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Using systematic literature reviews to develop guidelines for the management of inflammatory arthritis

by

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ABSTRACT

FACULTY OF MEDICINE

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USING SYSTEMATIC LITERATURE REVIEWS TO DEVELOP GUIDELINES FOR THE MANAGEMENT OF INFLAMMATORY ARTHRITIS

Alexandra Nicole Bourn

The vast amount of research published on clinical areas can make awareness of current data difficult. Systematic literature reviews (SLR) are performed in order to identify, appraise and summarise the available evidence relating to specific clinical questions, and form the basis of the process used to produce clinical guidelines.

This thesis describes the different processes used to produce guidelines using SLR. It includes a review of the literature on imaging in the management of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) as examples.

To perform the RA review, key clinical questions were generated on the role of imaging in RA, which included the use of conventional radiography (CR), ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), dual-emission X-ray absorptiometry (DXA), digital X-ray radiogrammetry (DXR), scintigraphy and positron emission tomography (PET). A comprehensive SLR was then performed resulting in recommendations on the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease activity, progression and remission. A similar process was used to produce recommendations in the management of JIA; however the lack of quality data meant that 'points to consider' were created.

The thesis also considers the quality of existing recommendations with potential areas for improvement discussed. It concludes with a discussion of the overall benefit of guidelines.

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List of Publications and Presentations

The following publications and presentations have resulted from the work completed as part of the candidature for Doctor of Medicine.

Academic publications:

AN Colebatch-Bourn, CJ Edwards, P Collado *et al*. EULAR-PRES points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. Ann Rheum Dis 2015;74:1946-1957.

AN Colebatch-Bourn, NK Arden, PG Conaghan, C Cooper, CJ Edwards. Are guidelines good value for money? Rheumatology (Oxford) 2015;54:2121-2123.

AN Colebatch-Bourn, PG Conaghan, NK Arden, C Cooper, M Dougados, CJ Edwards. Raising the quality of rheumatology management recommendations: lessons from the EULAR process ten years after provision of standard operating procedures. Rheumatology (Oxford) 2015;54:1392-1396.

AN Colebatch, CJ Edwards, M Ostergaard *et al*. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis 2013;72(6):804-814.

Conference oral presentations:

AN Colebatch-Bourn, CJ Edwards, P Collado *et al*. EULAR-PRES points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. PReS 2015 Young Investigator Meeting.

AN Colebatch-Bourn, PG Conaghan, NK Arden, C Cooper, M Dougados, CJ Edwards. The quality of EULAR management recommendations: a review ten years after publication of standardised operating procedures. EULAR 2014 Annual Conference.

PG Conaghan, **AN Colebatch-Bourn**, CJ Edwards. EULAR-PRES points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice: SLR progress. EULAR 2014 Annual Conference.

CJ Edwards, **AN Bourn**. EULAR recommendations for the use of imaging of joints in the clinical management of rheumatoid arthritis: SLR final results. EULAR 2012 Annual Conference.

Conference poster presentations and abstracts:

AN Colebatch-Bourn, C Malattia, P Collado *et al*. The patients' experience of imaging: views from a group convened to support the development of points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis [abstract]. Ann Rheum Dis 2015;74(Suppl 2):380.

AN Colebatch-Bourn, CJ Edwards, P Collado *et al*. EULAR-PRES points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice [abstract]. Ann Rheum Dis 2015;74(Suppl 2):611.

AN Colebatch-Bourn, C Malattia, P Collado *et al*. The patients' experience of imaging: views from a group convened to support the development of points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis. PReS 2015 Young Investigator Meeting, poster presentation.

AN Bourn, PG Conaghan, NK Arden, C Cooper, M Dougados, CJ Edwards. The quality of EULAR management recommendations: a review ten years after publication of standardised operating procedures [abstract]. Ann Rheum Dis 2014;73(Suppl 2):173.

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EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice

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ABSTRACT

To develop evidence based points to consider the use of imaging in the diagnosis and management of juvenile idiopathic arthritis (JIA) in clinical practice. The task force comprised a group of paediatric rheumatologists, rheumatologists experienced in imaging, radiologists, methodologists and patients from nine countries. Eleven questions on imaging in JIA were generated using a process of discussion and consensus. Research evidence was searched systematically for each question using MEDLINE, EMBASE and Cochrane CENTRAL. Imaging modalities included were conventional radiography, ultrasound, MRI, CT, scintigraphy and positron emission tomography. The experts used the evidence obtained from the relevant studies to develop a set of points to consider. The level of agreement with each point to consider was assessed using a numerical rating scale. A total of 13 277 references were identified from the search process, from which 204 studies were included in the systematic review. Nine points to consider were produced, taking into account the heterogeneity of JIA, the lack of normative data and consequent difficulty identifying pathology. These encompassed the role of imaging in making a diagnosis of JIA, detecting and monitoring inflammation and damage, predicting outcome and response to treatment, use of guided therapies, progression and remission. Level of agreement for each proposition varied according to the research evidence and expert opinion. Nine points to consider and a related research agenda for the role of imaging in the management of JIA were developed using published evidence and expert opinion.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of conditions with onset under the age of 16 years with unknown aetiology and persistence of symptoms for over 6 weeks.[1] Imaging plays an important role in diagnosis and monitoring of patients with JIA, but until recently there were few studies in this area.

A European League against Rheumatism (EULAR)—Pediatric Rheumatology European Society (PReS) task force was convened to produce evidence and consensus-based recommendations on the use of imaging in the diagnosis and management of JIA in clinical practice for use by secondary care professionals caring for children with JIA, to help define standards of care for appropriate imaging.

METHODS

An expert group of paediatric rheumatologists, rheumatologists with imaging expertise, radiologists, methodologists and a fellow (16 people, representing 9 countries) participated. The task force used a rigorous procedure as described in the updated EULAR standardised operating procedures.[2 3] Full methodological details are given in the online supplementary material S1.

At an initial meeting, members developed questions relevant to key aspects of the use of imaging in JIA. Eleven research questions were agreed by consensus, encompassing the role of imaging in making a diagnosis, detecting inflammation and damage, predicting outcome and response to treatment, the use of guided treatment, monitoring disease progression, and remission (see online supplementary text research questions S2). A detailed systematic search of the published literature was performed on studies involving the use of imaging in children with JIA. Imaging modalities included were X-ray described as conventional radiography (CR), ultrasound (US), MRI, CT, scintigraphy and positron emission tomography. Included studies were evaluated for risk of bias and applicability using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool.[4] Following presentation of the literature review at a second meeting, experts produced points to consider (PTC) with final agreement by a process of discussion and consensus. The available evidence for each recommendation was scored according to the Oxford Centre for Evidence-Based Medicine level of evidence.[5] The experts anonymously scored their level of agreement for each proposition using a 0–10 numerical rating scale (0=do not agree at all, 10=fully agree). Scores reflected research evidence and clinical expertise.[2] An agenda for future research was also agreed upon following presentation of the literature review.

Three patient representatives (one child and two young adults with a diagnosis of JIA) and two parents of children with JIA participated in the development of the PTC at a Patient and Public Involvement event; further details are given in the online supplementary material S1.

RESULTS

The database search (November 2013) resulted in 13 277 records leaving 10 925 articles after

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Table 1 Points to consider, level of evidence, grade of recommendation and level of agreement

	Point to consider	Level of evidence	Grade of recommendation	Level of agreement, mean NRS 0–10 (range)
1	US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, in diagnosis and assessing extent of joint involvement.	3b	C	9.07 (6–10)
2	When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.	3b	C	9.43 (9–10)
3	If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.	3b	C	8.71 (5–10)
4	In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the TMJ and axial involvement.	3b	C	9.64 (8–10)
5	Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.	4	C	9.07 (5–10)
6	In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.	3b	C	9.07 (7–10)
7	The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.	3b	C	8.29 (5–10)
8	US can be used for accurate placement of intra-articular injections.	3b	C	9.64 (8–10)
9	US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.	3b	C	8.86 (5–10)

The level of evidence and grade of recommendation are based on the Oxford Centre for Evidence-Based Medicine system.[5]
Level of evidence scale, 1a–5; grade of recommendation scale; A–D. NRS, numerical rating scale (0–10; 0=do not agree at all, 10=fully agree).
CR, conventional radiography; JIA, juvenile idiopathic arthritis; TMJ, temporomandibular joint; US, ultrasound.

deduplication. Four hundred and thirty-three articles were included for detailed review once exclusions were made based on title or abstract. All full text articles written in English were retrieved for review, of which 244 articles were excluded leaving 189 articles for inclusion. The hand search identified 15 additional articles, resulting in a total of 204 articles for inclusion (see flow chart in the online supplementary figure S4). Articles that were relevant to multiple research questions were included in the review as necessary. The number of articles included per question is shown in the online supplementary table S5.

The task force produced nine PTC which are presented with the level of evidence, grade of recommendation and level of agreement in table 1. The task force felt that the supporting data was not sufficient to produce 'recommendations' so they were categorised as 'points to consider'. Scores for risk of bias and applicability of the included studies according to QUADAS-2, a full reference list for articles included in each recommendation, and feedback given at the Patient and Public Involvement meeting are given in the online supplementary text S6 S7 and S8.

Overarching principles

The task force produced general statements that should be considered when interpreting the PTC. These principles cover the imaging needs of inflammatory arthritis is children and assume that other important differentials such as infection have been ruled out.

- 'JIA' is an umbrella term for all forms of inflammatory arthritis that begins before the age of 16 years, persists for more than 6 weeks and is of unknown origin. This heterogeneous group of diseases is currently classified according to the International League of Associations for Rheumatology classification.[6] There is a lack of information on imaging related to JIA categories at present.
- There is a paucity of data on the joint-specific imaging features present during growth and skeletal development in healthy children. Understanding normative data is essential for interpretation of imaging abnormalities. For example, some physiological features of recently ossified bones can be misinterpreted as cortical erosions, cartilage thickness may vary with skeletal maturation and vascularity of epiphyses will change with ageing.
- Joint inflammation at certain developmental time points may cause specific structural changes, further challenging imaging assessment.
- The appropriateness and feasibility of different imaging modalities differs with age, related to radiation exposure and requirement for sedation. Every effort should be made to avoid unnecessary radiation exposure. However, there is a long established experience with the use of CR to demonstrate damage.
- Patient experience with different imaging modalities is affected by their age and development. It is important to provide a 'child friendly' environment.

Points to consider

Making a diagnosis of JIA

PTC 1: US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, in diagnosis and assessing extent of joint involvement.

Sixty-five studies compared clinical examination with imaging in the detection of inflammation in various joints, 40 with US, 27 with MRI, 5 with CR and 1 with positron emission tomography (table 2). The data is represented according to detection rates; for example, how many times more (>one fold) or less (<one fold) does imaging detect inflammation over clinical examination; this has the potential to increase false positive results. In general, US and MRI were able to detect joint inflammation more frequently than clinical examination; for example

Table 2 Point to consider 1: Summary of included studies comparing imaging with CE in the detection of joint inflammation

Ultrasound **US knees vs CE** **13 studies**[13 14 33 34 38 76–83]		**MRI** **MRI knees vs CE** **studies**[13–15 36 72 84–87]		**CR** **CR knees vs CE** **3 studies**[13 15 85]	
	Detection rate, mean (range) US vs CE		Detection rate, mean (range) MRI vs CE		Detection rate, mean (range) CR vs CE
Synovitis/effusion (12 studies)[13 14 34 38 76–83]	1.19-fold (0.14–3.67-fold)	Synovitis vs clinical swelling (3 studies)[14 85 86]	1.02-fold (0.96–1.12-fold)	Joint distension vs swelling (3 studies)[13 15 85]	0.69-fold (0.45–1.0-fold)
		Effusion vs swelling (5 studies)[13–15 36 85]	1.07-fold (0.75–1.33-fold)		
Effusion (1 study)[33]	Agreement k=0.54 CE missed a significant no. of effusions	Effusion vs pain (1 study)[13]	1.45-fold (1.33–1.57-fold)		
PD vascularity (2 studies)[38 82]	1.63-fold (0.96–2.71-fold)	Synovial volume vs CRP (1 study)[87]	r=0.51–0.80 p=0.000–0.036	Joint distension vs pain (1 study)[13]	1.57-fold
		Synovial hypertrophy vs pain (1 study)[84]	r=0.68–0.74		

US hip vs CE **5 studies**[13 16 78 88 89]		**MRI hip vs CE** **5 studies**[13 15 90–92]		**CR hip vs CE** **1 study**[15]	
Synovitis/effusion (5 studies)[13 16 78 88 89]	0.85-fold (0.13–1.39-fold)	MRI inflammation (4 studies)[13 15 90 91]	0.88-fold (0.50–1.78-fold)	Joint distension vs clinical effusion (1 study)[15]	0.80-fold
Synovitis/effusion vs LOM (1 study)[89]	Association p=0.006				
Synovitis/effusion vs pain (1 study)[89]	Association p=0.103	Synovial enhancement (1 study)[91]	0.94-fold		

US hands/wrists vs CE **4 studies**[38 40 93 94]		**MRI hands/wrists vs CE** **2 studies**[19 95]		**CR hands/wrists vs CE** **1 study**[93]	
Synovitis/effusion (3 studies)[38 93 94]	0.93-fold (0.47–1.33-fold)	Synovitis volume vs total hand swelling score (1 study)[95]	r=0.52–0.72 p<0.05	Joint distension vs clinical effusion (1 study)[93]	0.63-fold
PD vascularity (2 studies)[38 40]	0.96-fold GS synovitis had weaker correlation with clinical disease activity than PD	Synovitis volume vs LOM (1 study)[95]	r=0.76 p<0.05		
Flexor/extensor tenosynovitis (1 study)[40]	Significant association with clinical disease activity	Synovitis score vs wrist swelling score (1 study)[19]	MRI score significantly higher with higher swelling score p<0.00001		

US ankles/feet vs CE **5 studies**[38 79 96–98]		**MRI ankles/feet vs CE** **1 study**[99]	
Synovitis/effusion (3 studies)[38 79 96]	0.97-fold (0.86-1.04-fold)	Tibiotalar synovitis (1 study)[99]	1.00-fold
PD vascularity (1 study)[38]	0.57-fold	Subtalar synovitis (1 study)[99]	3.33-fold

US TMJ vs CE3 studies[25 100 101]		**MRI TMJ vs CE** **8 studies**[25 41 42 102–106]	
Synovitis/effusion (2 studies)[25 100]	11.7-fold (0.35–23.0-fold)	Synovitis (6 studies)[25 41 42 104–106]	2.46-fold (1.10–5.91-fold)
		Synovitis vs reduced MIO (4 studies)[25 102 103 105]	Significantly correlated Reduced MIO best predictor of active MRI changes
		Acute changes (1 study)[41]	71% asymptomatic 63% normal CE

Continued

Table 2 Continued

US enthesitis vs CE **3 studies**[107–109]				**MRI enthesitis vs CE** **1 study**[110]		
US enthesitis vs CE **3 studies**[107–109]				**MRI enthesitis vs CE** **1 study**[110]		
Enthesitis (3 studies)[107–109]	0.79-fold (0.53–1.09-fold)			Enthesitis (1 study)[110]	0.50-fold	
US VARIOUS MULTIPLE JOINTS vs CE **9 studies**[48 50 64 111–117]		**MRI VARIOUS MULTIPLE JOINTS vs CE** **1 study**[110]			**CR VARIOUS MULTIPLE JOINTS vs CE** **1 study**[118]	
Synovitis/effusion (6 studies)[48 111–114 116]	1.85-fold (1.00–3.33-fold)	Synovitis/effusion (1 study)[110]	1.08-fold		Soft tissue swelling vs clinical swelling (1 study)[118]	1.05-fold
Association US changes vs swelling (1 study)[48]	SH: r=0.63 Effusion: r=0.66 PD: r=0.50					
Association synovitis vs CE (2 studies)[50 117]	Swelling: r=0.50 LOM: r=0.40 Pain: r=0.21 CE missed inflammation in 25.2% joints	MRI cervical spine vs CE 1 study[20]				
		Synovitis/SH (1 study)[70]	4.25-fold			
		MRI SIJ vs CE 2 studies[23 119]				
		Sacroiliitis (2 studies)[23 119]	0.93-fold CE was normal in 22.9% patients with MRI sacroiliitis			

CE, clinical examination; CR, conventional radiography; CRP, C reactive protein; GS, grey scale; LOM, limitation of movement; MIO, maximal incisional opening; PD, power Doppler; SIJ, sacroiliac joint; SH, synovial hypertrophy; TMJ, temporomandibular joint; US, ultrasound.

the mean (range) detection rate for synovitis and effusion at the knee was 1.19-fold (0.14–3.67-fold) for US and 1.02-fold (0.96–1.12-fold) for MRI knee synovitis.

PTC 2: When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.

The diagnosis of JIA is mainly based on clinical features and the exclusion of other causes of chronic arthritis. However this point illustrates the role of imaging when there is diagnostic doubt; no specific imaging signatures for JIA have been described yet, but imaging is helpful to narrow the differential diagnosis. Four studies compared imaging features in suspected/proven JIA with either controls or other disease entities, including infectious arthritis, acute lymphoblastic leukaemia and haemophilia.[7–10] US detected more joint inflammation than clinical examination; two studies specifically described US improving the diagnostic certainty in subjects with suspected JIA.[11 12]

Detecting damage

PTC 3: If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.

Thirty-seven studies compared joint damage (erosions, joint space narrowing (JSN), deformity) detected by imaging with clinical findings suggestive of underlying damage, such as tenderness, limitation of movement and crepitus. In general, all imaging modalities appeared to detect less joint damage than suggested by clinical examination; for example the mean (range) detection rate for cartilage loss at the knee was 0.32-fold for US, 0.63-fold (0.20–1.0-fold) for MRI and 0.46-fold (0.23–0.71-fold) for CR when compared with pain.[13–15] This reflects the poor sensitivity of pain as an indicator of underlying damage.

When the imaging modalities are directly compared MRI and US detected more joint damage than CR, particularly at the hip (MRI vs CR detection rate, mean (range) 1.54-fold (1.08–2.0-fold); US vs CR detection rate, mean 2.29-fold), and at the wrist (MRI vs CR detection rate, 1.36-fold (1.0–2.0-fold)).[13 15–19]

Imaging specific joints

PTC 4: In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the temporomandibular joint (TMJ) and axial involvement.

Cervical spine MRI appears better at detecting inflammation than clinical examination; one study showed 20% of patients had pain and/or limitation of movement whereas 85% had MRI inflammatory changes suggesting that cervical spine involvement in JIA is often clinically silent.[20] MRI and CR have shown better detection rates than clinical examination for structural changes in the cervical spine (4.5-fold and mean, range 2.29 (1.58–3.0-fold)), respectively.[21 22] Abnormal sacroiliac joint (SIJ) imaging is also demonstrated despite a high rate of normal examination; for example, normal SIJ examination in 42.9% and 22.9%, in patients with CR and MRI sacroiliitis, respectively.[23 24]

Muller *et al*[25] compared TMJ clinical examination and US with MRI changes, and found that examination correctly identified 58% patients with active MRI TMJ arthritis compared with 33% for US, and missed inflammation in 42% and 67%, respectively. They described reduced maximal incisal opening to be the best predictor of active MRI changes.[26] Full data comparing the various imaging modalities with clinical examination of the TMJ is given in the online supplementary text S9.

Prognosis

PTC 5: Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.

Thirteen observational studies examined the relationship between baseline imaging and subsequent radiographic and clinical outcome; 11 with CR and 2 with MRI at baseline. The statement on US inflammation is therefore based on expert opinion; the findings are given in full in table 3. In general, CR damage in the 1st year has a moderate correlation with functional deterioration according to Steinbocker class, Childhood Health Assessment Questionnaire and physician/parent disability scores at 5 years, as well as with CR progression at 5 years.[27–29] A baseline CR wrist adapted Sharp van der Heijde score >1 was shown to be predictive of CR progression at 5 years (OR, 8.2), and patients with erosions and/or JSN in the first 6 months of the study spent more time with clinically active disease and were less likely to achieve clinical remission on medication.[30 31] Just one study described the correlation of baseline MRI wrist synovial volume with MRI erosive progression at 1 year; this found a moderate correlation, and all patients with high synovial volume at baseline had erosive progression.[32]

Monitoring inflammation

PTC 6: In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.

Data comparing imaging with clinical examination in detecting joint inflammation is discussed in PTC 1, and specific information on imaging the TMJ and for axial involvement is summarised in PTC 4. This section will consider the comparison of the ability of imaging to detect inflammation, responsiveness of imaging to change in inflammation, and which joints should be assessed.

