the Working Group was to undertake activities required to fulfil the aims of the project as outlined in the funding agreement, including:

- carrying out a review of literature as per NHMRC requirements, and
- developing clinical practice guidelines based on the evidence obtained within the literature review.

Establishment of the Working Group

In accordance with the project contract, membership of the Working Group endeavoured to include:

- three or more experts in each field – medical (including one GP) and allied health
- one expert National Arthritis and Musculoskeletal Conditions Advisory Group member
- one consumer representative
- one departmental representative
- a consultant appointed by the NHMRC.

In addition, a nominee of the Australian Rheumatology Association or the Australian and New Zealand Bone and Mineral Society was represented in accordance with the project contract.

Acknowledgments

The Working Group would like to acknowledge the contributions and dedicated work of the late Associate Professor Peter Waxman and the late Emeritus Professor Fay Gale.

Membership of RACGP Rheumatoid Arthritis Working Group

Member	Representation	Qualifications
Associate Professor Lyn March (Chair) Rheumatologist	Australian Rheumatology Association, NSW	MBBS, MSc(EpidemiolBiostats), PhD, FAFPHM, FRACP
Dr Claire Barrett	Rheumatologist, Qld	BSc, MBBS, MRCP, FRACP
Emeritus Professor Fay Gale Consumer representative (deceased)	Consumers' Health Forum of Australia, SA	AO, BA(Hons), PhD, DUniv(Hons), DLitt, FASSA
Associate Professor Marissa Lassere	Rheumatologist, NSW	MBBS, GradDipEpiN'cle, PhD UNSW, FAFPHM, FRACP
Jean McQuade Manager, Health Education and Research programs, Arthritis and Osteoporosis	Registered nurse/health educator, WA	RN, RHV, DipGrad(HV/PH), BSc(HlthPromEduc), GradDipArts (Counselling)
Dr Lyndal Trevena GP	RACGP, NSW	MBBS(Hons), MPhilPH, DipChildHealth, PhD
Dr John W Bennett GP	RACGP, Qld	BMedSc, MBBS, BA(Hons), PhD, FACHI, FRACGP
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