Comparison of the ability of imaging to detect inflammation

Several studies compared US with MRI in the detection of inflammation, particularly at the knee.[13 14 33 34] These studies have shown MRI to be better in detecting knee inflammation than US (mean detection rate 1.20-fold, range 0.63–1.56-fold) and in particular MRI was better than US in differentiating pannus from effusion.[13] Knee MRI with contrast enhancement was more reliable at localising and differentiating synovial hypertrophy from synovial fluid particularly when there was <5 mm of synovial hypertrophy, but the addition of contrast did not provide additional information in the assessment of inflammatory bone marrow lesions.[35–37] Comparison of power Doppler with grey-scale wrist US has resulted in conflicting results, whereas the use of contrast significantly increased knee US synovial pixel intensity in those with symptomatic disease ($p=0.004$) and asymptomatic disease ($p=0.0001$), but not in those in clinical remission.[38–40]

Studies comparing TMJ US with MRI have shown a poor correlation between these modalities, with US missing 67–75% of TMJ MRI inflammation.[25 41] The use of MRI contrast enhancement improved the detection of MRI TMJ inflammation from 35.7% to 86.7%.[42] One study examined the CR findings in patients with TMJ MRI synovitis and found significant correlation with abnormal condyle morphology and accentuated antegonial notching on CR, and joints with both of these changes

Table 3 Point to consider 5: Summary of included studies describing the prognostic value of the imaging modalities

Reference	No. of subjects	Duration of follow-up (months)	Radiological or clinical assessment	Outcome assessed	Correlation	
Baseline CR predictive factors						
Susic *et al*[120]	87	48	Wrist involvement	CHAQ-DI	Significant correlation p<0.01	
			Hip involvement		Significant correlation p<0.001	
			JADI-A		Significant correlation p<0.01	
Ravelli *et al*[29]	96	min. 60	CR wrist changes at: baseline in 1st year in 1st 5 years	No. of joints with LOM	Baseline: low r=0.16 1st year: low r=0.35 1st 5 years: moderate r=0.59	
				JADI-A	Baseline: low r=0.21 1st year: moderate r=0.53 1st 5 years: moderate r=0.60	
				Steinbocker functional class	Baseline: low r=0.21 1st year: moderate r=0.48 1st 5 years: moderate r=0.55	
				CR progression at 5 years	Baseline: low r=0.38 1st year: moderate r=0.61 1st 5 years: high r=0.89	
Pederzoli *et al*[30]	130	min. 60	CR wrist a SH score > 1	CR progression at 5 years	Significant predictor OR 8.2	
Magni-Manzoni *et al*[28]	94	54			Baseline Poznanski score	CR progression in 1st yr
			Baseline Poznanski score	Yearly CR progression	r=0.88 p=0.47	r=0.62, p<0.001 OR 14.32, p<0.0001
			CR wrist progression in 1st year	Final Poznanski score	r=0.58 p<0.0001	r=0.59, p<0.0001 OR 6.49, p=0.0006
				CHAQ	r=0.20 p=0.14	r=0.39, p=0.003 OR 8.42, p=0.002
Bertamino *et al*[27]	148	max. 132	CR hip progression in 1st year	CHAQ	r=0.24, p=0.1	
				SJC	r=0.03, p=0.86	
				TJC	r=0.06, p=0.65	
				No. of joints with LOM	r=0.46, p=0.0005	
				Steinbocker functional class	r=0.50, p=0.005	
				JADI-A	r=0.45, p=0.01	
				Physician disability score	r=0.40, p=0.05	
				Parent disability score	r=0.53, p=0.007	
Oen *et al*[121]	136	min. 60	Early (<2 years) erosions/JSN	CHAQ	No correlation	
Selvaag *et al*[122]	197	36	Baseline swelling/osteopenia	CR erosive progression	OR 7.95, p<0.001	
					Less patients with CR progression had CHAQ of 0, p=0.045	

Continued

Table 3 Continued

Reference	No. of subjects	Duration of follow-up (months)	Radiological or clinical assessment	Outcome assessed	Correlation
Ringold *et al*[31]	104	29.9	Early (<6 months) erosions/JSN vs normal	Time with active disease CRM	More time with active disease p<0.001 Less chance of CRM, RR=0.34, p<0.001
			RF +ve vs −ve		More time with active disease p=0.07
Oen *et al*[54]	88	Early (<2 years) Late (1–20.8 years)	Late vs early JSN	CHAQ	Significant correlation Explains 17.7% of variation in CHAQ
			Joint pain		Explains 32.4% of variation in CHAQ
Habib *et al*[123]	68	–	ACPA	CR erosions	Significant correlation p=0.004
Arvidsson *et al*[124]	103	324	Baseline/early TMJ involvement	Micrognathia	66.7% patients with micrognathia had baseline TMJ involvement; 33.3% had CR TMJ involvement within 2 years
Baseline MRI predictive factors					
Malattia *et al*[32]	58	12	Baseline wrist synovial volume	MRI erosive progression	Correlation r=0.42 p<0.02 All patients with high synovial volume had erosive progression
			Baseline CRP		Correlation r=0.40 p<0.02
Gardner-Medwin *et al*[125]	10	12	Baseline synovial hypertrophy in a clinically normal joint	Disease extension from monoarthritis	100% patients developed clinical arthritis in other joints

ACPA, anticyclic citrullinated peptide antibody; aSH, adapted Sharp van der Heijde score; CHAQ-DI, Childhood Health Assessment Questionnaire disability index; CR, conventional radiography; CRM, clinical remission on medication; CRP, C reactive protein; JADI-A, Juvenile Arthritis Damage Index for articular damage; JSN, joint space narrowing; LOM, limitation of movement; RF, rheumatoid factor; +ve, positive; −ve, negative; RR, relative risk; SJC, swollen joint count; TJC, tender joint count; TMJ, temporomandibular joint.

on CR were 7.5 times more likely to have MRI synovitis (OR 7.55, 95% CI 1.66 to 34.4, p=0.009).[43]

Responsiveness of imaging to change in inflammation

US and MRI have been shown to have good responsiveness to change in inflammation, as measured by standardised response means (SRM, ≥0.20 small change, ≥0.50 moderate, ≥0.80 good). The mean (range) SRM for MRI wrist synovitis was good at 1.27 (0.51 to 1.69) and demonstrated ability to discriminate between different levels of clinical responder categories, whereas the SRM for MRI wrist bone marrow oedema was small at 0.22.[19 32 44] Similar levels of SRM have been described for MRI knee synovial hypertrophy (0.68–0.70) and bone marrow oedema (0.15).[45 46] A comparison of MRI wrist synovitis score with US showed higher MRI responsiveness (1.61) when compared with US grey-scale (0.87) and US power Doppler (0.71).[47]

Which joints to assess

Studies describing the frequency of US joint inflammation in JIA have shown these changes to be most common in the knee (~30%) and wrist (~20%), then ankle, proximal interphalangeal joint and metatarsophalangeal joint (~10% each).[48 49] US power Doppler activity was most common in the wrist (~35%).[48 49] One study examined the frequency of US peripheral synovitis and found changes more commonly in the metatarsophalangeal joint (61.9%) than in the metacarpophalangeal joint (39%), with the first metatarsophalangeal joint and second metacarpophalangeal joint most frequently affected (20% and 13%, respectively).[50]

Monitoring damage

PTC 7: The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.

As for PTC 6, this section will consider the comparison of the ability of imaging to detect damage, responsiveness of imaging to change in damage, and which joints should be assessed. Data comparing imaging with clinical examination in detecting joint damage and comparing CR with MRI and US in detecting damage is discussed in part in PTC 3.

Comparison of the ability of imaging to detect damage

El-Miedany *et al*[14] examined the role of MRI, US and CR in the detection of knee JSN and described a 3.14-fold detection rate of MRI compared with US, 4.40-fold for MRI compared with CR and 1.4-fold for US compared with CR. The addition of contrast to MRI enhanced the appreciation of depth of cartilage involvement by 1.42-fold. Data describing the detection of wrist erosive changes have shown a detection rate for MRI compared with US of 1.92-fold, MRI compared with CR of 1.36-fold and US compared with CR of 1.0-fold.[17–19 40]

In terms of detecting damage of the TMJ, Muller *et al*[25] showed that MRI condylar damage was detected in 25% of their cohort, whereas US detected only 17% (1.47-fold). Weiss *et al*[41] also described a poor correlation between these modalities, with only 50% agreement (detection rate 2.44-fold).

Responsiveness of imaging to change in damage

Several studies examined the responsiveness of imaging to detect change in damage at the wrist, particularly with CR and MRI. The rate of change in CR score (Larsen, Sharp, Poznanski) appears to be greatest in the 1st year, which is mainly due to progression in JSN.[28 51] This seems to slow after the 1st year, whereas the rate of erosive change is steady from baseline to year 3; the rate of progression overall slows after 3rd third year. In general, the rate of JSN exceeds that of erosions and total score.[29] When compared with CR, Malattia *et al*[44] described the relative efficacy of MRI compared with CR erosion score to be <1 at year 1; that is, MRI was less responsive than CR in detecting erosive progression; the fact that cartilage assessment was not included in the MRI scoring systems might explain this result. A study of TMJ condylar changes showed that MRI identified significantly more changes than CR (p≤0.003), and MRI was superior to CR in following condylar changes over time: MRI condylar changes at baseline were found in 58.6% compared with 80% at year 2; CR condylar changes were stable at baseline and year 2 at 30%.[52]

Which joints to assess

Studies describing the distribution of CR changes in 'early' (within 2 years of disease onset) and 'late' (up to 20.8 years of follow-up) disease have shown JSN to be most common in early disease in the wrist (20%), hips (16%), cervical spine (5%), ankles (4%) and knees (3%) compared with 34%, 25%, 38%, 15% and 6%, respectively in late disease.[53 54] Rostom *et al*[55] observed CR hip disease to start after 4 years of disease, whereas 80% had developed hip disease at 6 years, and 100% after 14 years. Other studies describing radiological features of JIA found most CR changes in the hands (57%), knees (47%), ankles (27%) and feet (36%), with erosions mainly in hands (18%) and feet (25%).[56] The hands and feet were the area most likely to show CR damage progression at 6 months and 5 years.[57 58]

Guided treatment

PTC 8: US can be used for accurate placement of intra-articular injections.

Studies summarising the role of imaging for guiding intra-articular steroid injections are given in online supplementary text S10, along with additional data on the use of imaging to assess and monitor efficacy of steroid injections. All studies used triamcinolone injections; doses and preparations varied according to the age of the patient and the joint being injected. Young *et al*[59] used US to assess the accuracy of needle placement for steroid injections at various sites (joints and tendon sheaths), and described that US allowed accurate visualisation of the injection point in all 1444 injections. A study by Parra *et al*[60] used CT to establish if US-guided TMJ injections had been accurately placed; needle placement was shown to be acceptable in 91% (75% required no needle adjustment, 16% required minor adjustment) and unacceptable in 9% where the needle required major readjustment. A study of the efficacy of TMJ injections used MRI to assess needle placement accuracy according to the location (intra-articular or extra-articular) of the injected material on MRI acquired after injection; MRI confirmed that 65% of injections were accurately placed.[61] A similar study using postinjection MRI of the SIJ described technical success in 100%.[62]

Remission

PTC 9: US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.

Several studies addressed the discrepancy between clinical remission and inflammation seen on US and MRI; these are summarised in the online supplementary text S11. Evidence of ongoing US synovitis has been described in 56.1–94.1% of patients with clinically inactive joints, and 32% of patients with

inactive disease showed US signs of synovial hypertrophy, effusion and power Doppler activity.[63–65] In clinical remission, US grey-scale synovitis was seen in up to 84.1% of joints, and power Doppler activity in up to 48.6% of joints, with a non-significant trend to more US inflammation in clinical remission on medication compared with clinical remission off medication.[39 66–71] MRI knee inflammation has been demonstrated in up to 50% of patients in clinical remission and bone marrow oedema in 33.3% patients with clinically inactive joints.[72–74] Recent pilot studies have demonstrated that patients with subclinical US or MRI inflammation are more likely to develop active disease and disease progression, even within 6 months of follow-up.[64 70 74 75]

Research agenda

The group formulated a research agenda based on areas identified with a lack of currently available evidence, shown in box 1.

DISCUSSION

These EULAR-PReS considerations for imaging provide important and novel advice for JIA in clinical practice. There is still significant research needed in this field, in particular consensus on understanding normative data to allow the interpretation of imaging abnormalities, agreement on appropriate MRI protocols and definitions of bone marrow oedema, synovitis and erosions, and suitability of the imaging modalities for detecting changes at specific joints. Our data is limited by the lack of specific information for each JIA disease subtype; this is reflected in the research agenda.

There are significant conceptual differences between imaging in adult and paediatric conditions, and consideration must be given to the appropriateness and feasibility of different imaging modalities which differs with age and developmental stage, as well as to economic issues such as the cost-effectiveness of the intervention. Repeated unnecessary exposure to radiation from imaging should also be considered. We appreciate that access to individual imaging modalities may be insufficient to allow full implementation of these PTC; however most of the points include the use of US which is generally readily available. An economic evaluation was not included in the process as the primary aim was to discuss the clinical implications of imaging; overall the cost of implementing the PTC should be low.

After dissemination of the PTC by means of publication and presentation at European meetings, we would propose to perform a survey of awareness and their use, for example:

- Do you have access to musculoskeletal US and MRI routinely?
- Are you aware of and implementing the EULAR-PReS JIA imaging PTC?
- Have the PTC changed your clinical practice?

The task force agreed that it was not appropriate to create audit or implementation tools as the strength of data was only sufficient to develop PTC rather than recommendations.

In summary, we have developed nine PTC on the role of imaging in various clinical aspects in JIA. We would recommend that a similar rigorous process is followed to reassess the available data after an interval of 5 years.

Box 1 Research agenda

1. What are the age-specific changes in imaging, including age-specific intervals for imaging, development of an atlas of age-specific normal images and a registry as mechanism for pooling of data
2. Development of validated scoring systems including pathology definition (eg, differentiating reversible structural abnormalities from damage), imaging acquisition protocols and quantification
3. What are the imaging characteristics of the subtypes of JIA, and which target sites should be imaged?
4. What is the clinical significance of imaging-detected subclinical disease in diagnosis, monitoring and remission?
5. What is the usefulness of imaging-guided injection over non-imaging guided injection?
6. What is the prognostic value of specific imaging features, for example BM oedema?
7. Can imaging be used to assess and monitor disease progression and response to treatment including the development of structural damage?
8. What is the feasibility, cost and appropriate training for using US and MRI in JIA in clinical practice?

JIA, juvenile idiopathic arthritis; BM, bone marrow; US, ultrasound.

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Editorial

Are guidelines good value for money?

Strapline: Is it time to rethink guidelines?

The perfect clinical guideline will merge published literature with expert and patient opinion, be easy to understand and have widespread uptake and support. All of this will lead to measurable improvements in patient care. Over the past decade, guidelines have become a key part of the landscape and the number of guidelines has grown rapidly (Fig. 1). An estimate from a selection of prominent societies suggests that more than 120 clinical rheumatology guidelines have been produced in the last 15 years. This seems a good time to ask if current guidelines are fit for purpose, whether they make any difference to clinical practice, how they can be improved, and whether they provide good value for money.

There are a number of validated processes to ensure that guidelines are of a high quality. Some organizations publish instructions on how to assemble guidelines using standardized operating procedures (SOPs). The EULAR has produced an SOP for guideline development that uses the Appraisal of Guidelines for Research & Evaluation (AGREE)-II instrument for quality assessment [1]. This SOP, first published in 2004 and updated in 2014, seems to have raised standards. A review of the quality of EULAR management recommendations found the use of the SOP for guideline development has been associated with improved quality over recent years [2]. While the process of literature review and development of key recommendations seems well established, areas for improvement identified included the need for more patient involvement, planning for dissemination and the need for regular updates. All guidelines should include a research agenda and implementation and audit tools, and they need to be updated at regular intervals with a frequency determined by the subject matter and how quickly new research is produced in the field. A recent analysis of clinical guidelines suggested that one in five guideline publications were outdated after just 3 years [3].

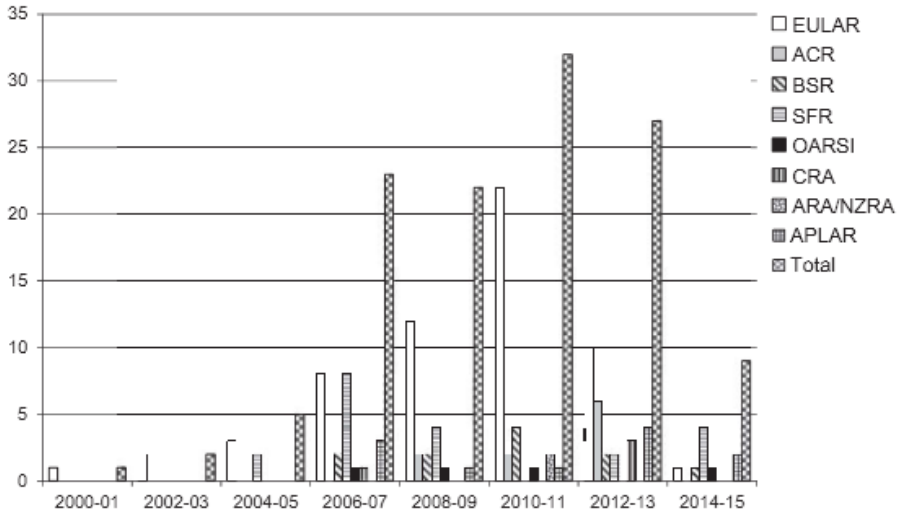
It is not always easy to tell if guidelines lead to improvements in the quality of patient care; however, some examples do exist. The British Society for Rheumatology guidelines for the management of early RA published in 2006 appears to have been associated with a step up in the prescription of MTX in the first year after diagnosis [4]. Conversely, failure to adhere to the EULAR treatment guidelines for early arthritis was associated with an increased risk of radiographic progression and functional impairment [5].

For guidelines to be successful, they must seem reasonable, be accessible and be readily accepted by the clinician. This requires awareness of the guideline in the first place, agreement with the guideline, and a desire to adopt and then adhere to it [6]. Leakage in guideline use may occur at all of these steps [7]. Currently a large number of clinical guidelines are produced by various organisations, sometimes on the same area of management, making it difficult for clinicians to choose which one to follow. There are also disease areas in which multiple organisations have produced guidelines with differing recommendations or covering different therapies. For example, EULAR have included guidance related to glucocorticoid use in their recommendations on the treatment of RA, whereas the ACR 2012 guidelines have omitted this [8]. Guidelines can only be really effective if there is also a plan for dissemination, and a process that assesses the clinician's agreement with the guideline is vital. This level of agreement is not only an important measure of quality but also provides an opportunity to broaden the clinician involvement that has been exploited in the development process for some guidelines. The Evidence, Expertise, Exchange Initiative provided a model of guideline production that effectively canvassed the views of several hundred international rheumatologists at multiple times during the development process [9]. Digital technology and social media web-based systems might also be used to improve access to clinical guidelines and allow increased interaction between those that produce and those that use the guidelines.

Given the large number of guidelines in circulation, we need to think carefully about which guidelines we really want to produce. Increased efficiency could be introduced by considering the common themes across guidelines. For example, all rheumatology guidelines could start with common generic recommendations that are important to all disease types, such as stopping smoking and losing weight. Given all of the difficulties in adhering to clinical guidelines, awareness at least would be improved if all guidelines were available from a limited number of sources. This need has been recognized, with increasing collaborations between EULAR and ACR in a number of clinical areas. While guidelines rely on the combination of evidence and expertise, the specific information needed from trials is often not available. With this in mind, the process of guideline development should be considered as an important opportunity and resource to demonstrate the gaps in current knowledge.

So what about value for money? High-quality guidelines appear to improve quality of care; however, the true value of any guideline is difficult to quantify precisely. The process of guideline development consumes large amounts of resources that can be measured in time given by experts, assembling the required clinical expertise, clinical fellows, task force meetings, time taken to go through the rigorous

FIG. 1 Summary of the number of guidelines produced by a selection of major rheumatology societies, 2000–15



SFR: Société Française de Rhumatologie; OARSI: Osteoarthritis Research Society International; CRA: Canadian Rheumatology Association; ARA: Australian Rheumatology Association; NZRA: New Zealand Rheumatology Association; APLAR: Asia Pacific League of Associations for Rheumatology.

process involved and the necessary financial support by rheumatology organizations. It might make an interesting project to accurately determine the true cost of this.

The numbers and quality of clinical guidelines has increased in recent years. This has partly been driven by the presence of SOPs and by an increased body of experience in the methodology used. Guidelines need to be adapted to complicated clinical situations and for this reason cannot be too rigid. However, there is some evidence that guidelines can lead to improvements in the quality of care and that failure to comply can be associated with poorer outcomes. Preventing clinicians from being overwhelmed by too many guidelines could be achieved by greater focus on those that are the most important to them, and by identifying common themes between guidelines to produce generic stems and approaches. These steps are likely to improve adoption and adherence to guidelines, which will in turn help to maximize value for money.

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Raising the quality of rheumatology management recommendations: lessons from the EULAR process 10 years after provision of standard operating procedures

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Abstract

Objective. To increase understanding of how to raise the quality of rheumatology guidelines by reviewing European League Against Rheumatism (EULAR) management recommendations, using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, 10 years after publication of the EULAR standardized operating procedures (SOP) for the production of recommendations. It was hoped that this work could help inform improvements in guideline development by other societies and organizations.

Methods. The SOP were published in 2004 to ensure the quality of EULAR-endorsed recommendations. We reviewed 27 published EULAR recommendations for management using the AGREE II tool. This provides a framework to assess the quality of guidelines across six broad domains using 23 specific questions.

Results. Overall the EULAR recommendations reviewed have been performed to a high standard. There are particular strengths in the methodology and presentation of the guidelines; however, the results indicate areas for development in future recommendations: in particular, stakeholder involvement and applicability of the recommendations. Improvements in quality were evident in recent years, with patient representation in 9 of 15 (60.0%) recommendations published 2010–14 compared with 4 of 12 (33.3%) published 2000–09.

Conclusion. In the last 10 years the overall quality of recommendations was good, with standards improving over the decade following publication of the SOP. However, this review process has identified potential areas for improvement, especially in patient representation and provision of implementation tools. The lessons from this work can be applied to the development of rheumatology guidelines by other societies and organizations.

Key words: clinical practice guideline, health care quality assessment, rheumatology.

CLINICAL

Rheumatology key messages

- SOPs for guideline development can raise the quality of rheumatology management recommendations.
- Patient representation and implementation tools are often lacking in the development of rheumatology management recommendations.
- Uniform international approaches to developing rheumatology management recommendations could improve quality and comparability.

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Introduction

Ensuring the quality of rheumatology management guidelines by using robust and reliable methodology is vital in maintaining the confidence of clinicians. The European League Against Rheumatism (EULAR) executive committee published their standardized operating procedures (SOP) for the elaboration, evaluation, dissemination and implementation of recommendations in 2004 to provide a formal structure for ensuring the quality of EULAR-endorsed recommendations [1]. The SOP describes in detail methodological aspects for consideration when producing recommendations, including a clear statement of the objectives, target population and appropriate steering group members, and use of a vigorous evidence-based approach to review and assess the quality of the literature, including a description of categories of evidence and strength of the recommendations. It also describes the subsequent presentation of the recommendations, assessment of their relevance, and the process for dissemination, implementation and updating of such recommendations.

A decade after the publication of the SOP for the production of recommendations, we assessed the quality of existing EULAR management recommendations according to the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool [2]. The original AGREE instrument was published in 2003 by a group of international guideline developers and researchers, the AGREE collaboration, to provide a standardized structure for guidelines in development in order to improve consistency in quality, and provide a framework for assessing the quality of published guidelines. The AGREE instrument was updated on its 10th anniversary in 2013, funded by a grant from the Canadian Institute of Health Research, and includes six quality domains using 23 specific questions. The domains cover the scope and purpose; the extent of stakeholder involvement; rigour of the methodology and development process; clarity of presentation of the guideline; consideration of applicability, including barriers to and facilitators of guideline implementation and resource implications; and editorial independence. We were interested to learn lessons from this review that would be useful in raising the standards of rheumatology guidelines developed by other international societies and organizations.

Methods

Published EULAR management recommendations were identified through the EULAR website [3]. Supporting publications describing the systematic literature review process were also accessed where necessary. Each recommendation was assessed according to the AGREE II tool using the AGREE guideline online appraisal system [4]. The recommendations were scored on each question using the 7-point response scale (from 7 = strongly agree to 1 = strongly disagree), which results in a score for each domain. The recommendations were given an overall quality score and a statement on whether the use of the recommendation could be supported. A summary of the areas assessed by each domain is given in Supplementary Table S1, available at *Rheumatology* Online, with full details given on the AGREE enterprise website [4].

Results

There are 30 documents listed on the EULAR management recommendations section of the EULAR website (last accessed May 2014), of which 27 met our criteria and were included for evaluation. The three documents that were excluded were a description of perspectives among patients and rheumatologists (rather than management recommendations), a patient version of a recommendation and a systematic review for a recommendation. The 27 EULAR recommendations for management that have been published to date between 2000 and 2014 are on diverse topics ranging from the inflammatory arthropathies and OA to recommendations on vaccination and the management of FM syndrome and Behçet's disease [3]. A full reference list for the included recommendations is given in the online supplementary data, available at *Rheumatology* Online.

Overall the EULAR recommendations reviewed scored highly using the AGREE II tool, thereby supporting their ongoing use. The mean and range scores for each domain and the overall scores are provided in Table 1, and the trend in changes in the domain scores, as a percentage of the total possible score, is shown in Fig. 1a (see supplementary Table S2, available at *Rheumatology* Online, for a summary of scores for each recommendation). This highlights the improvement in these areas following the publication of the SOP in 2004, and in particular the strengths in the areas of scope and purpose, rigour of development and clarity of presentation of the guidelines. The scores also show areas for development in future recommendations, with potential to improve stakeholder involvement, transparency of editorial independence and applicability of the recommendations. However, improvements in quality were evident over recent years, with patient representation in 9 of 15 (60.0%) recommendations published 2010–14 compared with 4 of 12 (33.3%) published 2000–09 (Fig. 1b).

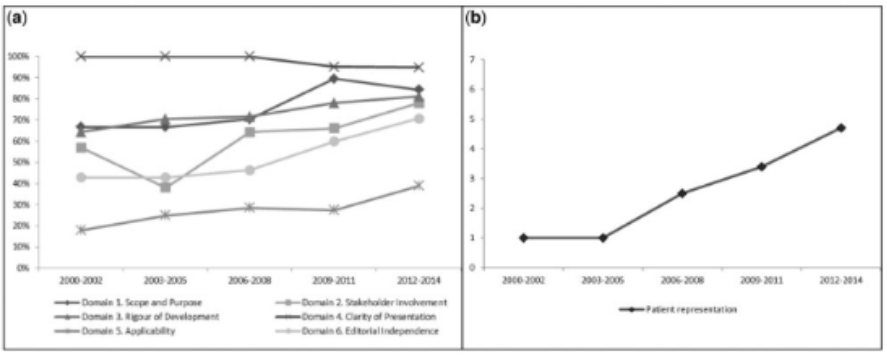
Discussion

The publication of the EULAR SOP in 2004 has provided a framework for the production of high-quality recommendations written in a consistent format. This study has assessed the quality of all EULAR management recommendations published between 2000 (including recommendations published before the SOP in 2004) and 2014. It has demonstrated that the overall quality of recommendations has been good in the last 10 years, with standards improving over the decade. However, the review process has also identified potential areas for improvement, especially in applicability, editorial independence and stakeholder involvement. The recommendation publications assessed consistently scored low

TABLE 1 Mean and range for each domain and overall score

	Domain 1: scope and purpose (0–21)	Domain 2: stakeholder involvement (0–21)	Domain 3: rigour of development (0–56)	Domain 4: clarity of presentation (0–21)	Domain 5: applicability (0–28)	Domain 6: editorial independence (0–14)	Overall score (1–7)
Mean score (range)	16.8 (11–21)	13.9 (6–21)	42.5 (32–54)	20.4 (15–21)	8.4 (4–24)	8.0 (2–12)	4.9 (4–7)

FIG. 1 Line chart illustrating the trend in changes in scores over the last 14 years



(**a**) Changes in domain scores. Scores are given as a percentage of possible scores for each domain. (**b**) Changes in patient representation. Possible score range 1–7.

on all four of the questions addressing applicability, which specifically deals with the description of facilitators of and barriers to application of the recommendation, inclusion of tools to put the recommendation into practice, consideration of the potential resource implications of the recommendation and the inclusion of monitoring or audit criteria. These areas should be given more attention in future recommendation publications. We also suggest more transparency in the declaration of editorial independence, which should include a statement of the source of funding (EULAR in this case), as well as its influence on the content of the recommendation, and a detailed description of competing interests of all co-authors and how these may have influenced the development of the recommendations. There is also potential for improvement in stakeholder involvement, although there has been a trend towards improvement in this domain over the last 5 years. This has mainly been as a result of an increase in patient involvement in the recommendation development process, and future recommendation publications should be encouraged to describe how patients have been involved and how their input informed the recommendation development process. Finally, although the recommendation publications tended to score quite highly in the rigour of development domain, it is important to ensure that the strengths and limitations of the evidence considered are clearly described, and this should include quality and risk of bias assessments.

Clinical guidelines are used across the world to inform and optimize patient care, but there have been concerns raised about their quality and structure [5]. Appraisal systems such as the AGREE tools help to guide the methodological standards framework and quality assessment. The AGREE instruments are widely accepted as validated assessment tools by various organizations; they have been endorsed by the National Institute for Health and Care Excellence in the UK [6]. There have been a number of publications that have used the AGREE tools to assess the quality of existing guidelines, but to date none of the major rheumatology societies has assessed the quality of all of their own guidelines using this or another tool. They have performed a few appraisals of condition-specific guidelines, for example Nuki [7] assessed the quality of the 2012 ACR guidelines on the management of gout using AGREE II, and Zhang *et al*. [8] performed a critical appraisal of existing guidelines on the management of hip and knee OA using AGREE, in preparation for the production of new guidelines for these conditions for the Osteoarthritis Research Society International . There are also a number of other rheumatological guidelines that have been quality assessed using an AGREE tool [9–17]. The tools are widely used across

all specialties; for example Hu *et al*. [18] used AGREE to assess the quality of all Chinese clinical practice guidelines published between 2006 and 2010.

The EULAR recommendations are divided into three broad categories: those on conducting and reporting clinical studies, those on classification and diagnostic/response criteria and those on management. We have only included the latter group in this review process because the AGREE II tool includes questions that are not applicable to the other categories. For example, the different options for management of the condition or health issue are clearly described. There does not seem to be an alternative tool that could be used for the other categories; however, it is possible that the existing AGREE II tool could be modified in order to better accommodate them.

The 2004 SOP has provided a robust framework, resulting in well-designed recommendations, but this review has identified that there is potential for further improvement. We hope that this work underpins an update of the SOP, a decade on from the original publication, using the AGREE II tool as a framework. This is an approach that is already being used by other European rheumatology societies, such as the French Society for Rheumatology [19–22]. Our work shows how the use of a standard approach and quality framework can lead to improvements in the production of guidelines. This knowledge can be widely applied to other organizations tasked with similar work.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis

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ABSTRACT

Objective To develop evidence-based recommendations on the use of imaging of the joints in the clinical management of rheumatoid arthritis (RA).

Methods The task force comprised an expert group of rheumatologists, radiologists, methodologists and experienced rheumatology practitioners from 13 countries. Thirteen key questions on the role of imaging in RA were generated using a process of discussion and consensus. Imaging modalities included were conventional radiography, ultrasound, MRI, CT, dual-emission x-ray absorptiometry, digital x-ray radiogrammetry, scintigraphy and positron emission tomography. Research evidence was searched systematically for each question using MEDLINE, EMBASE and Cochrane CENTRAL. The experts used the evidence obtained from the relevant studies to develop a set of 10 recommendations. The strength of recommendation was assessed using a visual analogue scale.

Results A total of 6888 references was identified from the search process, from which 199 studies were included in the systematic review. Ten recommendations were produced encompassing the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease activity, progression and remission. The strength of recommendation for each proposition varied according to both the research evidence and expert opinion.

Conclusions Ten key recommendations for the role of imaging in the management of RA were developed using research-based evidence and expert opinion.

INTRODUCTION

Structural damage in rheumatoid arthritis (RA) can occur early in the disease. Prompt treatment has been shown to reduce inflammation thereby limiting structural damage.[1 2] Although conventional radiography (CR) has been considered the gold standard for imaging in RA, its sensitivity for structural damage in RA diagnosis is low, and disease activity cannot be assessed.[3] Significant advances have been made within the field of imaging in rheumatic diseases over the past decade.[4]

A European League Against Rheumatism (EULAR) task force was therefore convened to develop evidence-based recommendations on the use of imaging of the joints in the clinical management of RA.

METHODS

An expert group of rheumatologists, radiologists, methodologists and experienced rheumatology practitioners (19 people, representing 13 countries) participated in the study. The objectives were to formulate key clinical questions relating to the role of imaging in RA, to identify and critically appraise the available evidence, and to generate recommendations based on both evidence and expert opinion.

At the initial task force meeting, members contributed clinically relevant questions related to key aspects of the use of imaging in RA. The research questions were agreed by consensus and 13 final research questions were selected, which encompassed the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression, and remission (see supplementary material, S1. Research questions, available online only).

A systematic search of articles was performed and the bibliographies of included papers were hand searched for evidence of other studies for inclusion. Specific medical subject headings and additional keywords were used to identify all relevant studies (see supplementary material, S2. Search strategy, available online only).

Titles and abstracts of all citations identified were screened, and potentially relevant articles were reviewed in full text using predetermined inclusion and exclusion criteria. Studies, published in English, on the use of imaging in adults (≥18 years of age) with a clinical diagnosis of RA were included. Imaging modalities included were CR, ultrasound, MRI, CT, dual-emission x-ray absorptiometry (DXA), digital x-ray radiogrammetry (DXR), scintigraphy and positron emission tomography (PET). Study types included randomised controlled trials, systematic reviews, controlled clinical trials, cohort, case–control and diagnostic studies. Studies were considered for inclusion when they provided information on the role of imaging in making a

diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression and remission.

Following presentation of the data from the literature review, the experts produced 10 recommendations based on the 13 clinical questions with final agreement by a process of discussion and consensus. The experts scored the perceived strength of recommendation (SOR) for each proposition using a 0–10 visual analogue scale (VAS; 0=not recommended at all, 10=fully recommended). Scores reflected both research evidence and clinical expertise.[5]

Evidence was categorised according to study design using a hierarchy of evidence in descending order according to quality.[6] Greater emphasis was given to the best available evidence when answering questions, although all data were collected and reviewed.

Recommendations for future research were agreed by consensus following presentation of the literature review.

RESULTS

The search of databases (performed in June 2011) resulted in 6888 records, of which 2567 were duplicates. Of the remaining 4321 articles, 3975 were excluded based on title or abstract, leaving 346 articles for detailed review. All full text articles written in English were retrieved for review; 175 articles were excluded after reviewing the full text leaving 171 articles for inclusion (see supplementary figure S3, available online only). The hand search identified 28 additional articles for inclusion, resulting in a total of 199 articles for inclusion. Articles that were relevant to more than one research question were included in the review more than once. The number of articles included in each question is shown in supplementary table S4 (available online only).

Ten recommendations were produced, and the final wording of the propositions was adjusted using e-mail exchange and at the closing meeting of the group. The recommendations, SOR (mean VAS and 95% CI) and level of evidence are presented in table 1.[5] A full reference list for articles included in each recommendation is given in the supplementary material, S5 (available online only).

Recommendations

Making a diagnosis of RA (in patients with at least one joint with definite clinical synovitis):

Recommendation 1: When there is diagnostic doubt, CR, ultrasound or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.

Strength of recommendation: 9.1 (95% CI 8.6 to 9.6)

Five observational studies described the impact of imaging on confirming a diagnosis of RA when the diagnosis could not be confirmed using conventional methods, two with ultrasound and three with MRI. Three of these studies examined the hand joints (wrist, metacarpophalangeal and proximal interphalangeal joints), but none compared sites.[7–11] One study showed that ultrasound synovitis improved the certainty of RA diagnosis from 42.0% to 53.2% (p 0.17),[7] and another described how synovitis seen with ultrasound helped confirm (65.2%) or change the diagnosis (11.1%); ultrasound was superior to

Table 1 Recommendations, SOR and level of evidence

	Recommendation*	SOR, mean VAS 0–10 (95% CI)	Level of evidence
1	When there is diagnostic doubt, CR, ultrasound or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone†	9.1 (8.6 to 9.6)	III
2	The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis	7.9 (6.7 to 9.0)	III
3	Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation	8.7 (7.8 to 9.7)	III
4	CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA)	9.0 (8.4 to 9.6)	IV
5	MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage detected by conventional radiographs, MRI or ultrasound can also be considered for the prediction of further joint damage	8.4 (7.7 to 9.2)	III
6	Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment	7.8 (6.7 to 8.8)	III-IV
7	Given the improved detection of inflammation by MRI and ultrasound than by clinical examination, they may be useful in monitoring disease activity	8.3 (7.4 to 9.1)	III
8	The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly ultrasound) is more responsive to change in joint damage and can be used to monitor disease progression	7.8 (6.8 to 8.9)	III
9	Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed	9.4 (8.9 to 9.8)	III
10	MRI and ultrasound can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation	8.8 (8.0 to 9.6)	III

*Recommendations are based on data from imaging studies that have mainly focused on the hands (particularly wrists, metacarpophalangeal and proximal interphalageal joints). There are few data with specific guidance on which joints to image.
†In patients with at least one joint with definite clinical synovitis, which is not better explained by another disease.
Categories of evidence: Ia, evidence for meta-analysis of randomised controlled trials; Ib, evidence from at least one randomised controlled trial; IIa, evidence from at least one controlled study without randomisation; IIb, evidence from at least one other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.
CR, conventional radiography; RA, rheumatoid arthritis; SOR, strength of recommendation; VAS, visual analogue scale (0–10; 0=not recommended at all, 10=fully recommended).

clinical examination in 75% of patients.[8] Compared to clinical classification criteria, the demonstration of MRI synovitis increased the diagnosis of RA,[9 10] and was more valuable than anti-cyclic citrullinated peptide antibody (ACPA) determination in the absence of rheumatoid factor (RF).[11]

Recommendation 2: The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.

Strength of recommendation: 7.9 (95% CI 6.7 to 9.0)

Several studies assessed the prognostic value of imaging in patients with undifferentiated inflammatory arthritis (UIA), mainly using ultrasound or MRI. A recent systematic review identified 11 studies relating to MRI.[12] The presence of bone oedema or both synovitis and erosion on MRI increased the likelihood of developing RA (positive likelihood ratio 4.5 and 4.8, respectively), whereas the absence of MRI synovitis decreased the probability of progression to RA (negative likelihood ratio 0.2). A prediction model including clinical hand arthritis, morning stiffness, positivity for RF and bone oedema on MRI correctly predicted progression to RA in 82% of UIA patients.[13] MRI flexor tenosynovitis has also been described as a predictor of early RA (sensitivity 0.60, specificity 0.73).[14] Of the three strongest predictors of RA (MRI flexor tenosynovitis, RF and ACPA), ACPA was found to be the strongest predictor (OR 13.8) and flexor tenosynovitis the weakest (OR 5.0), but its additional value in diagnosing RA was significant.

In a longitudinal study ultrasound significantly increased the detection of joint involvement in all joint regions. When combined with the Leiden prediction rule,[15] power Doppler counts significantly improved area under the curve (AUC) values for the prediction of progression to RA (0.905 to 0.962).[16] Salaffi *et al*[17] described the likelihood of progression of UIA to RA using the presence of power Doppler on ultrasound (scores higher than grade 1), with OR 9.9 if one joint was involved, and 48.7 if more than three were involved; OR with high titre ACPA or RF was 10.9.

Detecting inflammation and damage:

Recommendation 3: Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for a more accurate assessment of inflammation.

Strength of recommendation: 8.7 (95% CI 7.8 to 9.7)

This recommendation examines the added benefit of assessing joint inflammation by imaging over clinical examination. Sensitivity and specificity were initially extracted from the data; however, as clinical examination was used as the reference these results are difficult to use clinically. To overcome this we recorded detection rates; for example, how many times more (>onefold) or less (<onefold) does imaging detect inflammation over clinical examination. Our chosen approach may increase the number of false positive results.

We identified 51 studies comparing imaging and clinical examination in the detection of inflammation in various joints; 29 with ultrasound,[18–36] 16 with MRI,[21 26 29 30 37–44] 14 with scintigraphy,[41 45–47] and two with PET (table 2). In general, ultrasound and MRI detected joint inflammation more frequently than clinical examination; the mean detection rate for synovitis at the hand and wrist was 2.18-fold for ultrasound and 2.20-fold for MRI.[30] Using scintigraphy and PET were found to provide little benefit over clinical examination.

Recommendation 4: CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if CR do not show damage and may be used to detect damage at an earlier time point (especially in early RA).

Strength of recommendation: 9.0 (95% CI 8.4 to 9.6)

Three studies compared tissue damage (erosions or loss of joint space) detected by imaging with abnormal clinical examination. Caution is needed when interpreting these studies as bony involvement shown on imaging was compared with clinical signs of inflammation as reference.

Prognosis in RA: predicting outcome:

Recommendation 5: MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage detected by CR, MRI or ultrasound can also be considered for the prediction of further joint damage.

Strength of recommendation: 8.4 (95% CI 7.7 to 9.2)

Forty-eight longitudinal studies described how baseline changes in imaging predicted outcome, in particular erosive progression; 26 with MRI, 11 with ultrasound, 19 with CR, seven with DXA or DXR and three with scintigraphy. Of these, 46 studies examined the hands and 14 also included the feet; none compared the benefit of imaging different joints.

Bone marrow oedema

Of baseline MRI features, bone marrow (BM) oedema was a strong, independent predictor of erosive progression. Hetland *et al*[48 49] have provided compelling data supporting this association; baseline MRI BM oedema was the only independent predictor of radiographic change in their 2 and 5-year follow-up studies (coefficient 0.75, $p<0.001$; and coefficient 0.82, $p<0.001$, respectively). Haavardsholm *et al*[50] also identified baseline MRI BM oedema (score >2 RAMRIS units) as an independent predictor of radiographic (OR 2.77, 95% CI 1.06 to 7.21) as well as MRI erosive progression (unstandardised β, B 0.21, 95% CI 0.08 to 0.34). This is supported by McQueen *et al*[51] who described BM oedema to be predictive of MRI erosive progression, OR 6.47, $p<0.001$. This study also demonstrated that the development of radiological erosions at 1 year was highly unlikely in the absence of baseline MRI inflammatory changes (negative predictive value 0.92). Patients with erosive progression on CT also have higher baseline MRI BM oedema scores (relative risk (RR) of CT progression 3.8, 95% CI 1.5 to 9.3).[52]

Synovitis

Baseline synovitis, detected by MRI or ultrasound, is a predictor of erosive progression. Dohn *et al*[52] reported the RR of CT erosive progression with baseline ultrasound grey-scale synovitis as 11.2, 95% CI 0.65 to 195.7, p 0.1, baseline ultrasound power Doppler activity RR 7.6, 95% CI 0.91 to 63.2, p 0.061, and baseline MRI synovitis RR 0.68, 95% CI 0.04 to 11.5, p 0.79. [52] The predictive value of baseline ultrasound grey-scale synovitis for MRI erosive progression performed better than MRI synovitis with positive likelihood ratios of 1.75 and 1.47, respectively, and accuracy of 70% and 62%, respectively.[53] Conaghan *et al*[54] described a close correlation between the degree of MRI synovitis and the number of new erosions, with the AUC for MRI synovitis the only significant predictor of erosive progression (AUC for MRI synovitis r 0.420, $p<0.007$).

Table 2 Recommendation 3: Summary of included studies comparing imaging and CE in the detection of joint inflammation

Ultrasound **29 studies, mean no. of subjects (range): 40.7 (6–100)**		**MRI** **16 studies, mean no. of subjects (range): 47.3 (6–318)**		**Scintigraphy** **14 studies, mean no. of subjects (range): 22.6 (8–38)**	
Ultrasound hand/wrist vs CE (article reference)		**MRI hand/wrist vs CE (article reference)**		**Scintigraphy hand/wrist vs CE (article reference)**	
	Detection rate, mean (range) Ultrasound vs CE		Detection rate, mean (range) MRI vs CE		Detection rate, mean (range) Scintigraphy vs CE
Synovitis[18–24]	2.18-fold (0.55–8.96-fold)	MRI synovitis, vs clinical synovitis[21–24 37–40]	2.20-fold (0.58–5.43-fold) accuracy: 0.72	vs tenderness/swelling [45 46]	1.19-fold Validity: 0.45 Coefficient of association: −0.16
		vs pain[41]	0.71-fold	vs tenderness[41]	0.70-fold
			κ: 0.36, p 0.009		κ: 0.32, p 0.008
		vs swelling[41]	1.36-fold	vs swelling[41]	1.33-fold
			κ: 0.60, p 0.019		κ: 0.64, p 0.023
		Correlation with DAS28[42]	r 0.30–0.40 p<0.01		
Tenosynovitis[25]	1.06-fold	Relative efficacy for tenosynovitis[26]	2.48–4.69		
Relative efficacy of Ultrasound at detecting any inflammation vs TJC[26]	0.61–1.33	Relative efficacy of MRI synovitis vs TJC[26]	3.03–3.86		
Ultrasound foot/ankle vs CE		**MRI foot/ankle vs CE**		**Scintigraphy feet vs CE**	
Effusion[27 28]	0.52–0.99-fold κ: 0.04–0.16 % agreement: 71%			vs tenderness/swelling[45]	0.42-fold
Inflammation[29]	2.21-fold % agreement: 63%				
Synovitis[30]	0.87-fold	Synovitis[29 30 40 43]	1.71-fold (0.93–2.8-fold) % agreement: 45.5–71%		
Tenosynovitis[30]	0.58-fold	Tenosynovitis[30]	% agreement: 54.5–90.9%		
Ultrasound knees vs CE		**MRI knees vs CE**		**Scintigraphy knees vs histology**	
Baker's cyst[31–33]	1.88-fold (1.17–2.5-fold)	Synovitis vs clinical synovitis[44]	1.6–3.15-fold	vs histology[47]	1.11-fold
Suprapatellar bursitis[33]	1.7-fold			Swelling vs histology[47]	0.72-fold
Effusion[34]	1.27-fold (1.17–1.4-fold)				
Synovitis vs clinical synovitis[35 36]	r 0.9, p 0.0001				
vs DAS28	Strong correlation, p 0.006				
vs SJC	Weak correlation, p 0.038				

CE, clinical examination; DAS28, disease activity score in 28 joints; TJC, tender joint count; SJC, swollen joint count.

Tenosynovitis

Baseline tenosynovitis on ultrasound appears to be predictive of erosive progression at 1 year (OR 7.18) and 3 years (OR 3.4).[55] This effect has not been seen with MRI tenosynovitis,[56] but baseline MRI tendinopathy has been shown to be predictive of tendon rupture at 1 year (OR 1.57, p 0.02) and 6 years (OR 1.52, p 0.03).[57]

Erosions

Baseline erosions detected by various imaging techniques appear to be predictive of further erosions at 6 months; MRI erosions (β 0.63, p<0.001), radiographic erosions (β 0.68, p 0.04), with ultrasound erosions less significant (β 0.57, p 0.07).[58] Several studies have reported that baseline MRI erosions are predictive of erosive progression;[59 60–62] and the absence of baseline MRI erosions predicts that radiographic or MRI erosions are unlikely (negative predictive value 1.0).[61] Baseline radiographic erosions independently predict further radiographic progression (at 3 years, OR 8.47; at 10 years, OR 5.64–18.1).[63–65] In addition, the baseline Larsen score is shown to predict an annual radiological progression rate greater than the median (OR 2.6, 95% CI 1.3 to 5.3).[65]

Digital x-ray radiogrammetry/dual-emission x-ray absorptiometry

Early hand bone loss measured by change in estimated bone mineral density in the first year of disease by DXR appears to be an independent predictor of erosive progression, even up to 20 years.[53 66 67] Baseline femoral neck osteopenia or osteoporosis are also predictive of radiographic erosive progression.[68]

Scintigraphy

Baseline inflammatory disease measured by scintigraphy appears to be associated with radiographic progression.[69] In addition, multiple regression analysis has demonstrated that progression of radiographic joint destruction was primarily predicted by ^{99m}Tc-IgG scintigraphy; joint swelling, ESR and IgM RF were not predictive. This suggests that scintigraphy may be superior to conventional clinical and laboratory measurements in the prediction of joint destruction.[70] However, when comparing scintigraphy to other baseline imaging predictors of progression, baseline MRI BM oedema score (Spearman's correlation, r 0.67), MRI synovitis score (r 0.57), and ^{99m}Tc-NC scintigraphy uptake (r 0.45) were predictive of change in MRI erosion score from baseline to 2 years. In the multivariate analysis, the BM oedema score was the only baseline variable that predicted erosive progression (OR 4.2, 95% CI 1.3 to 13.8).[71]

Prognosis in RA: Predicting response to treatment:

Recommendation 6: Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.

Strength of recommendation: 7.8 (95% CI 6.7 to 8.8)

Two prospective cohort studies have assessed the use of clinical measures and imaging to predict response to anti-tumour necrosis factor (TNF) therapy. Ellegaard *et al*[72] measured ultrasound Doppler activity and clinical parameters at baseline to predict which patients would benefit from treatment, assessed by treatment persistence at 1 year. They identified ultrasound Doppler activity to be the only baseline parameter to predict treatment persistence (p 0.024); baseline clinical measures including tender and swollen joint counts, C-reactive protein, 28-joint disease activity score (DAS28) and health assessment questionnaire showed no significant association. Elzinga *et al*[73] used changes in PET uptake 2 weeks after treatment to predict future treatment response, according to DAS28. A significant correlation was seen between the changes in PET activity at 2 weeks and DAS28 at 14 and 22 weeks after treatment (r 0.62, p<0.05; r 0.65, p<0.01 respectively).

Monitoring disease progression:

Recommendation 7: Given the improved detection of inflammation by ultrasound and MRI than by clinical examination, they may be useful in monitoring disease activity.

Strength of recommendation: 8.3 (95% CI 7.4 to 9.1)

No published data were identified that specifically addressed how imaging should be used to monitor RA disease activity. In the absence of this information, data were extracted on each factor separately.

Comparison of the ability of imaging to detect inflammation

Several studies compared ultrasound and MRI in the detection of joint inflammation, with MRI considered the reference technique. There seems to be significant association between these modalities,[23 24] but aside from access to imaging, there may be advantages to using each technique in certain situations. For example, ultrasound has been shown to detect more joint and tendon sheath effusions than MRI,[58] whereas MRI appears to be more sensitive in identifying tenosynovitis.[74] Comparisons of conventional high-field MRI with dedicated, low-field extremity MRI have shown high agreement for synovitis, with lower agreement for BM oedema and tenosynovitis detected by low-field MRI, with high-field MRI as reference.[75 76] Low-field MRI without contrast also demonstrates poor sensitivity in the detection of synovitis, compared with power Doppler ultrasound.[77] Only one study compared scintigraphy with more modern imaging techniques, and showed strong correlation between uptake on scintigraphy and inflammatory changes seen on MRI.[78]

Responsiveness to change in inflammation

Ultrasound and MRI appear to show good responsiveness to change. A study of responsiveness of MRI and ultrasound to change in inflammation with treatment has shown that MRI synovitis (standardised response mean (SRM) −0.79 to −0.92), MRI tenosynovitis (SRM −0.70 to −1.02) and BM oedema (SRM −1.05–−1.24) were responsive to change, but ultrasound inflammation (synovitis, tenosynovitis and effusion) was less responsive (SRM −0.37–−0.54).[26] A study by Haavardsholm *et al*[79] reported MRI to have a higher potential to detect change in wrist BM oedema than in synovitis over 1 year. The smallest detectable difference for a range of ultrasound measures including power Doppler was low in a large 1-year observational multiple-reader study of RA patients treated with anti-TNF agents, demonstrating both the reliability of this measure and the ability to detect individual-level important change. At the group level, there were significant changes in all ultrasound synovial assessments in parallel with DAS28 changes.[80] When comparing the changes in power Doppler and grey-scale ultrasound activity with response to treatment, grey-scale ultrasound appears to perform better,[81] as does the addition of contrast enhancement.[82]

Which joints to assess

Only one study directly compared the assessment of inflammation by imaging different areas; Calisir *et al*[40] described MRI

synovitis and BM oedema in the hands and feet of patients with early RA and found no significant difference in MRI inflammation in these regions.

Recommendation 8: The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly ultrasound) is more responsive to change in joint damage and can be used to monitor disease progression.

Strength of recommendation: 7.8 (95% CI 6.8 to 8.9)

As for the previous recommendation, there were no specific data on the recommended frequency of imaging in the assessment of progressive joint damage.

Comparison of the ability of imaging to detect damage

Dohn *et al*[52] performed comparison studies of the ability of CR, CT, ultrasound and MRI to detect erosive damage.[52 83] With CT as the reference technique, CR was shown to have an accuracy of 81%, MRI of 89% and ultrasound of 80%, with high specificities and lowest sensitivity for CR.[52 83] A previous systematic review has described ultrasound to be more effective for erosion detection than CR, with comparable efficacy to MRI.[84] A summary of data comparing the different imaging modalities in the detection of erosions is given in table 3.[24 26 29 39 43 52 58 75 76 83 85–102]

Studies assessing tendon damage have shown ultrasound to be more sensitive than MRI in the detection of finger extensor tendon tears later confirmed at surgery;[103] and moderate agreement between ultrasound and MRI (used as the reference technique) in the assessment of shoulder tendon involvement.[104]

Responsiveness to change in damage

CR is the standard imaging technique used to detect and monitor joint damage. There are some data suggesting that CR is responsive to change in erosions on an individual level, particularly after the first 12 months of disease.[26] Radiographic progression appears to be most rapid in the first 2 years of disease, with 75% of all damage seen in the first 5 years of a 10-year study.[105] MRI seems to be more responsive to change at earlier time points, but measures of annual progression rates are similar with MRI and CR.[26] This is supported by Østergaard *et al*,[106] who found that 78% of new radiographic bone erosions were seen at least 1 year earlier by MRI, in fact MRI detection of new erosions preceded CR by a median of 2 years.

Which joints to assess

Early erosive changes on CR appear to be more common in the feet than in the hands, but from year 3 onwards these areas are more equally affected.[105 107]

Recommendation 9: Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed.

Strength of recommendation: 9.4 (95% CI 8.9 to 9.8)

Thirteen studies described the assessment of cervical spine involvement in RA, summarised in table 4.[108–120] No studies explored the appropriate frequency for monitoring change in the cervical spine; Yurube *et al*[118] investigated baseline features on CR predictive of future cervical instability and found that patients with baseline deforming hand changes, cervical vertical subluxation (VS), and subaxial subluxation showed more progression in VS and subaxial subluxation at 5 years, and Reijnierse *et al*[120] identified that baseline MRI atlas erosions and reduced subarachnoid space were associated with clinical neurological dysfunction at 1 year.

Comparison studies of different imaging modalities of the cervical spine have shown variation in the detection of the different pathologies, according to the imaging technique used. Fezoulidis *et al*[108] found CR and CT to be comparable and better than MRI in detecting atlanto-axial and atlanto-occipital lesions, but MRI to be superior in identifying odontoid lesions. MRI also seems to be better at showing erosions of the dens.[117]

Independent of the imaging modality used, dynamic lateral views of the cervical spine are more useful than static, neutral views in detecting atlanto-axial subluxation (AAS), in particular anterior AAS.[111] Flexion and neutral views are used commonly, with evidence to suggest greater change in the atlanto-dental interval with these views.[110] The open mouth view is used for imaging the odontoid peg and to assess for lateral and rotatory AAS; whereas posterior AAS can be measured with neutral and extension views, and VS with a lateral neutral view, although these types of AAS are much less common than anterior AAS.[117]

Table 3 Recommendation 8: Summary of included studies comparing imaging in the detection of erosions

Comparator vs reference technique (article reference)	Sensitivity	Specificity	Accuracy	κ	Detection rate, mean (range)
Hand/wrist erosions:					
MRI vs CT[52 83 85–87]	0.61–0.68	0.92–0.96	0.77–0.89	0.63	0.71-fold (0.60–0.81-fold)
Ultrasound vs CT[52 83]	0.42–0.44	0.91–0.95	0.80–0.84	0.44	
CR vs CT[52 83 85–88]	0.14–0.54	0.92–1.0	0.63–0.81	0.29	0.34-fold (0.16–0.60-fold)
CR vs MRI[24 26 39 58 75 89 90–100]	0.0–0.55	0.5–1.0	0.23–0.92		0.38-fold (0.06–0.80-fold)
CR vs ultrasound[24 58 97–101]	0.48	1.0			0.60-fold (0.18–1.21-fold)
Ultrasound vs MRI[24 58 97–100]	0.33–0.87	0.68–1.0	correlation coefficient 0.68–0.9	p<0.0005–<0.001	0.77-fold (0.35–1.51-fold)
Low vs high-field MRI[75 76 91 95]	0.46–0.94	0.93–0.94	0.55–0.94		0.94-fold (0.46–1.16-fold)
Feet erosions:					
CR vs MRI[29 43]	0.32–0.80	0.85–0.98		0.65 p 0.002	1.19-fold (0.55–1.83-fold)
CR vs ultrasound[29 102]					0.53-fold (0.42–0.64-fold)
Ultrasound vs MRI[29]	0.79	0.97	0.96		1.3-fold

CR, conventional radiography..

Table 4 Recommendation 9: Summary of included studies comparing imaging in the assessment of the cervical spine

Article year, (reference)	No. of subjects	Cervical spine imaging modality	Parameter assessed	Outcome
1989[108]	55	CR (AP, lateral F/E, OM) MRI CT	Atlanto-axial lesions Atlanto-occipital lesions Odontoid lesions Odontoid fibro-ostosis	Atlanto-axial lesions: CR = CT > MRI Atlanto-occipital lesions: CR = CT > MRI Odontoid lesions: MRI > CR/CT Odontoid fibro-ostosis: CR = CT > MRI
2000[109]	5 known AAS	CR (F/E) MRI (F/E)	AAS	More detail seen with MRI, and using F/E views
2005[110]	31	CR (F/E) MRI (F/E)	ADI Dense erosions	CR showed greater ADI in flexion than MRI, p 0.001 No significant difference in neutral/extension Assessment of dens erosions easier with MRI
1998[111]	65 unstable AAS	CR (lateral N/ F/E)	AAS	Significant difference between AAS in neutral and flexion/ extension, p <0.0001
1998[112]	28 symptomatic	CR (AP, lateral N/F, OM) MRI CT	AAS Odontoid erosions/cysts	Combination on MRI with CR showed more involvement than CT with CR (1.25-fold more VS; 1.13-fold more erosions/cysts)
2000[113]	42 symptomatic	MRI (N/F)	Reduction in subarachnoid space Brainstem compression	Flexion views showed more: brainstem compression (1.17-fold) reduction in the subarachnoid space at the atlanto-axial level (1.06-fold) and below C2 (1.13-fold)
2000[114]	25	CR (AP, lateral F/E, OM)	Odontoid erosions	Lateral views showed more erosions (1.57-fold) than open mouth views
2011[115]	56 symptomatic	CR (lateral) CT	CT factors predictive of VS on CR	VS greater in presence of odontoid erosions, p<0.05 Odontoid erosions significantly associated with odontoid osteoporosis, p<0.05
1995[116]	136 symptomatic	CR (AP, lateral F/E) MRI	MRI findings in normal CR	All MRI abnormal with normal CR: Effusion: 28% Pannus: 62%
2009[117]	40	CR (lateral N/ F/E, OM) MRI (N/F/E) CT	AAS Dens erosions	% patients with C-spine involvement on: CR 47.5%, MRI 70%, CT 28.2% Anterior AAS seen more in flexion on CR than MRI, p<0.005 CT best at detecting lateral AAS Dens erosions: CR 12.5%, MRI 67.5%, CT 41%
2011[118]	267	CR (lateral N/F/E)	Baseline features predictive of VS and SAS at 5 years	Prediction of VS: AAS, p 0.01; VS, p<0.01; SAS, p 0.06 Prediction of SAS: AAS, p 0.29; VS, p<0.01; SAS, p<0.01
1987[119]	18 symptomatic	CR (AP, lateral F/E) MRI	AAS CS SAS Dens erosions	MRI vs CR: AAS: 0.88-fold CS: 1.0-fold SAS: 0.5-fold Dens erosions: 1.27-fold
2001[120]	46 symptomatic	CR (lateral N/F, OM) MRI	Baseline CR and MRI features predictive of clinical neurological dysfunction at 1 year	CR not predictive (odontoid erosions, AAS) Dysfunction according to MRI (OR): Dens erosion: 1.5; atlas erosion: 4.9 Decreased subarachnoid space: 12.0 Decreased atlanto-axial space: 2.4 Brainstem compression: 2.3

AAS, atlantoaxial subluxation; ADI, atlanto-dental interval; AP, anteroposterior; CR, conventional radiography; CS, craniovertebral settling; E, extension; F, flexion; N, neutral; OM, open mouth; SAS, subaxial subluxations; VS, vertical subluxations.

When using CR to assess odontoid erosions, lateral cervical spine views appear to be more sensitive than open mouth views.[114]

Imaging in clinical remission:

Recommendation 10: Ultrasound and MRI can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation.

Strength of recommendation: 8.8 (95% CI 8.0 to 9.6)

The role of imaging in the detection of inflammation and subsequent prediction of outcome has been discussed previously (recommendation 5). There is good evidence to support the disparity between clinical remission and evidence of ongoing inflammation seen with various imaging modalities. Power Doppler activity has been found in 15–62% of patients in clinical remission according to DAS28, American College of Rheumatology or simplified disease activity index remission criteria,[121–124] MRI synovitis in 96% and BM oedema in 52%.[124 125] In one study, 60% of patients in disease activity score remission had increased uptake on scintigraphy.[126]

The significance of persistent inflammation, shown in a number of studies, is summarised in table 5.[127–133] The presence of ultrasound synovial hypertrophy, power Doppler activity and MRI synovitis at baseline in clinical remission has been shown to be significantly associated with structural progression at 1 year, even in asymptomatic joints.[127] Baseline ultrasound inflammatory activity in clinical remission also seems predictive of future disease flare, with 20% of patients experiencing a flare within 12 months in the absence of baseline ultrasound power Doppler activity, compared with 47% in patients with baseline power Doppler activity

Table 5 Recommendation 10: Summary of included studies describing outcome in the presence of image-detected inflammation in clinical remission

Article year (reference)	No. of subjects	Duration of follow-up (months)	Baseline assessment modality	Outcome parameter assessed	Results
2008[127]	102	12	Ultrasound SH, PD synovitis MRI synovitis	CR progression (Genant score)	SH: OR 2.31, p 0.032 PD synovitis: OR 12.21, p<0.001 OR 2.98, p 0.002
2011[128]	94	12	Ultrasound SH, PD synovitis, remissions (no SH or PD synovitis)	Relapse rate	% patients having flare: in ultrasound remission: 20.0% With ultrasound PD activity: 47.1%, p 0.009
2009[129]	106	24	Ultrasound joint count, PD synovitis	Relapse rate	Unsustained remission vs sustained remission: higher PD: OR 12.8, p<0.05 Higher ultrasound joint count: OR 4.6, p<0.05
2005[130]	32	12	Ultrasound RI	Relapse rate	Relapse rate higher with low RI se 0.80, sp 1.0, acc 0.96, p<0.01
2007[131]	169	24	Sustained ACR/DAS remission	CR progression (Larsen score)	Increase in Larsen score in (unsustained vs sustained): ACR remission: p 0.017 DAS remission: p<0.001
2004[132]	187	24	Sustained ACR/DAS remission	CR progression (SHS)	Increase in SHS score in (unsustained vs sustained): ACR remission: p 0.053 DAS remission: p 0.017
2012[133]	535	24	Remission according to DAS, SDAI, CDAI, ACR/EULAR	CR progression (SHS)	% patients with CR progression with baseline remission: DAS: 30% SDAI: 24% CDAI: 19% ACR/EULAR: 20%

ACR, American College of Rheumatology; CDAI, clinical disease activity index; CR, conventional radiography; DAS, disease activity score; EULAR, European League Against Rheumatism; PD, power Doppler; RI, resistive index; SDAI, simplified disease activity index; SH, synovial hypertrophy; SHS, Sharp/van der Heijde score.

(p 0.009).[128] Although radiographic progression can still be seen in clinical remission, individuals with sustained clinical remission show fewer signs of structural progression compared with patients with clinically relapsing disease.[131–133]

Future research agenda

The most important topics for future research according to currently available evidence and clinical practice were formulated by the group, shown in table 6.

DISCUSSION

These are the first recommendations produced by a EULAR task force on imaging in RA clinical practice. The recommendations were developed by an international group of experts with detailed literature review, and aimed to address clinical questions relevant to current practice. We acknowledge there is still a large amount of research required to optimise the use of imaging tools in routine clinical practice, in particular which joints should be used for disease assessment and monitoring and consideration of the feasibility, costs and appropriate training required to use ultrasound and MRI in clinical practice. In view of a lack of literature at the time of the review, these recommendations have not focused on detecting joint space narrowing, which is important to consider in view of the impact on functional status.[134] We have made specific reference to this in our proposed future research agenda.

In summary, we have developed 10 recommendations on various aspects of imaging in RA. These are based on the best available evidence and clinical expertise supported by an international panel of experts. We aimed to produce recommendations that are practical and valuable to clinical practice.

Table 6 Future research agenda

Research agenda	
1	Further evaluation of the specific joints to be assessed, timing of assessment (s) and the evaluation system to be employed in order to optimise the role of modern imaging modalities in diagnosis, prognosis and outcome measurement of RA
2	To assess algorithms using established and modern imaging modalities to examine their cost-effectiveness in clinical practice diagnosis, prognosis and outcome measurement of RA
3	To elucidate further the importance of subclinical (imaging-alone detected) inflammation, including synovitis, bone marrow oedema and tenosynovitis, especially in low disease activity states and to define key thresholds to guide intervention
4	To assess further the importance of imaging, in particular MRI and ultrasound, in the evaluation of damage, including joint space narrowing and cartilage loss
5	Assessing the feasibility, costs and appropriate training required to use ultrasound and MRI in clinical practice

RA, rheumatoid arthritis.

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DECLARATION OF AUTHORSHIP

I, Alexandra Nicole Bourn, declare that this thesis entitled:

'Using systematic literature reviews to develop guidelines for the management of inflammatory arthritis'

and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as listed above.

Signed:.....

Date:.....

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Definitions and Abbreviations

AAS……Atlanto-Axial Subluxation

ACPA……Anti-Citrullinated Protein Antibody

ACR……American College of Rheumatology

AGREE……Appraisal of Guidelines for Research and Evaluation

APR……Acute Phase Response

AUC……Area Under the Curve

BM……Bone Marrow

BSR……British Society for Rheumatology

CEBM……Oxford Centre for Evidence-based medicine

CI……Confidence Interval

COI……Conflict of Interest

CR……Conventional Radiography

CRP……C-Reactive Protein

CT……Computed Tomography

DAS……Disease Activity Score

DMARD……Disease Modifying Anti-Rheumatic Drug

DXA……Dual-emission X-ray Absorptiometry

DXR……Digital X-ray Radiogrammetry

ESR……Erythrocyte Sedimentation Rate

EULAR……European League Against Rheumatism

HAQ……Health Assessment Questionnaire

HLA……Human Leucocyte Antigen

IA……Inflammatory Arthritis

JIA……Juvenile Idiopathic Arthritis

JSN……Joint Space Narrowing

LOM……Limitation Of Movement

LR+……Positive Likelihood Ratio

LR-……Negative Likelihood Ratio

MeSH……Medical Subject Headings

MRI……Magnetic Resonance Imaging

NICE……National Institute for Health and Care Excellence

NPV……Negative Predictive Value

OR……Odds Ratio

PD……Power Doppler

PET……Positron Emission Tomography

PReS……Paediatric Rheumatology European Society

PTC……Points to Consider

QUADAS……Quality Assessment of Diagnostic Accuracy Studies

RA……Rheumatoid Arthritis

RAMRIS……Rheumatoid Arthritis MRI Scoring System

RCT……Randomised Controlled Trials

RF……Rheumatoid Factor

RR……Relative Risk

SIJ……Sacroiliac Joint

SH……Synovial Hypertrophy

SJC……Swollen Joint Count

SLR……Systematic Literature Review

SOP……Standardized Operating Procedures

SRM……..Standardised Response Mean

TJC……..Tender Joint Count

TMJ……..TemporoMandibular Joint

TNF……Tumour Necrosis Factor

UIA……Undifferentiated Inflammatory Arthritis

US……..UltraSound

VAS……Visual Analogue Scale

VS……Vertical Subluxation

Chapter 1: Introduction and overview of methodology

1.0 Introduction

Inflammatory arthritis (IA) encompasses a group of conditions characterised by joint inflammation and subsequent destruction if disease control is not achieved. Joint damage is often detected and monitored using conventional radiography (CR), but advances in imaging techniques have increased the potential to identify damage and inflammation more readily.

1.1 Main thesis aim

This thesis aims to review the use of systematic literature reviews (SLR) to develop guidelines for the management of IA, the process of producing guidelines and their quality. It includes a review of the literature on the role of imaging in the management of patients with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA), with a view to providing evidence based recommendations for European League Against Rheumatism (EULAR) that can be readily used in clinical practice. It also considers the quality of all EULAR management recommendations and areas where improvements could be made.

The thesis has been structured as follows:

Chapter 2: 'Background: inflammatory arthritis, imaging and systematic literature reviews'. This chapter summarises the current understanding of the aetiology, diagnosis, monitoring and management of patients with RA and JIA. It also describes the imaging modalities used in IA, and the methodology used to perform a SLR and to produce guidelines, which provide the basis of this thesis.

Chapter 3: 'Developing EULAR recommendations for use in imaging of the joints in the clinical management of RA'. This chapter describes the specific process used to develop recommendations on the use of imaging of the joints in the management of RA. The recommendations produced are discussed in detail, with consideration given to important future research topics.

Chapter 4: 'Developing EULAR points to consider for use in imaging of the joints in the clinical management of JIA'. This chapter presents the SLR performed to

produce points to consider (PTC) on the use of imaging in the diagnosis and management of JIA in clinical practice. A research agenda and lay summary of the findings are also included.

Chapter 5: 'Ensuring the quality of rheumatology management recommendations'. This chapter provides a review of EULAR management recommendations, using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, 10 years after publication of the EULAR standardized operating procedures (SOP) for the production of recommendations.

Chapter 6: 'Discussion, conclusions & future research'. This chapter summarises the findings of the three main studies included in this thesis, and considers potential improvements in the work performed, and recommendations for future research that has become evident as a result of this research programme.

Chapter 2: Background: inflammatory arthritis, imaging and systematic literature reviews

2.0 Introduction

This chapter provides an overview of the diagnosis, monitoring and treatment of RA (section 2.1) and JIA (section 2.2). Section 2.3 describes the different imaging modalities used in IA, and section 2.4 summarises the process involved in producing clinical guidelines, with particular attention given to SLR.

2.1 Rheumatoid arthritis

RA is a chronic systemic autoimmune condition which primarily causes joint inflammation in a symmetrical distribution. The diagnosis is largely a clinical one, relying particularly in the early stages on the history and examination of the patient, with further investigations sometimes helping to confirm the diagnosis.

Patients with RA typically present with pain, morning stiffness and joint swelling with clinical evidence of synovitis usually of the small joints of the hands and feet. RA is considered an autoimmune condition as it is often associated with autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), which can precede the clinical onset of RA by a number of years. Joint damage is rarely present in the very early stages of disease, but tends to develop over time. Classification criteria have been developed which are mainly used for patient selection for clinical trials, with the 1987 American College of Rheumatology (ACR) classification criteria being replaced by the 2010 ACR/EULAR RA classification criteria (figure 1)[1,2]. This update allowed for earlier diagnosis and management of RA as the presence of bony damage, in the form of erosions, was included in the 1987 criteria.

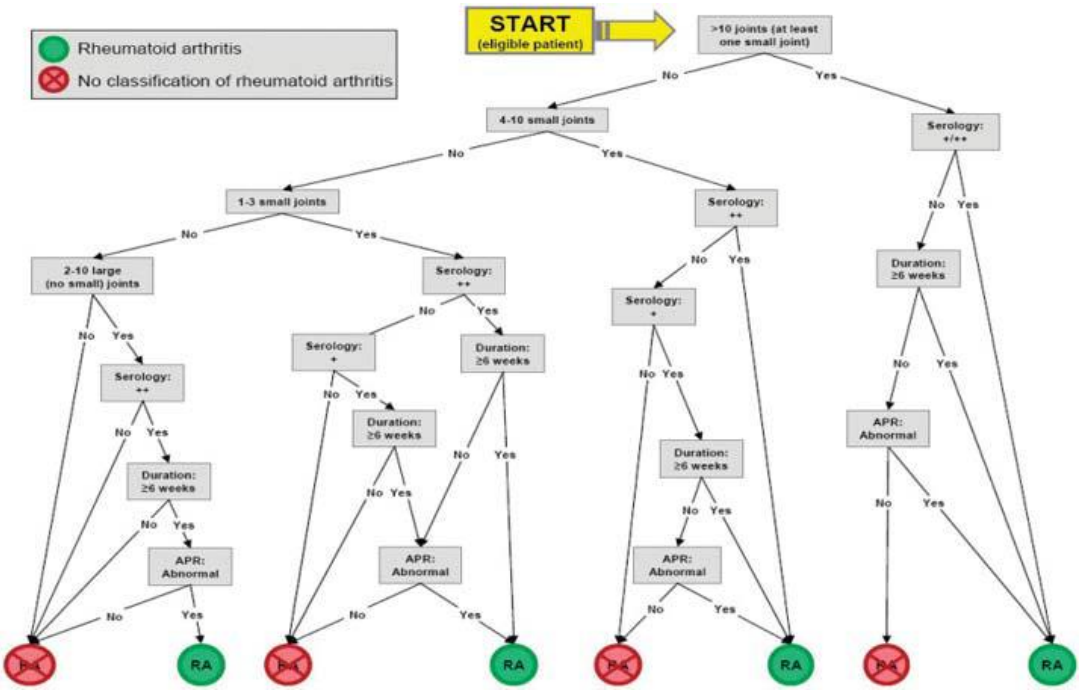

Figure 1. 2010 RA Classification Tree.

The 2010 tree algorithm for classifying definite RA (green circles) or for excluding its presence (red circles) among those who are eligible to be assessed by the 2010 ACR-EULAR RA classification criteria.

APR, acute-phase response, serology: +, low-positive for rheumatoid factor (RF) or anti - citrullinated protein antibody (ACPA); serology: ++, high-positive for RF or ACPA; serology: +/++, serology either + or ++.

Reproduced from 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Aletaha D, Neogi T, Silman AJ, et al., 69, 1580-8, 2010 with permission from BMJ Publishing Group Ltd[1].

There are approximately 400,000 people with RA in the UK, with an incidence of about 3.6/100,000 in women and 1.5/100,000 in men which equates to a new diagnosis of RA being made in about 12,000 people per year[3,4].

The precise trigger for RA is unknown but the condition is thought to develop from the interaction of genetic and environmental risk factors. The human

leucocyte antigen (HLA), particularly the 'shared epitope' HLA-DRB1, provides a strong genetic association with a relative risk of developing RA of 3.8 - 6 in homozygous Caucasian patients[5]. Twin studies have suggested genetic factors to account for about 60% of the variation in disease liability[6]. Environmental factors that are thought to influence disease susceptibility include smoking, exposure to silica dust, various infections such as Epstein-Barr virus and Parvovirus B19, and early life factors such as maternal smoking during pregnancy and high birth weight[7].

The pathophysiology of RA involves the interaction of T- and B-cells, and pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-6, which results in local and systemic inflammation (figure 2)[8,9].

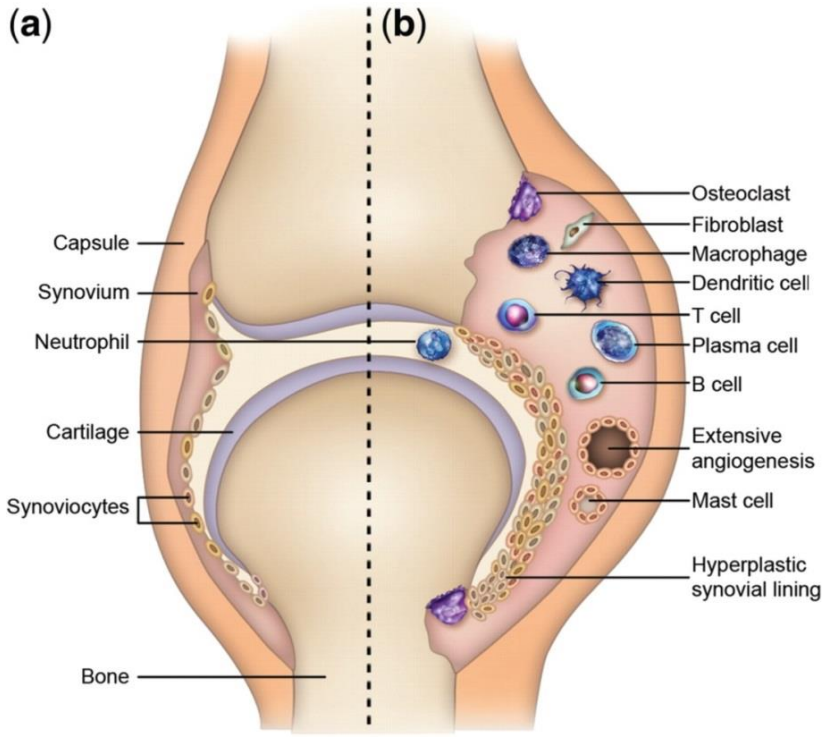

Figure 2. Schematic view of (a) a normal joint and (b) a joint affected by RA

The joint affected by RA (b) shows increased inflammation.

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The diagnosis of RA is largely based on the clinical history and examination, but the presence of raised inflammatory markers, in particular erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and positive immunology (RF and ACPA) can be useful. Musculoskeletal imaging is also often performed, usually to provide a baseline record of radiographic changes, as it is now unusual to detect abnormalities on CR in the early stages of the disease. Ultrasound (US) and magnetic resonance imaging (MRI) can also be used to look for inflammatory changes; the role of imaging in RA is discussed in detail later in this thesis. These modalities are also used to monitor disease progression, but the disease activity score (DAS)-28 is the most routinely used clinical measure of disease activity[10].

There is currently no cure for RA, but medical treatment aims to relieve symptoms, modify disease progression, slow functional impairment, and reduce the risk of potential comorbidities. Treatment should be started promptly in patients with newly diagnosed RA as there appears to be a 'window of opportunity' when RA is more susceptible to treatment[11]. Patients are managed with analgesic preparations as required but the primary treatment of RA is with conventional, synthetic disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine, sulfasalazine and leflunomide; biologic DMARDs and other selective non-biologic DMARDs. Use of these agents is generally reserved for those patients who have failed or been intolerant to treatment with conventional DMARDs[12].

Treatment aims to improve symptoms and to achieve clinical remission, often measured using the DAS score. Poor prognostic factors include positive RF or ACPA, functional limitation, high disease activity and evidence of early erosive damage on CR[13].

2.2 Juvenile idiopathic arthritis

Contrary to RA, JIA is an umbrella term for several types of arthritis. It is a heterogeneous group of conditions with onset under the age of 16 years, unknown aetiology, persistence of symptoms for over 6 weeks, and exclusion of other rheumatic or infectious causes (table 1)[14].

Table 1. Classification of Subtypes of Juvenile Idiopathic Arthritis

Subtype (% of JIA)	Definition
Oligoarthritis (60%)	Arthritis affecting 1 - 4 joints during the first 6 months of disease. 1. Persistent oligoarthritis: Affecting ≤ 4 joints throughout the disease course 2. Extended oligoarthritis: Affecting > 4 joints after the first 6 months of disease
Polyarthritis (RF negative) (30%)	Arthritis affecting ≥ 5 joints during the first 6 months of disease RF negative
Systemic Onset (10%)	Arthritis in ≥1 joints with or preceded by fever of at least 2 weeks' duration documented daily ('quotidian') for at least 3 days, and one or more of the following: 1. Evanescent (non-fixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis
Polyarthritis (RF positive) (<10%)	Arthritis affecting ≥ 5 joints during the first 6 months of disease RF positive on 2 or more occasions, at least 3 months apart
Psoriatic Arthritis (<10%)	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative
Enthesitis Related Arthritis (<10%)	Arthritis and enthesitis, or arthritis OR enthesitis with at least 2 of the following: 1. Sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. HLA-B27 positive 3. Arthritis in a male over 6 years of age 4. Acute anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis (Reiter's syndrome), or acute anterior uveitis in a first-degree relative
Undifferentiated Arthritis (<10%)	Arthritis that fulfils criteria in no subtype or in more than one of the above subtypes

RF, rheumatoid factor. *Table created using text adapted from Petty et al*[14].

JIA is the most common paediatric rheumatological condition, with a reported prevalence of 0.07 – 4.01/1000 children and incidence of 0.008 – 0.226/1000 children per annum[15]. As with RA, the precise aetiology of JIA is unknown and includes similar genetic and environmental factors. The concordance rate of JIA in monozygotic twins has been reported between 25% and 40%[16]. Proposed causative environmental factors include passive exposure to cigarette smoke and air pollution[17,18]. Much like in RA, the whole immune system appears to be involved in the immune response involved in the pathophysiology of JIA (figure 3)[19].

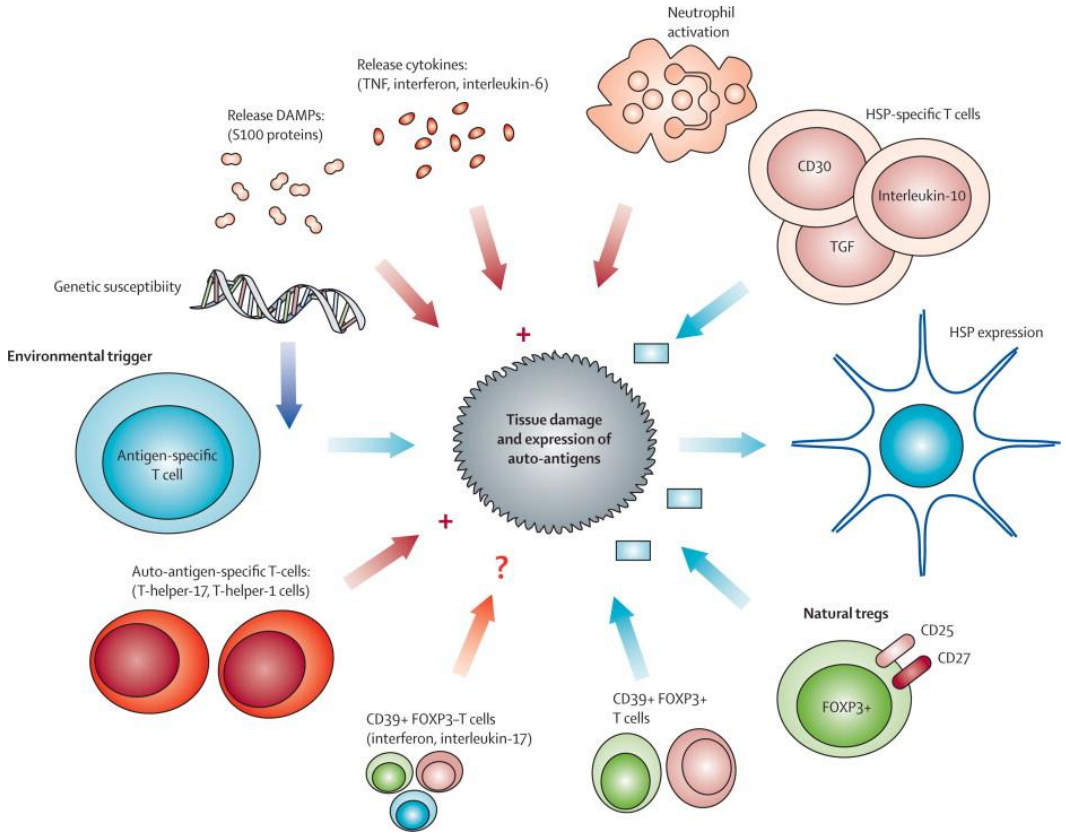

Figure 3. The balance between tolerance and inflammation in juvenile idiopathic arthritis.

In a genetically susceptible individual, an environmental trigger leads to local tissue damage, the expression of auto-antigens (such as heat shock proteins), and inflammation, which activates a range of innate and adaptive immune responses that can either down-regulate (blue arrows) or promote (red arrows) local inflammation.

DAMPs, damage-associated molecular pattern molecules; HSP, heat-shock protein; TGF, tumour growth factor; TNF, tumour necrosis factor.

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A diagnosis of JIA should be considered in the presence of joint inflammation for 6 weeks or more, with specific features dependent on the subtype as described in table 1. Blood tests are less useful than in RA as inflammatory markers may be raised and RF is only positive in a small proportion of patients. Of all children with JIA, less than 10% have the RF-positive polyarticular subtype[20]. Imaging plays a similar role in detecting joint damage and inflammation as in RA, dependent on the disease subtype. CR is particularly used to exclude other possible diagnoses and provide a baseline for monitoring progression of damage; other changes on CR usually develop as a late complication. US and MRI have more specific roles in identifying inflammation, which will be described fully in Chapter 4. As in RA, imaging can also be used to monitor disease progression in JIA, with clinical tools for monitoring patients, particularly with polyarticular JIA (pJIA), including DAS-28 and the juvenile arthritis disease activity score (JADAS)[21].

Treatment depends on the JIA subtype; treatment of pJIA in particular has progressed significantly over recent years, with historically options including intra-articular steroid injections and methotrexate, with the subcutaneous preparation used more routinely than in the adult population. Biological agents are also used in case of treatment failure; etanercept, adalimumab, abatacept, tocilizumab and canakinumab have been approved to date by the European Medicine Agency in at least one of the JIA subtypes[22].

2.3 Imaging in inflammatory arthritis

The most commonly used imaging modalities in IA include CR, US and MRI with computed tomography (CT), dual-emission X-ray absorptiometry (DXA), digital X-ray radiogrammetry (DXR), scintigraphy and positron emission tomography (PET) used less frequently in specific clinical circumstances.

CR is a non-invasive imaging technique that uses a small dose of ionising radiation to produce two-dimensional images that provide an overview of the imaged joint, with features predominantly of bone, such as erosions, juxta-articular osteopenia and joint space narrowing (JSN), rather than the soft tissues. It is the most commonly used imaging modality, is readily available to all clinicians, with low cost and few risks; the process is quick and well tolerated. However CR does not assess inflammatory disease activity, provides only static images, and may be less sensitive to change than other imaging modalities. It is

still considered the 'gold standard' for the initial assessment and monitoring of structural change in inflammatory arthritis, and is used in various CR scoring techniques, such as the Sharp and Larsen scores[23].

Musculoskeletal US uses high frequency sound waves to assess the underlying structures. It is very readily available to clinicians; its use has increased recently with experience of US included in most current rheumatology training curricula. It does not involve exposure to radiation, has a relatively low cost (compared with MRI and CT) with potentially portable equipment, and has the ability to provide dynamic scans and be used to guide procedures including joint aspirations, injections and synovial biopsies. As well as detecting bony changes, US demonstrates soft tissue and inflammatory changes which is enhanced by the use of high-resolution grey-scale and power Doppler (PD). However the accuracy of US is operator dependant and has poor bone penetration, limiting its use in detecting bone marrow (BM) lesions which can be more accurately identified by MRI[24].

MRI is based on nuclear magnetic resonance, which involves non-ionising radiation in a strong magnetic field to align hydrogen protons that resonate producing their own magnetic field that is used to create the image. It provides accurate assessment of bone and soft tissue lesions, including erosions, JSN, synovitis and BM oedema; contrast such as gadolinium can emphasise inflammatory changes. RA MRI scoring systems, such as the RA-MRI score, have been developed to grade and monitor joint pathology severity[25]. The equipment involvement is expensive to purchase, operate, and maintain, is generally fixed and immobile, can cause claustrophobia due to the small bore of the magnet used and requires the patient to remain completely still for the duration of the procedure. MRI is usually contraindicated in the presence of implanted magnetic metal devices.

CT uses a rotating x-ray source to generate high resolution, cross-sectional images which can then be reconstructed and manipulated using computer processed combinations of the images. CT can involve significant radiation exposure dependant on the site imaged, but it provides useful information on subtle cortical disease and erosions[26]. Periarticular osteoporosis is one of the earliest radiological features of RA; DXA uses low dose ionising radiation to measure bone mineral density, usually in the spine and hip although whole body scans are often performed in children; DXR can be used to measure more localised bone involvement through the use of radiogrammetry[27,28]. Scintigraphy is

a functional study that uses radioisotopes to provide a whole body scan, but areas of increased uptake are non-specific with high sensitivity but low specificity as changes may be caused by increased bone turnover or joint inflammation, which does not always correlate with disease activity[29]. PET also uses radiolabelled ligands combined with structural imaging, usually CT, to detect inflammatory changes at a cellular level, resulting in high sensitivity and specificity and can provide a whole body scan relatively quickly. However PET has lower spatial resolution and is not as readily available to clinicians as other imaging modalities, and involves radiation exposure[30].

Other than the key technical differences between the imaging modalities, there are practical differences that can be important when considering the role of imaging in children with JIA. Table 2 summarises the advantages and limitations of US, MRI and CR in JIA[31].

Overall, the specific role of the imaging modalities in IA is unclear; use of imaging is extensive but it is not currently standardised. Performing SLR in this field provides an important opportunity to address this and provide best practice guidelines.

Table 2. Advantages and limitations of US compared to MRI and CR in children with JIA

Imaging modality	Advantages	Limitations
US	Lack of exposure to ionizing radiation	Difficulties in carrying out in case of severe joint limitation
	Rapidity of performance	Relatively small field of view
	Ease of repeatability	Inability to assess the whole joint space
	High patient acceptability	Acoustic shadowing from overlying bones
	Demonstration of soft tissue inflammation	Limited value in the assessment of axial skeleton and TMJ
	Direct visualization of cartilage	Dependency on the properties and sensitivity of the ultrasound equipment
	Early detection of bone erosions	Need of continuous practice after appropriate training
	Ability to scan multiple joints in a single session	Reliability, standardization and validation in children under investigation
	Support in guidance of procedures (e.g. intra- articular corticosteroid injections)	
	Relatively inexpensive	
MRI	Lack of exposure to ionizing radiation	Intravenous contrast agent often required
	Multiplanar tomographical imaging	Possible allergic reaction to contrast agents
	Ability to assess the whole joint space	General anaesthesia required in younger children
	Demonstration of soft tissue inflammation	Long examination time
	Direct visualization of cartilage	Evaluation limited to one target joint
	Early detection of bone erosions	Reliability, standardization and validation in children under investigation
	Visualization of BM oedema	High cost
	High tissue contrast	Variable availability worldwide

	Suitable for assessment of axial skeleton and TMJ	
CR	Rapidity of performance	Exposure to ionizing radiations
	Applicability to all joints	Inability to directly visualize cartilage and soft tissue inflammation
	Demonstration of JSN, disturbances of bone growth and maturation	Late detection of bone erosions and JSN
	Detection of bone erosions	Projectional superimposition
	Validated scoring methods in children	
	Suitable for longitudinal evaluation of damage progression	
	Low cost	
	Widespread availability	

TMJ, temporomandibular joint; BM, bone marrow; JSN, joint space narrowing.

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2.4 Systematic literature reviews and producing guidelines

Clinical guidelines are produced to assist clinicians in providing the most appropriate management of patients, and have been defined by the Institute of Medicine (IOM) of the National Academies as[32]:

> 'statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options'(p 4).

The IOM describes 8 standards for producing trustworthy clinical guidelines[32]:

1) Establishing transparency
2) Management of Conflict of Interest
3) Guideline Development Group Composition
4) Clinical Practice Guideline–Systematic Review Intersection

5) Establishing Evidence Foundations for and Rating Strength of Recommendations
6) Articulation of Recommendations
7) External Review
8) Updating

This chapter will focus on standard 4, the process involved in producing systematic reviews, which are fundamental to this thesis. The IOM has also published 21 standards for developing high-quality systematic reviews which are summarised in table 3 and will be used to structure this chapter[33].

2.4.1 Recommended Standards for Initiating a Systematic Review

2.4.1.1 Establish a team with appropriate expertise and experience to conduct the systematic review

The first stage in performing a systematic review is involving all suitable people with the required expertise. This includes a team convenor; those with the relevant clinical knowledge; individuals with experience in performing systematic reviews in particular completing searches of databases, for example, a methodologist, librarian and research fellow; and members of the target population, including patients with the relevant diagnosis.

2.4.1.2 Manage bias and conflict of interest (COI) of the team conducting the systematic review

This stage is essential to ensure that end users of any recommendations produced have full confidence in the credibility of the review. All members of the review team must therefore fully disclose any potential conflict of interest, and those with any potential financial or professional bias should be excluded from the group.

2.4.1.3 Ensure user and stakeholder input as the review is designed and conducted

It is important to ensure that all members of the team are able to make independent and informed decisions during the review process.

Table 3. IOM standards for developing systematic reviews

Recommended Standards for Initiating a Systematic Review	
	Establish a team with appropriate expertise and experience to conduct the systematic review
	Manage bias and COI of the team conducting the systematic review
	Ensure user and stakeholder input as the review is designed and conducted
	Manage bias and COI for individuals providing input into the systematic review
	Formulate the topic for the systematic review
	Develop a systematic review protocol
	Submit the protocol for peer review
	Make the final protocol publicly available, and add any amendments to the protocol in a timely fashion
Recommended Standards for Finding and Assessing Individual Studies	
	Conduct a comprehensive systematic search for evidence
	Take action to address potentially biased reporting of research results
	Screen and select studies
	Document the search
	Manage data collection
	Critically appraise each study
Recommended Standards for Synthesizing the Body of Evidence	
	Use a prespecified method to evaluate the body of evidence
	Conduct a qualitative synthesis
	Decide if, in addition to a qualitative analysis, the systematic review will include a quantitative analysis (meta-analysis)
	If conducting a meta-analysis, do additional statistical analyses
Recommended Standards for Reporting Systematic Reviews	
	Prepare final report using a structured format
	Peer review the draft report
	Publish the final report in a manner that ensures free public access

IOM, Institute of Medicine; COI, conflict of interest. *Table created using text adapted from Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research* [33].

2.4.1.4 Manage bias and COI for individuals providing input into the systematic review

2.4.1.5 Formulate the topic for the systematic review

It is firstly important to ensure that there is need for a review in a proposed topic, in particular that the review has not been performed recently already, and that the clinical need for the review exists.

Once the specific clinical question to be answered has been developed, it needs to rephrased into an epidemiological question, which should follow a structured format such as the 'PICO' (Patients, Population or Problem, Intervention, Control or Comparison and Outcomes) structure[34]. For example, if addressing the question 'In patients with recurrent tonsillitis, do prophylactic antibiotics, compared to no treatment, reduce the recurrence rate?', the population is patients with recurrent tonsillitis; the intervention is prophylactic antibiotics; the control is no antibiotics; and the outcome is reduction in recurrence rate of tonsillitis. This process is important as it helps to clarify the question to be answered and establishes specific keywords that can then be used to identify particular Medical Subject Headings (MeSH) which form the basis of the search strategy.

2.4.1.6 Develop a systematic review protocol; submit the protocol for peer review; make the final protocol publicly available, and add any amendments to the protocol in a timely fashion

The purpose of the review protocol is to develop a structure and plan for the review that can be agreed by the review team before any further work is performed. The protocol should include details of the background to performing the review; a summary of the existing literature that will include rationale why the review question is important; details of the review question and aims; an outline of the methods that will be used; and an anticipated time frame to complete the review. This will help to establish when the next meeting with the review team should be. Although it is important to develop and disseminate a protocol to the review team for all systematic reviews, it is generally not expected to fully publish these, other than for Cochrane reviews.

2.4.2 Recommended Standards for Finding and Assessing Individual Studies

2.4.2.1 Conduct a comprehensive systematic search for evidence

The search is the process used to identify evidence that addresses the review question. It is a complex process, so it is extremely helpful to work with a librarian experienced in performing systematic reviews. They can advise on formulating the search strategy according to the MeSH terms identified using the PICO structure. It is important to be clear about what resources and electronic databases are to be used for the search, as the search terms used for each will differ slightly. The most commonly used bibliographic databases are Cochrane Central Register of Controlled Trials (CENTRAL), Embase, MEDLINE and Database of Abstracts of Reviews of Effect (DARE), although subject-specific databases may be more useful dependant on the subject of the review.

2.4.2.2 Take action to address potentially biased reporting of research results

Although searching major bibliographic databases is likely to identify most available evidence, it is possible that including only these sources will exclude important data. For this reason it is good practice to 'hand search' electronic tables of contents of selected journals and relevant conference abstracts, particularly as it is reported that as few as 50% of conference abstracts are eventually published in full, with lowest publication rates for those abstracts without a positive finding[35]. Searching the citations of relevant publications identified from the search or from previous systematic reviews on a similar topic can also be useful. Other potential resources for searching for grey literature includes clinical trial registries and grey literature databases. These processes help to reduce publication bias, location bias and time-lag bias. It is also important to consider potential language bias, which can result if only research published in English is included in the review. Abstracts are often published in English, irrespective of the publication language of the full text article, so these can easily be screened for inclusion in the review. Any foreign language articles identified for inclusion through the search process can then be translated using online translation tools, or potentially by members of the review team depending on the languages involved.

2.4.2.3 Screen and select studies

It is incredibly helpful to use bibliographic software such as EndNote or Refworks when performing a review as this stores all of the studies identified through the search which can then be sorted and filed into relevant groups. The software can also identify any duplication of studies resulting from searching multiple bibliographic databases. Once the search has been performed, all identified studies need to be screened for potential eligibility for inclusion in the review based on the protocol's pre-specified criteria. The initial screening process is usually performed based on the study titles and abstracts, and should ideally be performed by two researchers independently. The studies should be sorted into folders either for inclusion or exclusion for broad reasons according to the PICO structure, for example wrong population, wrong intervention etc. The screeners should meet to discuss the screening process, review any areas for disagreement with the final decision lying with a senior member of the review team.

Once all studies have been screened, the full text articles of all those identified for potential inclusion need to be obtained to be screened further, also ideally by two independent reviewers. The screening process is repeated again according to the PICO criteria, and excluded studies should be filed according to reason for exclusion.

2.4.2.4 Document the search

The full search strategy used for each database needs to be recorded fully, including dates the searches were performed. Screening and sorting of studies is a complex process, particularly given the potentially large numbers of studies involved. For clarity and transparency, it is important that the screening process is clearly documented, including any reason for excluding studies. The simplest way to present this data is often using a flow chart (figure 4)[36].

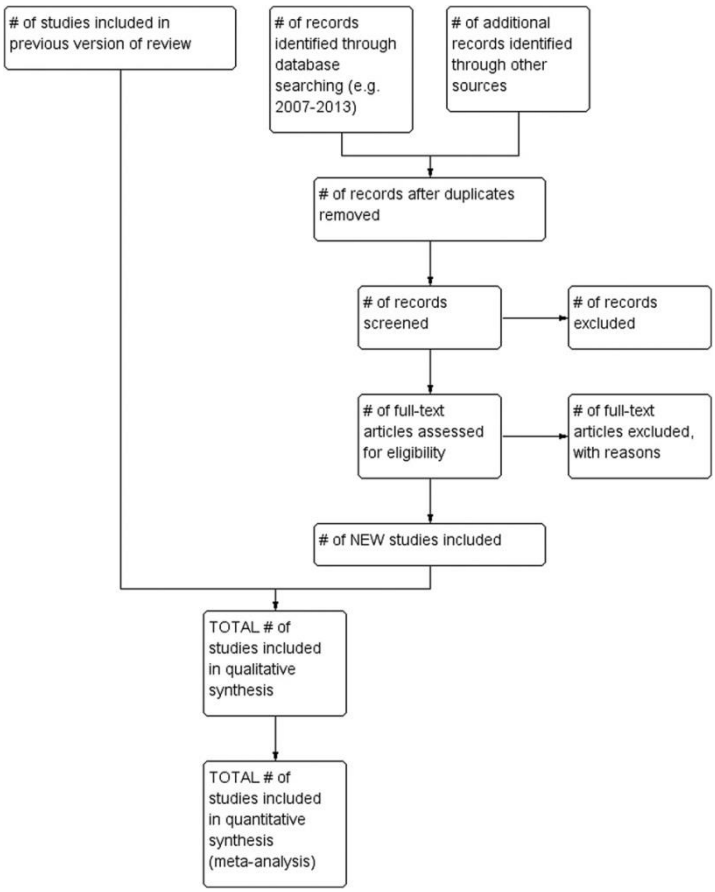

Figure 4. Adapted study flow diagram.

Study flow diagram for a review update with previous included studies incorporated into the results of an updated literature search.

Reprinted from Systematic Reviews, 3, Stovold E, Beecher D, Foxlee R, et al, Study flow diagrams in Cochrane systematic review updates: an adapted PRISMA flow diagram, 54, © (2014), http://creativecommons.org/licenses/by/4.0/, no changes made[36].

2.4.2.5 Manage data collection

Once all of the studies for inclusion have been identified which will require review of full text articles, the next stage is data extraction. This involves identifying and recording all relevant data from the included studies. The information extracted may be quantitative or qualitative. It is helpful to record this data in a bespoke data extraction form, which should be piloted for two or three of the included studies.

2.4.2.6 Critically appraise each study

The quality of all included studies needs to be assessed both in general terms and using specific tools, dependant on the study design. This can be described as the processes a study uses to reduce error and bias in the way it is designed, performed and analysed. The main types of bias to consider are selection bias, allocation bias, performance bias, detection bias, attrition bias, reporting bias, funding bias, and confounding.

The main tool used to evaluate randomised controlled trials (RCTs) is risk of bias, which considers sequence generation, allocation concealment, blinding of all participants, incomplete outcome data, selective outcome reporting and any other potential sources of bias that may not have been addressed by the tool[37]. Several tools also exist to assess the quality of non-randomised studies, including the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool for diagnostic accuracy studies, Newcastle-Ottawa Scales for cohort and case-control studies, with guidance for case series from the Centre for Reviews and Dissemination, and for controlled before-and-after studies and interrupted-time-series studies from the Cochrane Effective Practice and Organisation of Care Group[38-41]. The Cochrane Group has also recently developed the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool to assess risk of bias of the comparative effectiveness of interventions from studies that have not randomised[42]. An overall quality assessment can be made for each study using the Oxford Centre for Evidence-based medicine (CEBM) level of evidence, which gives studies a score for 'level of evidence' (1a-5) and a score for 'grade of recommendation' (A-D)[43].

2.4.3 Recommended Standards for Synthesizing the Body of Evidence

2.4.3.1 Use a prespecified method to evaluate the body of evidence

This is the process involved in reporting the overall quality of the whole body of evidence, now that the individual studies have been assessed. Similar characteristics should be considered, including risk of bias, consistency, precision, directness and reporting bias; and dose-response association, confounding and strength of association for observational studies[44].

2.4.3.2 Conduct a qualitative synthesis

The qualitative synthesis describes the subjective narrative that should be used to assess the quality of the included studies further, for example how many studies were included and why other studies were excluded, the range of study types and population sizes, what outcomes were considered, strengths and limitations and the study quality scores, as described above. This information allows the user of the review to make a judgment on the significance and robustness of the data presented with the specific clinical question in mind.

2.4.3.3 Decide if, in addition to a qualitative analysis, the systematic review will include a quantitative analysis (meta-analysis)

A meta-analysis involves the statistical combination of data from the included studies. As well as providing an overall quantitative analysis of the data, a meta-analysis can increase the power of the estimated effect of the intervention under review through a single pooled estimate, for example with an odds ratio (OR).

In order to appropriately perform a meta-analysis, the studies included need to be sufficiently homogeneous for the results to be combined. Studies will not be identical in all aspects, but it is important to consider the population characteristics of the study groups; the outcomes and comparators that the studies compare; the study outcomes, whether primary or secondary outcomes; and direction of treatment effects. It can still be possible to perform a meta-analysis if the studies are not homogenous in all of these areas but it is important that this is made clear in a discussion of the results.

2.4.3.4 If conducting a meta-analysis, do additional statistical analyses

Given the complexity of performing a meta-analysis, particularly as a result of study heterogeneity, it can be helpful to use the help of an expert methodologist to assist in the process although software packages do exist, such as the Cochrane Collaboration's software, RevMan. Heterogeneity should be assessed according to clinical, methodological and statistical aspects. Forest plots can identify heterogeneity through poor overlap of confidence intervals, or a more formal assessment of heterogeneity can be made using the chi-squared test. The degree of heterogeneity can be calculated using the I^2 statistic. The results of the meta-analysis can then be presented in a forest plot which will show the individual studies as well as the overall combined estimate of the treatment effect.

2.4.4 Recommended Standards for Reporting Systematic Reviews

2.4.4.1 Prepare final report using a structured format

A systematic review should be reported in sufficient detail for the review to be repeated using the same methods. As systematic reviews are a multi-faceted and complex process, it can be helpful to use a checklist such as that developed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[45].

2.4.4.2 Peer review the draft report

The systematic review report should be peer reviewed by a third party for accuracy, comprehensiveness, and clarity of the report. There should also ideally be a public comment period for the report.

2.4.4.3 Publish the final report in a manner that ensures free public access

2.4.5 Summary

Performing systematic reviews is a complex and time-consuming process, but using a structured format as outlined here can facilitate the process and help to ensure a high-quality end result. To summarise, the steps involved in producing a systematic review are illustrated in figure 5[46].

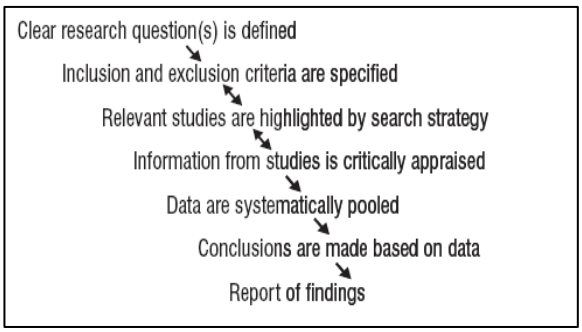

Figure 5. Stages of a systematic review.

Smith D, Reaney M, Speight J. *Conducting Literature Reviews to Support the Use of Patient-Reported Outcomes (PRO) Measures in Clinical Trials – The Benefits of a Systematic Search Strategy*. https://www.ispor.org/news/articles/July09/CLR.asp (accessed 22 November 2016)[46].

2.4.6 Producing guidelines

Performing systematic reviews is an essential process to provide an evidence-based summary of the available literature and for the production of clinical guidelines, which can then be used by clinicians to integrate best practice into clinical care. Several tools exist that can be used to guide the process involved in writing or assessing the quality of guidelines, including the EULAR SOP and the AGREE II instrument[47,48]. The procedure recommended by EULAR is illustrated in figure 6[48].

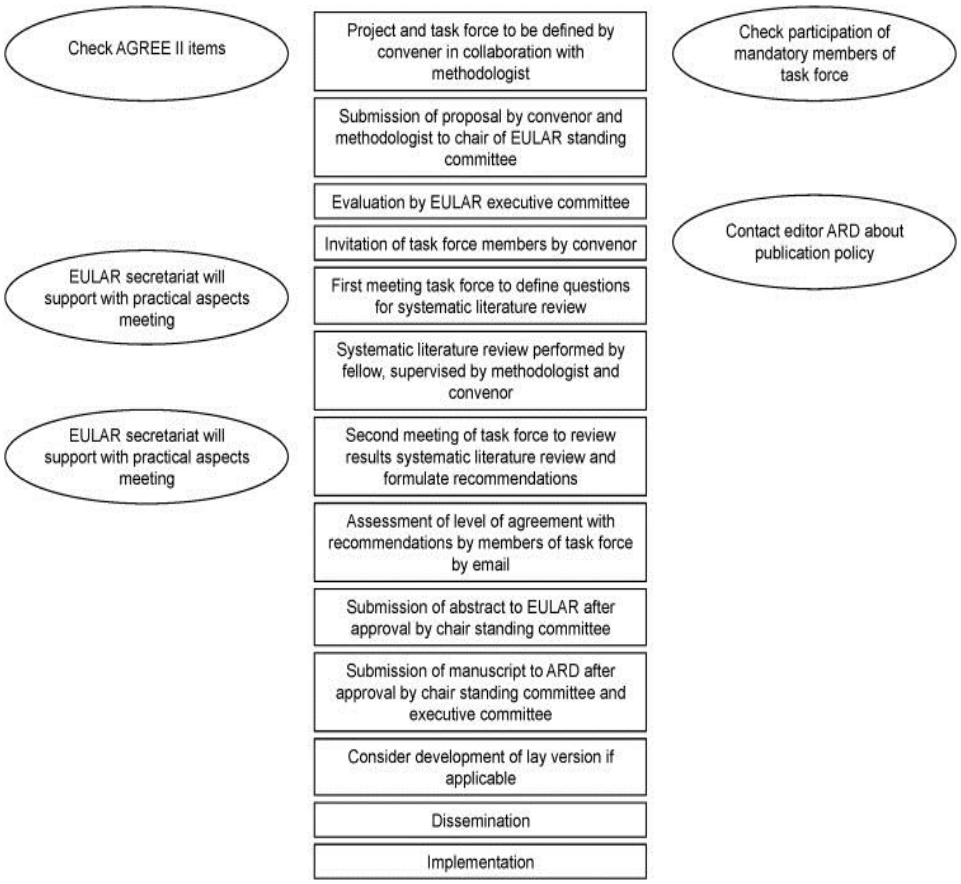

Figure 6. Flowchart of various steps during development of recommendations.

AGREE, Appraisal of Guidelines for Research and Evaluation; ARD, Annals of Rheumatic Diseases.

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There are differences in the methodology used by various organisations to

generate treatment guidelines. The model used by EULAR, described here, involves a universal approach with a panel of relevant experts, whereas the 3e (Evidence, Expertise, Exchange) Initiative used a model of guideline production that effectively canvassed the views of several hundred international rheumatologists to generate recommendations by integrating evidence synthesis with expert exchange[49]. The Cochrane Collaboration uses a stringent process for performing SLR, resulting in reviews that are 'internationally recognized as the highest standard in evidence-based health care resources'[50]. The Cochrane Handbook for Systematic Reviews of Interventions provides regularly updated detailed guidance on the methods used to prepare Cochrane Intervention reviews[51]. The National Institute for Health and Care Excellence (NICE) in the United Kingdom has accredited the process used by British Society for Rheumatology (BSR) to produce clinical guidelines, who developed a stringent protocol for creating guidelines in 2017 which is based on the AGREE II instrument[52,53].

Once a systematic review is performed, the data is presented to the review team or task force to review the results and formulate recommendations. The task force use the data presented to them to create recommendations, or PTC if the strength of data is not sufficient to substantiate a true recommendation. They can also use their expert opinion to devise the recommendations where good quality data may be missing. The level of evidence and grade of the recommendation should be categorised, for example using the CEBM described earlier[43]. The task force then anonymously score their level of agreement for each proposed recommendation using a 0–10 numerical rating scale (0, do not agree at all; 10, fully agree), with scores reflecting research evidence and clinical expertise[48]. An agenda for future research can also be discussed based on areas of poor data identified from the literature review.

In addition to presentation and publication of the systematic review as described earlier, the final recommendations produced should also be similarly presented and published. Consideration should also be given to the production of a lay summary of the recommendations for patients. The final recommendations publication should include discussion of any potential facilitators or barriers (including financial) to the application of the recommendations, as well as any implementation, monitoring or audit tools that may be available. The final stage is to consider when it may be appropriate to update the recommendations, which is dependent on how rapidly progression occurs in the topic under review.

Chapter 3: Developing EULAR recommendations for use in imaging of the joints in the clinical management of RA

3.0 Chapter abstract

Objective:

To develop evidence based EULAR recommendations on the use of imaging of the joints in the clinical management of RA.

Methods:

The task force convened consisted of an expert group of rheumatologists, radiologists, methodologists and experienced rheumatology practitioners from 13 countries. Thirteen key questions on the role of imaging in RA were generated using a process of discussion and consensus. Imaging modalities included were CR, US, MRI, CT, DXA, DXR, PET. A systematic search of the research evidence was performed for each question using MEDLINE, EMBASE and Cochrane CENTRAL. The experts used the evidence obtained from the relevant studies to develop a set of 10 recommendations. The level of agreement with each recommendation was assessed using a visual analogue scale.

Results:

The search process identified a total of 6888 references, from which 199 studies were included in the systematic review. Ten recommendations were produced encompassing the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease activity, progression and remission. Level of agreement for each proposition varied according to the research evidence and expert opinion.

Conclusions:

Ten key recommendations for the role of imaging in the management of RA were developed using research based evidence and expert opinion.

3.1 Introduction

Structural damage in RA can occur early in the disease. Prompt treatment has been shown to improve disease activity and delay structural damage[54,55]. Although CR has been considered the gold standard for imaging in RA, its sensitivity for diagnosis of RA is low and disease activity cannot be assessed[56]. Significant advances have been made within the field of imaging in rheumatic diseases over the last decade. In particular, MRI and US appear to be superior to CR through more sensitive detection of inflammation and damage[57].

A EULAR task force was formed to develop evidence-based recommendations on the use of imaging of the joints in the clinical management of RA. The recommendations address the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression, and remission.

3.2 Methods

An expert group of rheumatologists, radiologists, methodologists, experienced rheumatology practitioners and a research fellow experienced in performing systematic reviews (19 people, representing 13 countries) participated in the study. The group declared no relevant conflicts of interest. The objectives were to formulate key clinical questions relating to the role of imaging in RA, to identify and critically appraise the available evidence, and to generate recommendations based on both evidence and expert opinion.

At the initial task force meeting, members contributed clinically relevant questions related to important aspects on the use of imaging in RA. The research questions were agreed by consensus and 13 final research questions were selected, which included the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression, and remission (table 4). The systematic review protocol is given in appendix A.

Table 4. RA imaging review research questions

Making a diagnosis of rheumatoid arthritis	
Q1	What is the evidence for the differential diagnostic value of individual imaging modalities for RA?
Q2	What is the evidence for the diagnostic value above clinical criteria of individual imaging modalities for RA?
Detecting inflammation and damage	
Q3	What is the evidence for the added value (sensitivity, specificity etc.) of individual imaging modalities in detecting inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical evaluation?
Q4	What is the evidence of the added value above clinical examination for the comparative value (sensitivity, specificity etc.) of individual imaging modalities in detecting tissue damage (bone, cartilage, tendons, ligaments)?
Predicting prognosis in RA: Outcome	
Q5	What is the evidence for the prognostic (prediction of outcome) value of individual imaging modalities for RA?
Q6	What is the evidence for the prognostic (prediction of outcome) value above other known prognostic markers of individual imaging modalities for RA?
Predicting prognosis in RA: Response to treatment	
Q7	What is the evidence for the prognostic (prediction of therapeutic response) value of individual imaging modalities for RA?
Q8	What is the evidence for the prognostic (prediction of therapeutic response) value above other known prognostic markers of individual imaging modalities for RA?
Monitoring disease progression	
Q9	When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease inflammation?
Q10	When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease damage?
Q11	When (time and under what clinical circumstances), where (which joints), how (modality specifics) how often, and with what imaging modality do we need to image the spine in RA?
Imaging in clinical remission	
Q12	What is the relationship between individual imaging modalities and clinical remission in RA?
Q13	What is the impact with respect to outcome of imaging-detected inflammation /damage in the patient in clinical remission?

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A systematic search of articles was performed and the bibliographies of included papers were hand searched to identify other potential studies for inclusion. MeSH and additional keywords were used to identify all relevant studies with the help of an expert librarian (see appendix B). The search strategy was performed using EMBASE (1980 to June 2011); MEDLINE (1948 to June 2011); and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, second quarter 2011) without language restrictions. The Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) were also searched to ensure all potential studies were identified.

The research fellow screened titles and abstracts of all citations identified, and potentially relevant articles were reviewed in full text using predetermined inclusion and exclusion criteria. Studies, published in English, on the use of imaging in adults (≥18 years of age) with a clinical diagnosis of RA were included. Imaging modalities included were CR, US, MRI, CT, DXA, DXR, scintigraphy and PET. Study types included RCT, systematic reviews, controlled clinical trials, cohort, case-control and diagnostic studies. Studies were considered for inclusion when they provided data on the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression and remission.

Following presentation of the data from the literature review, the experts produced 10 recommendations based on the 13 clinical questions with final agreement by a process of discussion and consensus. The experts scored their perceived level of agreement for each proposition using a 0-10 visual analogue scale (VAS; 0, not recommended at all; 10, fully recommended). Scores reflected both research evidence and clinical expertise[48].

Evidence was graded for each recommendation according to the design of studies included in the recommendation, using a hierarchy of evidence in descending order according to quality[59]. Greater emphasis was given to the best available evidence when answering questions, although all data were collected and reviewed.

Recommendations for future research were agreed by consensus following presentation of the literature review.

3.3 Results

The search of databases, performed in June 2011, resulted in 6888 records, of which 2567 were duplicates. Of the remaining 4321 articles, 3975 were excluded based on title or abstract, leaving 346 articles for detailed review. All full text articles written in English were retrieved for review; 175 articles were excluded after reviewing the full text leaving 171 articles for inclusion (figure 7). The hand search identified 28 additional articles for inclusion, resulting in a total of 199 articles for inclusion. Articles that were relevant to more than one research question were included in the review more than once. The number of articles included in each question is given in appendix C.

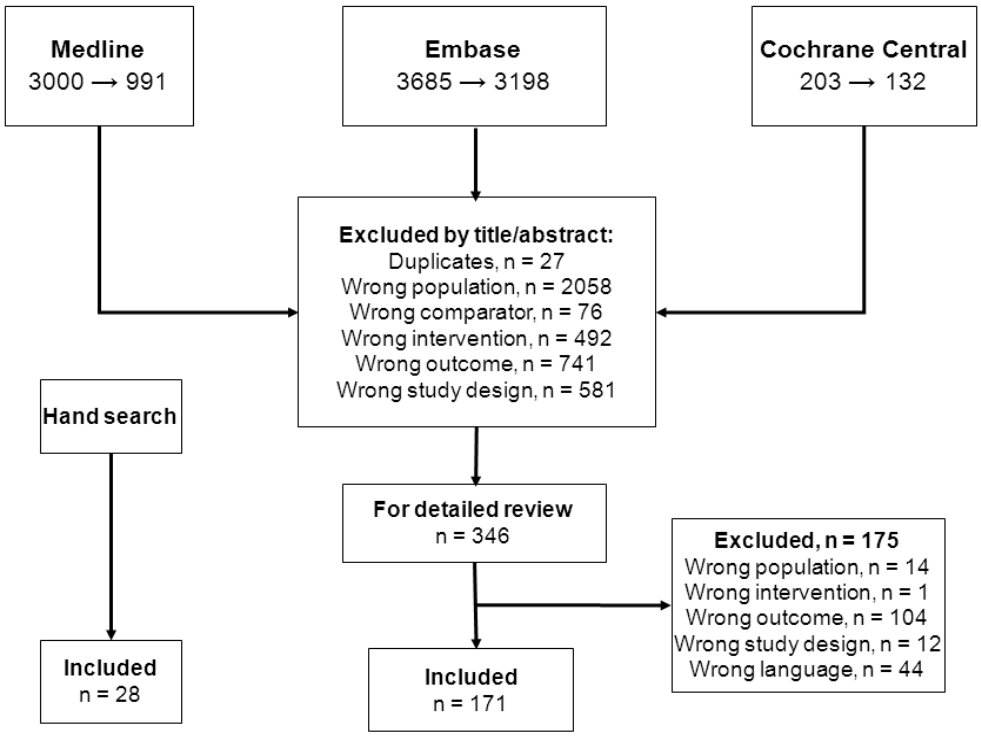

Figure 7. Flowchart of RA imaging literature search

Flowchart showing the literature search of 6888 articles, from which 346 articles were selected for detailed review; 199 articles met the inclusion criteria.

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Ten recommendations were produced; the final wording of the propositions was adjusted using e-mail exchange and at the closing meeting of the group. The recommendations, level of agreement (mean VAS and 95% confidence internal, CI) and level of evidence are given in table 5[60]. A full reference list for articles included in each recommendation is given in appendix D.

Table 5. RA imaging recommendations, level of agreement and level of evidence

Recommendation*		Level of agreement, mean VAS 0-10 (95% CI)	Level of evidence
1	When there is diagnostic doubt, conventional radiography, US or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone**	9.1 (8.6-9.6)	III
2	The presence of inflammation seen with US or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis	7.9 (6.7-9.0)	III
3	US and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation	8.7 (7.8-9.7)	III
4	Conventional radiography of the hands and feet should be used as the initial imaging technique to detect damage. However, US and/or MRI should be considered if conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA)	9.0 (8.4-9.6)	IV
5	MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or US as well as joint damage detected by conventional radiographs, MRI or US can also be considered for the prediction of further joint damage	8.4 (7.7-9.2)	III
6	Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment	7.8 (6.7-8.8)	III-IV

7	Given the improved detection of inflammation by MRI and US than by clinical examination, they may be useful in monitoring disease activity	8.3 (7.4-9.1)	III
8	The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly US) is more responsive to change in joint damage and can be used to monitor disease progression	7.8 (6.8-8.9)	III
9	Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed	9.4 (8.9-9.8)	III
10	MRI and US can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation	8.8 (8.0-9.6)	III

VAS, visual analogue scale (0–10: 0, not recommended at all; 10, fully recommended); CI, confidence interval.

Categories of level of evidence: Ia, evidence for meta-analysis of randomised controlled trials; Ib, evidence from at least one randomised controlled trial; IIa, evidence from at least one controlled study without randomisation; IIb, evidence from at least one other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

* Recommendations are based on data from imaging studies that have mainly focused on the hands (particularly wrists, metacarpophalangeal and proximal interphalangeal joints. There is little data with specific guidance on which joints to image.

** In patients with at least one joint with definite clinical synovitis, which is not better explained by another disease

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3.3.1 Recommendations

Making a diagnosis of RA (in patients with at least one joint with definite clinical synovitis)

Recommendation 1: When there is diagnostic doubt, conventional radiography, US or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.

Level of agreement: 9.1 (95% CI 8.6 to 9.6)

Five observational studies described the impact of imaging on confirming a diagnosis of RA when the diagnosis could not be confirmed using conventional methods, two with US and three with MRI. Three of these studies examined the hand joints (wrist, metacarpophalangeal and proximal interphalangeal joints), but none compared sites[61-65]. One study showed that US synovitis improved the certainty of RA diagnosis from 42.0% to 53.2% (p 0.17)[62], and another described how synovitis seen with US helped confirm (65.2%) or change the diagnosis (11.1%); US was superior to clinical examination in 75% of patients. Compared to clinical classification criteria, evidence of MRI synovitis increased the diagnosis of RA[64,65] and was more valuable than a positive ACPA in the absence of RF[63].

Recommendation 2: The presence of inflammation seen with US or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.

Level of agreement: 7.9 (95% CI 6.7 to 9.0)

Several studies evaluated the prognostic value of imaging in patients with undifferentiated inflammatory arthritis (UIA), mainly using US or MRI. A recent systematic review identified 11 studies relating to MRI[66]. The presence of bone oedema or both synovitis and erosion on MRI increased the likelihood of developing RA (positive likelihood ratio (LR+) 4.5 and 4.8 respectively), whereas the absence of MRI synovitis decreased the probability of progression to RA (negative likelihood ratio (LR-) 0.2). A prediction model including clinical hand arthritis, morning stiffness, positivity for RF, and bone oedema on MRI correctly predicted progression to RA in 82% of UIA patients[67]. MRI flexor tenosynovitis has also been described as a predictor of early RA (sensitivity 0.60, specificity 0.73)[68]. Of the three strongest predictors of RA (MRI flexor tenosynovitis, RF and ACPA), ACPA was found to be the strongest predictor (OR 13.8) and flexor tenosynovitis the weakest (OR 5.0), but its additional value in diagnosing RA was significant.

In a longitudinal study US significantly increased detection of joint involvement in all joint regions. When combined with the Leiden prediction rule[69], PD counts significantly improved area under the curve (AUC) values for prediction of progression to RA (0.905 to 0.962)[70]. Salaffi et al described the likelihood of progression of UIA to RA using the presence of PD on US (scores higher than grade 1), with OR 9.9 if one joint was involved, and 48.7 if more than three were involved; OR with high titre ACPA or RF was 10.9[71].

Detecting inflammation and damage

Recommendation 3: US and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation.

Level of agreement: 8.7 (95% CI 7.8 to 9.7)

This recommendation examines the additional benefit of assessing joint inflammation using imaging over clinical examination. Sensitivity and specificity were initially extracted from the data, however as clinical examination was used as the reference these results are difficult to use clinically. To overcome this we recorded detection rates; for example, how many times more (>1-fold) or less (<1-fold) does imaging detect inflammation over clinical examination. Our chosen approach may increase the number of false positive results.

We identified 51 studies comparing imaging and clinical examination in the detection of inflammation in various joints; 29 with US[72-90], 16 with MRI[77,79,88,90-98], 14 with scintigraphy[96,99-101], and 2 with PET (table 6). In general, US and MRI detected joint inflammation more frequently than clinical examination; the mean detection rate for synovitis at the hand and wrist was 2.18-fold for US and 2.20-fold for MRI[90]. Scintigraphy and PET were found to provide little additional benefit over clinical examination.

Table 6. RA imaging recommendation 3. Summary of included studies comparing imaging and clinical examination in the detection of joint inflammation

ULTRASOUND **29 studies, mean no. of subjects (range): 40.7 (6-100)**		**MRI** **16 studies, mean no. of subjects (range): 47.3 (6-318)**		**SCINTIGRAPHY** **14 studies, mean no. of subjects (range): 22.6 (8-38)**	
US HAND/WRIST vs. clinical examination (CE) [Article reference]		**MRI HAND/WRIST vs. clinical examination** [Article reference]		**Scintigraphy HAND/WRIST vs. clinical examination** [Article reference]	
	Detection rate, mean (range) US vs. CE		**Detection rate, mean (range) MRI vs. CE**		**Detection rate, mean (range) Scintigraphy vs. CE**
Synovitis [76,79,81,83,86,87,89]	2.18-fold (0.55-8.96-fold)	**MRI synovitis, vs. clinical synovitis** [79,86,87,89,91,95,97,98]	2.20-fold (0.58-5.43-fold) accuracy: 0.72	**vs. tenderness/swelling** [100,101]	1.19-fold Validity: 0.45 Coefficient of association: -0.16
		vs. pain [96]	0.71-fold kappa: 0.36, p 0.009	**vs. tenderness** [96]	0.70-fold kappa: 0.32, p 0.008
		vs. swelling [96]	1.36-fold kappa: 0.60, p 0.019	**vs. swelling** [96]	1.33-fold kappa: 0.64, p 0.023
		correlation with DAS-28 [92]	r 0.30-0.40 p<0.01		
Tenosynovitis [78]	1.06-fold	**Relative efficacy for tenosynovitis** [77]	2.48-4.69		
Relative efficacy of US at detecting any inflammation vs. TJC [77]	0.61-1.33	**Relative efficacy of MRI synovitis vs. TJC** [77]	3.03-3.86		

US FOOT/ANKLE vs. clinical examination		MRI FOOT/ANKLE vs. clinical examination		Scintigraphy FEET vs. CE	
Effusion [82,85]	0.52-0.99-fold kappa: 0.04-0.16 % agreement: 71%			**vs. tenderness/swelling** [100]	0.42-fold
Inflammation [88]	2.21-fold % agreement: 63%				
Synovitis [90]	0.87-fold	**Synovitis** [88,90,91,93]	1.71-fold (0.93-2.8-fold) % agreement: 45.5-71%		
Tenosynovitis [90]	0.58-fold	**Tenosynovitis** [90]	% agreement: 54.5-90.9%		
US KNEES vs. clinical examination		**MRI KNEES vs. clinical examination**		**Scintigraphy KNEES vs. histology**	
Baker's cyst [72,75,80]	1.88-fold (1.17-2.5-fold)	**Synovitis vs. clinical synovitis** [94]	1.6-3.15-fold	**vs. histology** [99]	1.11-fold
Suprapatellar bursitis [80]	1.7-fold			**Swelling vs. histology** [99]	0.72-fold
Effusion [84]	1.27-fold (1.17-1.4-fold)				
Synovitis vs. clinical synovitis [73,74]	r 0.9, p 0.0001				
vs. DAS-28	Strong correlation, p 0.006				
vs. SJC	Weak correlation, p 0.038				

CE, clinical examination; TJC, tender joint count; SJC, swollen joint count. *Reproduced from Ann Rheum Dis, Colebatch AN, Edwards CJ, Østergaard M et al, 72, 804-14, 2013 with permission from BMJ Publishing Group Ltd.*[58]

Recommendation 4: Conventional radiography of the hands and feet should be used as the initial imaging technique to detect damage. However, US and/or MRI should be considered if conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA).

Level of agreement: 9.0 (95% CI 8.4 to 9.6)

Three studies compared tissue damage (erosions or loss of joint space) detected by imaging with abnormal clinical examination. Caution is needed when interpreting these studies as bony involvement shown on imaging was compared with clinical signs of inflammation as reference.

Prognosis in RA: Predicting Outcome

Recommendation 5: MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or US as well as joint damage detected by conventional radiographs, MRI or US can also be considered for the prediction of further joint damage.

Level of agreement: 8.4 (95% CI 7.7 to 9.2)

Forty-eight longitudinal studies described how baseline changes in imaging predicted outcome, in particular erosive progression; 26 with MRI, 11 with US, 19 with CR, 7 with DXA or DXR and 3 with scintigraphy. Of these, 46 studies examined the hands and 14 also included the feet; none compared the benefit of imaging different joints.

Bone marrow oedema

Of baseline MRI features, BM oedema was a strong, independent predictor of erosive progression. Hetland et al have provided convincing data supporting this association; baseline MRI BM oedema was the only independent predictor of radiographic change in their 2- and 5- year follow-up studies (coefficient 0.75, $p<0.001$; and coefficient 0.82, $p<0.001$ respectively)[102,103]. Haavardsholm et al also identified baseline MRI BM oedema (score >2 RAMRIS units) as an independent predictor of radiographic (OR 2.77, 95% CI 1.06 to 7.21) as well as MRI erosive progression (unstandardised β, B 0.21, 95% CI 0.08 to 0.34)[104]. McQueen et al also

described BM oedema to be predictive of MRI erosive progression, OR 6.47, p<0.001[105]. This study demonstrated that development of radiological erosions at one year was highly unlikely in the absence of baseline MRI inflammatory changes (negative predictive value (NPV) 0.92). Patients with erosive progression on CT also have higher baseline MRI BM oedema scores (relative risk (RR) of CT progression 3.8, 95% CI 1.5 to 9.3)[106].

Synovitis

Baseline synovitis, detected by MRI or US, is a predictor of erosive progression. Dohn et al reported the RR of CT erosive progression with baseline US grey-scale synovitis as 11.2, 95% CI 0.65 to 195.7, p 0.1; baseline US PD activity RR 7.6, 95% CI 0.91 to 63.2, p 0.061; and baseline MRI synovitis RR 0.68, 95% CI 0.04 to 11.5, p 0.79[106]. The predictive value of baseline US grey-scale synovitis for MRI erosive progression performed better than MRI synovitis with LR+ of 1.75 and 1.47 respectively, and accuracy of 70% and 62% respectively[107]. Conaghan et al described a close correlation between the degree of MRI synovitis and the number of new erosions, with the AUC for MRI synovitis the only significant predictor of erosive progression (AUC for MRI synovitis ρ 0.420, p<0.007)[108].

Tenosynovitis

Baseline tenosynovitis on US appears to be predictive of erosive progression at 1 (OR 7.18) and 3 years (OR 3.4)[109]. This effect has not been seen with MRI tenosynovitis[110], but baseline MRI tendinopathy has been shown to be predictive of tendon rupture at 1 (OR 1.57, p 0.02) and 6 years (OR 1.52, p 0.03)[111].

Erosions

Baseline erosions detected by various imaging techniques appear to be predictive of erosive progression at 6 months; MRI erosions (β 0.63, p<0.001), radiographic erosions (β 0.68, p 0.04), with US erosions less significant (β 0.57, p 0.07)[112]. Several studies have reported that baseline MRI erosions are predictive of further erosions[113-116]; and the absence of baseline MRI erosions predicts that radiographic or MRI erosions are unlikely to develop (NPV 1.0)[116]. Baseline radiographic erosions independently predict further radiographic progression (at 3 years, OR 8.47; at 10 years, OR 5.64-18.1)[117-119]. In addition, an annual radiological progression rate greater than the median was shown to be predicted by baseline Larsen score (OR 2.6, 95% CI 1.3 to 5.3)[119].

DXR/DXA

Early hand bone loss measured by change in estimated bone mineral density (BMD) in the first year of disease by DXR seems to be an independent predictor of erosive progression, even up to 20 years[110,120,121]. Baseline femoral neck osteopenia or osteoporosis are also predictive of radiographic erosive progression[122].

Scintigraphy

Baseline inflammatory disease measured by scintigraphy appears to be associated with radiographic progression[123]. In addition, multiple regression analysis has demonstrated that progression of radiographic joint destruction was primarily predicted by ^{99m}Tc-IgG scintigraphy; joint swelling, ESR and IgM rheumatoid factor were not predictive. This suggests that scintigraphy may be superior to conventional clinical and laboratory measurements in prediction of joint destruction[124]. However when comparing scintigraphy to other baseline imaging predictors of progression, baseline MRI BM oedema score (Spearman's correlation, ρ 0.67), MRI synovitis score (ρ 0.57), and ^{99m}Tc-NC scintigraphy uptake (ρ 0.45) were predictive of change in MRI erosion score from baseline to 2 years. In the multivariate analysis, the BM oedema score was the only baseline variable that predicted erosive progression (OR 4.2, 95% CI 1.3 to 13.8)[125].

Prognosis in RA: Predicting response to treatment

> *Recommendation 6: Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.*
>
> ***Level of agreement: 7.8 (95% CI 6.7 to 8.8)***

Two prospective cohort studies have assessed the use of clinical measures and imaging to predict response to anti-TNF therapy. Ellegaard et al measured US Doppler activity and clinical parameters at baseline to predict which patients would benefit from treatment, assessed by treatment persistence at one year[126]. They identified US Doppler activity to be the only baseline parameter to predict treatment persistence (p 0.024); baseline clinical measures including TJC, SJC, CRP, DAS-28 and health assessment questionnaire (HAQ) showed no significant association. Elzinga et al used changes in PET uptake two weeks after treatment to predict future treatment response according to DAS-28. A significant

correlation was seen between the changes in PET activity at two weeks and DAS-28 at 14 and 22 weeks after treatment (r 0.62, p<0.05; r 0.65, p<0.01 respectively)[127].

Monitoring disease progression

Recommendation 7: Given the improved detection of inflammation by US and MRI than by clinical examination, they may be useful in monitoring disease activity.

Level of agreement: 8.3 (95% CI 7.4 to 9.1)

No published data was identified that specifically addressed how imaging should be used to monitor RA disease activity. In the absence of this information, data was extracted on several separate factors.

Comparison of the ability of imaging to detect inflammation

Several studies compared US and MRI in the detection of joint inflammation, with MRI considered the reference technique. There seems to be significant association between these modalities[87,89] but aside from access to imaging, there may be advantages to using each technique in certain situations. For example, US has been shown to detect more joint and tendon sheath effusions than MRI[112], whereas MRI appears to be more sensitive in identifying tenosynovitis[128]. Comparisons of conventional high-field MRI with dedicated, low-field extremity MRI have shown high agreement for synovitis, with lower agreement for BM oedema and tenosynovitis detected by low-field MRI, with high-field MRI as reference[129,130]. Low-field MRI without contrast also demonstrates poor sensitivity in the detection of synovitis, compared with PD US[131]. Only one study compared scintigraphy with more modern imaging techniques, and showed strong correlation between uptake on scintigraphy and inflammatory changes seen on MRI[132].

Responsiveness to change in inflammation

US and MRI appear to show good responsiveness to change. A study of responsiveness of MRI and US to change in inflammation with treatment has shown that MRI synovitis (standardised response mean, SRM -0.79 to -0.92), MRI tenosynovitis (SRM -0.70 to -1.02) and BM oedema (SRM -1.05 to -1.24) were responsive to change, but US inflammation (synovitis, tenosynovitis and effusion)

was less responsive (SRM -0.37 to -0.54)[77]. Haavardsholm et al described MRI to have a higher potential to detect change in wrist BM oedema than in synovitis over one year[25]. The smallest detectable difference for a range of US measures including PD was low in a large one-year observational multiple-reader study of RA patients treated with anti-TNF agents, demonstrating both the reliability of this measure and the ability to detect individual level important change. At the group level, there were significant changes in all US synovial assessments in parallel with DAS-28 changes[133]. When comparing the changes in PD and grey-scale US activity with response to treatment, grey-scale US appears to perform better[134], as does the addition of contrast enhancement[135].

Which joints to assess

Only one study directly compared the assessment of inflammation by imaging different areas; Caliser et al described MRI synovitis and BM oedema in the hands and feet of patients with early RA and found no significant difference in MRI inflammation in these regions[91].

> *Recommendation 8: The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly US) is more responsive to change in joint damage and can be used to monitor disease progression.*
>
> ***Level of agreement: 7.8 (95% CI 6.8 to 8.9)***

As for the previous recommendation, there was no specific data on the recommended frequency of imaging in the assessment of progressive joint damage.

Comparison of the ability of imaging to detect damage

Dohn et al performed comparison studies of the ability of CR, CT, US and MRI to detect erosive damage[106,136]. Using CT as the reference technique, CR was shown to have an accuracy of 81%, MRI of 89% and US of 80% with high specificities and lowest sensitivity for CR[106,136]. A previous systematic review has described US to be more effective for erosion detection than CR with comparable efficacy to MRI[137]. A summary of data comparing the different imaging modalities in the detection of erosions is given in table 7[77,87,88,93,98,106,112,129,130,136,138-155].

Table 7. RA imaging recommendation 8: Summary of included studies comparing imaging in the detection of erosions

Comparator vs. reference technique [Article reference]	Sensitivity	Specificity	Accuracy	Kappa	Detection rate, mean (range)
Hand/wrist erosions:					
MRI vs. CT[106,136,141,142,149]	0.61-0.68	0.92-0.96	0.77-0.89	0.63	0.71-fold (0.60-0.81-fold)
US vs. CT[106,136]	0.42-0.44	0.91-0.95	0.80-0.84	0.44	
CR vs. CT[106,136,138,141,142,149]	0.14-0.54	0.92-1.0	0.63-0.81	0.29	0.34-fold (0.16-0.60-fold)
CR vs. MRI[77,87,98,112,129,139,140,143-148,150,151,153,154]	0.0-0.55	0.5-1.0	0.23-0.92		0.38-fold (0.06-0.80-fold)
CR vs. US [87,112,139,150,151,154,155]	0.48	1.0			0.60-fold (0.18-1.21-fold)
US vs. MRI [87,112,139,150,151,154]	0.33-0.87	0.68-1.0	correlation coefficient 0.68-0.9	p<0.0005 - <0.001	0.77-fold (0.35-1.51-fold)
Low- vs. high-field MRI [129,130,144,153]	0.46-0.94	0.93-0.94	0.55-0.94		0.94-fold (0.46-1.16-fold)
Feet erosions:					
CR vs. MRI[88,93]	0.32-0.80	0.85-0.98		0.65 p 0.002	1.19-fold (0.55-1.83-fold)
CR vs. US[88,152]					0.53-fold (0.42-0.64-fold)
US vs. MRI[88]	0.79	0.97	0.96		1.3-fold

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Studies assessing tendon damage have shown US to be more sensitive than MRI in the detection of finger extensor tendon tears confirmed surgically[156]; and moderate agreement between US and MRI (used as the reference technique) in the assessment of shoulder tendon involvement[157].

Responsiveness to change in damage

CR is the standard imaging technique used to detect and monitor joint damage. There is some data suggesting that CR is responsive to change in erosions on an individual level, particularly after the first 12 months of disease[77]. Radiographic progression appears to be most rapid in the first two years of disease, with 75% of all damage seen in the first five years of a 10-year study[158]. MRI seems to be more responsive to change at earlier time points, but measures of annual progression rates are similar with MRI and CR[77]. This is supported by Østergaard et al who found that 78% of new radiographic bone erosions were seen at least one year earlier by MRI; in fact MRI detection of new erosions preceded CR by a median of two years[159].

Which joints to assess

Early erosive change on CR appears to be more common in the feet than in the hands; these areas are more equally affected from year three onwards[158,160].

> *Recommendation 9: Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed.*
>
> ***Level of agreement: 9.4 (95% CI 8.9 to 9.8)***

Thirteen studies described the evaluation of cervical spine involvement in RA, summarised in table 8[161-173]. No studies explored the appropriate frequency for monitoring change in the cervical spine; Yurube et al investigated baseline features on CR predictive of future cervical instability and found that patients with baseline deforming hand changes, cervical vertical subluxation (VS), and subaxial subluxation showed more progression in VS and subaxial subluxation at 5 years[173], and Reijnierse et al identified that baseline MRI atlas erosions and reduced subarachnoid space were associated with clinical neurological dysfunction at one year[168].

Comparison studies of different imaging modalities of the cervical spine have shown variance in the detection of different pathologies, according to the imaging technique used. Fezoulidis et al found CR and CT to be comparable and better than MRI in detecting atlanto-axial and atlanto-occipital lesions, but MRI to be superior in identifying odontoid lesions[162]. MRI also seems to be better at showing erosions of the dens[172].

Independent of the imaging modality used, dynamic lateral views of the cervical spine are more informative than static, neutral views in detecting atlanto-axial subluxation (AAS), in particular anterior AAS[165]. Flexion and neutral views are used commonly, with evidence to suggest greater change in the atlanto-dental interval with these views[164]. The open mouth view is used for imaging the odontoid peg and to assess for lateral and rotatory AAS; whereas posterior AAS can be measured with neutral and extension views, and VS with a lateral neutral view, although these types of AAS are much less common than anterior AAS[172]. When using CR to assess odontoid erosions, lateral cervical spine views appear to be more sensitive than open mouth views[169].

Imaging in clinical remission

> *Recommendation 10: US and MRI can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation.*
>
> ***Level of agreement: 8.8 (95% CI 8.0 to 9.6)***

The role of imaging in the detection of inflammation and subsequent prediction of outcome has been discussed earlier in recommendation 5. There is good evidence describing the disparity between clinical remission and evidence of on-going inflammation seen with various imaging modalities. PD activity has been found in 15–62% of patients in clinical remission according to DAS-28, ACR or simplified disease activity index remission criteria[174-177], MRI synovitis in 96% and BM oedema in 52%[174,178]. 60% of patients in DAS remission had increased uptake on scintigraphy in one study[179].

Table 8. RA imaging recommendation 9: Summary of included studies comparing imaging in the assessment of the cervical spine

Article year, [reference]	No. of subjects	Cervical spine imaging modality	Parameter assessed	Outcome
1989[162]	55	CR (AP, lateral F/E, OM) MRI CT	Atlanto-axial lesions Atlanto-occipital lesions Odontoid lesions Odontoid fibro-ostosis	Atlanto-axial lesions: CR = CT > MRI Atlanto-occipital lesions: CR = CT > MRI Odontoid lesions: MRI > CR/CT Odontoid fibro-ostosis: CR = CT > MRI
2000[163]	5 known AAS	CR (F/E) MRI (F/E)	AAS	More detail seen with MRI, and using F/E views
2005[164]	31	CR (F/E) MRI (F/E)	ADI Dens erosions	CR showed greater ADI in flexion than MRI, p 0.001 No significant difference in neutral/extension Assessment of dens erosions easier with MRI
1998[165]	65 unstable AAS	CR (lateral N/ F/E)	AAS	Significant difference between AAS in neutral and flexion/extension, p <0.0001
1998[166]	28 symptomatic	CR (AP, lateral N/F, OM) MRI CT	AAS Odontoid erosions/cysts	Combination on MRI with CR showed more involvement than CT with CR (1.25-fold more vertical subluxations; 1.13-fold more erosions/cysts)
2000[167]	42 symptomatic	MRI (N/F)	Reduction in subarachnoid space Brainstem compression	Flexion views showed more: brainstem compression (1.17-fold) reduction in the subarachnoid space at the atlanto-axial level (1.06-fold) and below C2 (1.13-fold)
2000[169]	25	CR (AP, lateral F/E, OM)	Odontoid erosions	Lateral views showed more erosions (1.57-fold) than open mouth views

2011[170]	56 symptomatic	CR (lateral) CT	CT factors predictive of VS on CR	VS greater in presence of odontoid erosions, p<0.05 Odontoid erosions significantly associated with odontoid osteoporosis, p<0.05
1995[171]	136 symptomatic	CR (AP, lateral F/E) MRI	MRI findings in normal CR	All MRI abnormal with normal CR: Effusion: 28% Pannus: 62%
2009[172]	40	CR (lateral N/ F/E, OM) MRI (N/F/E) CT	AAS Dens erosions	% patients with C-spine involvement on: CR 47.5%, MRI 70%, CT 28.2% Anterior AAS seen more in flexion on CR than MRI, p<0.005 CT best at detecting lateral AAS Dens erosions: CR 12.5%, MRI 67.5%, CT 41%
2011[173]	267	CR (lateral N/F/E)	Baseline features predictive of VS and SAS at 5 years	Prediction of VS: AAS, p 0.01; VS, p<0.01; SAS, p 0.06 Prediction of SAS: AAS, p 0.29; VS, p<0.01; SAS, p<0.01
1987[161]	18 symptomatic	CR (AP, lateral F/E) MRI	AAS CS SAS Dens erosions	MRI vs. CR: AAS: 0.88-fold CS: 1.0-fold SAS: 0.5-fold Dens erosions: 1.27-fold
2001[168]	46 symptomatic	CR (lateral N/F, OM) MRI	Baseline CR and MRI features predictive of clinical neurological dysfunction at 1 year	CR not predictive (odontoid erosions, AAS) Dysfunction according to MRI (OR): Dens erosion: 1.5; atlas erosion: 4.9 Decreased subarachnoid space: 12.0 Decreased atlanto-axial space: 2.4 Brainstem compression: 2.3

AP, anteroposterior; F, flexion; E, extension; N, neutral; OM, open mouth; AAS, atlantoaxial subluxation; ADI, atlanto-dental interval; VS, vertical subluxations; SAS, subaxial subluxations; CS, craniovertebral settling; OR, odds ratio. *Reproduced from Ann Rheum Dis, Colebatch AN, Edwards CJ, Østergaard M et al, 72, 804-14, 2013 with permission from BMJ Publishing Group Ltd.*[58]

The significance of persistent inflammation has been described in a number of studies, summarised in table 9[180-186]. The presence of US synovial hypertrophy (SH), PD activity and MRI synovitis at baseline in clinical remission has been shown to be significantly associated with structural progression at one year, even in asymptomatic joints[180]. Baseline US inflammatory activity in clinical remission also seems predictive of future disease flare, with 20% of patients experiencing a flare within 12 months in the absence of baseline US PD activity, compared with 47% in patients with baseline PD activity (p 0.009)[184]. Although radiographic progression can still be seen in clinical remission, individuals with sustained clinical remission show fewer signs of structural progression compared with patients with clinically relapsing disease[181-183].

3.3.2 Future research agenda

The group formulated the most important topics for future research according to currently available evidence and clinical practice (table 10).

3.4 Conclusion

These are the first recommendations produced by a EULAR task force on imaging in RA clinical practice. The recommendations were developed by an international group of experts with detailed literature review, and aimed to address clinical questions relevant to current practice. There is still a large amount of research required to optimise use of imaging tools in routine clinical practice, in particular which joints should be used for disease assessment and monitoring and consideration of the feasibility, costs and appropriate training required to use US and MRI. In view of lack of literature at the time of the review, these recommendations have not focused on detecting JSN which is important to consider in view of the impact on functional status[187]. Specific reference is made to this in the proposed future research agenda.

In summary, we have developed 10 recommendations on various aspects of imaging in RA. These are based on the best available evidence and clinical expertise supported by an international panel of experts. We aimed to produce recommendations that are practical and valuable to clinical practice which have since been published[58].

Table 9. RA imaging recommendation 10: Summary of included studies describing outcome in the presence of image-detected inflammation in clinical remission

Article year, [reference]	No. of subjects	Duration of follow-up (months)	Baseline assessment modality	Outcome parameter assessed	Results
2008[180]	102	12	US SH, PD synovitis	CR progression (Genant score)	SH: OR 2.31, p 0.032 PD synovitis: OR 12.21, p<0.001
			MRI synovitis		OR 2.98, p 0.002
2011[184]	94	12	US SH, PD synovitis, remissions (no SH or PD synovitis)	Relapse rate	% patients having flare: In US remission: 20.0% With US PD activity: 47.1%, p 0.009
2009[185]	106	24	US joint count, PD synovitis	Relapse rate	Unsustained remission vs. sustained remission: Higher PD: OR 12.8, p<0.05 Higher US joint count: OR 4.6, p<0.05
2005[186]	32	12	US resistive index (RI)	Relapse rate	Relapse rate higher with low RI se 0.80, sp 1.0, acc 0.96, p<0.01
2007[182]	169	24	Sustained ACR/DAS remission	CR progression (Larsen score)	Increase in Larsen score in (unsustained vs. sustained): ACR remission: p 0.017; DAS remission: p<0.001
2004[183]	187	24	Sustained ACR/DAS remission	CR progression (SHS)	Increase in SHS score in (unsustained vs. sustained): ACR remission: p 0.053; DAS remission: p 0.017
2012[181]	535	24	Remission according to DAS, SDAI, CDAI, ACR/EULAR	CR progression (SHS)	% patients with CR progression with baseline remission: DAS: 30%, SDAI: 24%, CDAI: 19%, ACR/EULAR: 20%

SH, synovial hypertrophy; PD, power Doppler; RI, resistive index; ACR, American College of Rheumatology; DAS, disease activity score; SHS, Sharp/van der Heijde score; SDAI, simplified disease activity index; CDAI, clinical disease activity index; EULAR, European League Against Rheumatism. *Reproduced from Ann Rheum Dis, Colebatch AN, Edwards CJ, Østergaard M et al, 72, 804-14, 2013 with permission from BMJ Publishing Group Ltd.*[58]

Table 10. RA imaging future research agenda

	Research agenda
1	Further evaluation of the specific joints to be assessed, timing of assessment(s) and the evaluation system to be employed in order to optimise the role of modern imaging modalities in diagnosis, prognosis and outcome measurement of RA
2	To assess algorithms using established and modern imaging modalities to examine their cost-effectiveness in clinical practice diagnosis, prognosis and outcome measurement of RA
3	To further elucidate the importance of subclinical (imaging-alone detected) inflammation, including synovitis, bone marrow oedema and tenosynovitis, especially in low disease activity states and to define key thresholds to guide intervention
4	To further assess the importance of imaging, in particular MRI and US, in the evaluation of damage, including joint space narrowing and cartilage loss
5	Assessing the feasibility, costs and appropriate training required to use US and MRI in clinical practice

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Chapter 4: Developing EULAR points to consider for use in imaging of the joints in the clinical management of JIA

4.0 Chapter abstract

Objective:

To develop evidence based EULAR points to consider on the use of imaging in the diagnosis and management of JIA in clinical practice.

Methods:

The task force comprised a group of paediatric rheumatologists, rheumatologists experienced in imaging, radiologists, methodologists and patients from 9 countries. Eleven questions on imaging in JIA were generated using a process of discussion and consensus. Research evidence was searched systematically for each question using MEDLINE, EMBASE and Cochrane CENTRAL. Imaging modalities included were CR, US, MRI, CT, scintigraphy and PET. The experts used the evidence obtained from the relevant studies to develop a set of points to consider. The level of agreement with each point to consider was assessed using a numerical rating scale.

Results:

A total of 13,277 references were identified from the search process, from which 204 studies were included in the systematic review. Nine points to consider were produced, taking into account the heterogeneity of JIA, the lack of normative data and consequent difficulty identifying pathology. These encompassed the role of imaging in making a diagnosis of JIA, detecting and monitoring inflammation and damage, predicting outcome and response to treatment, use of guided therapies, progression and remission. Level of agreement for each proposition varied according to both the research evidence and expert opinion.

Conclusions:

Nine points to consider and a related research agenda for the role of imaging in the management of JIA were developed using published evidence and expert opinion.

4.1 Introduction

JIA is a heterogeneous group of conditions with onset under the age of 16, unknown aetiology and persistence of symptoms for over 6 weeks[19]. Imaging plays an important role in diagnosis and monitoring of patients with JIA, but until recently there were few studies in this area.

A EULAR – Pediatric Rheumatology European Society (PReS) task force was convened to produce evidence and consensus-based recommendations on the use of imaging in the diagnosis and management of JIA in clinical practice for use by secondary care professionals caring for children with JIA, to help define standards of care for appropriate imaging.

4.2 Methods

An expert group of paediatric rheumatologists, rheumatologists with imaging expertise, radiologists, methodologists and a fellow (16 people, representing 9 countries) participated. The group declared no relevant conflicts of interest. The task force used a rigorous procedure as described in the updated EULAR SOP[47,48].

At the initial task force meeting, members contributed clinically relevant questions related to key aspects of the use of imaging in JIA. The research questions were agreed by consensus and 11 final research questions were selected which encompassed the role of imaging in making a diagnosis of JIA, detecting inflammation and damage, predicting outcome and response to treatment, the use of guided treatment, monitoring disease progression, and remission (table 11). The systematic review protocol is given in appendix E.

A systematic search of articles was performed using MEDLINE (1946 to November 2013); EMBASE (1980 to November 2013); and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, third quarter 2013) without language restrictions. The Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) were also searched to ensure all potential studies were identified.

Table 11. JIA imaging review research questions

Making a diagnosis of JIA	
Q1	What is the evidence for the differential diagnostic value of individual imaging modalities for JIA?
Q2	What is the evidence for the diagnostic value above clinical criteria of individual imaging modalities for JIA?
Detecting inflammation and damage	
Q3	What is the evidence for the added value (sensitivity, specificity etc.) of individual imaging modalities in detecting inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical evaluation according to age?
Q4	What is the evidence for the added value above clinical examination for the comparative value (sensitivity, specificity etc.) of individual imaging modalities in detecting age-related structural abnormalities and damage in JIA (bone, cartilage, tendons, ligaments)?
Predicting prognosis in JIA: Outcome	
Q5	What is the evidence for the prognostic (prediction of therapeutic response) value of individual imaging modalities for JIA?
Predicting prognosis in JIA: Response to treatment	
Q6	What is the evidence for the prognostic (prediction of outcome) value of individual imaging modalities for JIA?
Q7	What is the role of imaging for the monitoring of systemic treatment (corticosteroids, synthetic and biological DMARDs) and the targeted delivery of local treatments such as intra-articular injections?
Monitoring disease progression	
Q8	When (time), where (which joints), how often and with what imaging modality should we monitor JIA disease inflammation?
Q9	When (time), where (which joints), how often and with what imaging modality should we monitor age-related structural abnormalities and damage in JIA?
Imaging in clinical remission	
Q10	What is the relationship between individual imaging modalities and clinical remission in JIA?
Q11	What is the impact with respect to outcome of imaging-detected inflammation /damage in the patient in clinical remission?

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The bibliographies of included papers were searched manually for evidence of other studies for inclusion. A hand search was performed of the ACR and the EULAR annual general meetings conference proceedings for 2012-13 to identify unpublished studies. MeSH and additional keywords were used to identify all relevant studies (appendix F).

Titles and abstracts of all citations identified were screened, and potentially relevant articles were reviewed in full text using predetermined inclusion and exclusion criteria. Studies, published in English, on the use of imaging in all patients with a clinical diagnosis of JIA were included. Imaging modalities included were CR, US, MRI, CT, scintigraphy and PET; study types included RCT, controlled clinical trials, cohort studies, case-control studies, diagnostic studies and case series where n≥10. Studies were considered for inclusion when they provided information on the role of imaging in making a diagnosis of JIA, detecting inflammation and damage, predicting outcome and response to treatment, the use of guided treatment, monitoring disease progression, and remission. Included studies were evaluated for risk of bias and applicability using the QUADAS-2 tool[41].

Following presentation of the data from the literature review, the experts produced PTC (the evidence was not deemed strong enough to produce recommendations) based on the 11 clinical questions with final agreement by a process of discussion and consensus. The available evidence for each recommendation was scored according to the CEBM level of evidence, which gives studies a score for 'level of evidence' (1a-5) and for 'grade of recommendation' (A-D)[43]. The experts anonymously scored their perceived level of agreement for each proposition using a 0–10 numerical rating scale (0, do not agree at all; 10, fully agree). Scores reflected both research evidence and clinical expertise[48]. An agenda for future research was agreed by consensus following presentation of the literature review.

Given the challenges of asking children or young adults to attend consensus meetings with the task force members, a separate Patient and Public Involvement event was arranged following the second task force meeting where the process and results were presented and all comments were recorded. The meeting was attended by three patients (one child and two young adults with a diagnosis of JIA), two parents of children with JIA, two consultant rheumatologists including one with a special interest in paediatric rheumatology and the task force

epidemiologist, a paediatric rheumatology nurse specialist and a paediatric research senior nurse. All proposed points to consider were reviewed by the patients for any alterations to be made as required, and thoughts and ideas related to a child's experience of imaging for JIA were generated.

4.3 Results

The database search, performed November 2013, resulted in 13,277 records leaving 10,925 articles after de-duplication. 433 articles were included for detailed review once exclusions were made based on title or abstract. All full text articles written in English were retrieved for review, of which 244 articles were excluded leaving 189 articles for inclusion. The hand search identified 15 additional articles, resulting in a total of 204 articles for inclusion (figure 8). Articles that were relevant to multiple research questions were included in the review as necessary. The number of articles included per question is shown in appendix G.

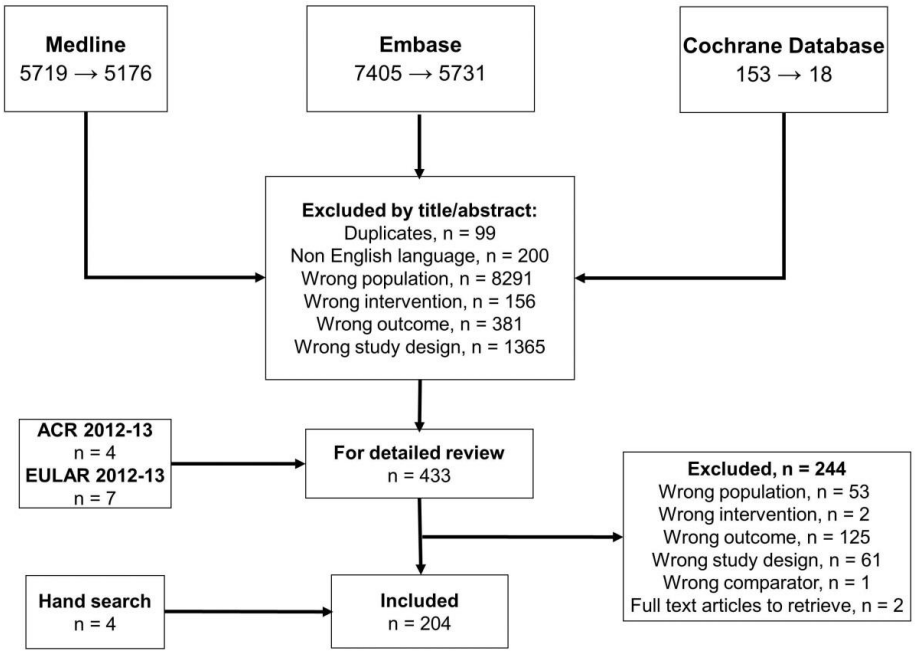

Figure 8. Flowchart of JIA imaging literature search

Flowchart showing the literature search of 13,277 articles, from which 433 articles were selected for detailed review; 204 articles met the inclusion criteria. *Reproduced from Ann Rheum Dis, Colebatch-Bourn AN, Edwards CJ, Collado P, et al, 74, 1946-57, 2015 with permission from BMJ Publishing Group Ltd*[188].

The task force produced nine points to consider which are presented with the level of evidence, grade of recommendation, and level of agreement in table 12. The task force felt that the supporting data was not sufficient to produce 'recommendations' so they were categorised as 'PTC'. Scores for risk of bias and applicability of the included studies according to QUADAS-2, and a full reference list for articles included in each recommendation are given in appendix H and I respectively.

4.3.1 Overarching principles

The task force produced general statements to be considered when interpreting the PTC.

- 'JIA' is an umbrella term for all forms of inflammatory arthritis that begins before the age of 16 years, persists for more than 6 weeks, and is of unknown origin. This heterogeneous group of diseases is currently classified according to the International League of Associations for Rheumatology (ILAR) classification[14]. There is a lack of information on imaging related to JIA categories at present.

- There is a paucity of data on the joint-specific imaging features present during growth and skeletal development in healthy children. Understanding normative data is essential for interpretation of imaging abnormalities. For example, some physiological features of recently ossified bones can be misinterpreted as cortical erosions, cartilage thickness may vary with skeletal maturation and vascularity of epiphyses will change with ageing.

- Joint inflammation at certain developmental time points may cause specific structural changes, further challenging imaging assessment.

- The appropriateness and feasibility of different imaging modalities differs with age, related to radiation exposure and requirement for sedation. Every effort should be made to avoid unnecessary radiation exposure.

- Patient experience with different imaging modalities is affected by their age and development. It is important to provide a 'child friendly' environment.

Table 12. JIA imaging points to consider, level of evidence, grade of recommendation and level of agreement

Point to consider	Level of evidence	Grade of recommendation	Level of agreement, mean NRS 0-10 (range)
US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, both in diagnosis and assessing extent of joint involvement.	3b	C	9.07 (6 - 10)
When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.	3b	C	9.43 (9 - 10)
If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.	3b	C	8.71 (5 - 10)
In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the TMJ and axial involvement.	3b	C	9.64 (8 - 10)
Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.	4	C	9.07 (5 - 10)
In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.	3b	C	9.07 (7 - 10)

The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.	3b	C	8.29 (5 - 10)
US can be used for accurate placement of intra-articular injections.	3b	C	9.64 (8 - 10)
US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.	3b	C	8.86 (5 - 10)

The level of evidence and grade of recommendation are based on the Oxford Centre for Evidence-Based Medicine system[43].

Level of evidence scale, 1a – 5; grade of recommendation scale; A-D. NRS, numerical rating scale (0–10; 0 = do not agree at all, 10 = fully agree)

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4.3.2 Points to consider (PTC)

Making a diagnosis of JIA

PTC 1: US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, both in diagnosis and assessing extent of joint involvement.

Sixty-five studies compared clinical examination with imaging in the detection of inflammation in various joints, 40 with US, 27 with MRI, 5 with CR and 1 with PET (table 13). The data is represented according to detection rates; for example, how many times more (>1-fold) or less (<1-fold) does imaging detect inflammation over clinical examination; this has the potential to increase false positive results. In general, US and MRI were able to detect joint inflammation more frequently than clinical examination; for example the mean (range) detection rate for synovitis and effusion at the knee was 1.19-fold (0.14-3.67-fold) for US and 1.02-fold (0.96-1.12-fold) for MRI knee synovitis.

PTC 2: When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.

The diagnosis of JIA is mainly based on clinical features and the exclusion of other causes of chronic arthritis. However this point illustrates the role of imaging when there is diagnostic doubt; no specific imaging signatures for JIA have been described yet, but imaging is helpful to narrow the differential diagnosis. Four studies compared imaging features in suspected/proven JIA with either controls or other disease entities, including infectious arthritis, acute lymphoblastic leukaemia and haemophilia[189-192]. US detected more joint inflammation than clinical examination; two studies specifically described US improving the diagnostic certainty in subjects with suspected JIA[193,194].

Detecting damage

PTC 3: If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.

Table 13. JIA imaging point to consider 1: Summary of included studies comparing imaging with clinical examination (CE) in the detection of joint inflammation

ULTRASOUND		MRI		CR	
US KNEES vs. CE **13 studies** [195-207]		**MRI KNEES vs. CE** **9 studies** [198,199,208-214]		**CR KNEES vs. CE** **3 studies** [198,209,212]	
	Detection rate, mean (range) **US vs. CE**		**Detection rate, mean (range)** **MRI vs. CE**		**Detection rate, mean (range)** **CR vs. CE**
Synovitis/effusion (12 studies) [195-206]	1.19-fold (0.14-3.67-fold)	**Synovitis vs. clinical swelling** (3 studies) [199,209,213]	1.02-fold (0.96-1.12-fold)	**Joint distension vs. swelling** (3 studies) [198,209,212]	0.69-fold (0.45-1.0-fold)
		Effusion vs. swelling (5 studies) [198,199,209,211,212]	1.07-fold (0.75-1.33-fold)		
Effusion (1 study) [207]	Agreement k 0.54 CE missed a significant no. of effusions	**Effusion vs. pain** (1 study) [198]	1.45-fold (1.33-1.57-fold)		
PD vascularity (2 studies) [197,205]	1.63-fold (0.96-2.71-fold)	**Synovial volume vs. CRP** (1 study) [214]	r 0.51-0.80 p 0.000-0.036	**Joint distension vs. pain** (1 study) [198]	1.57-fold
		Synovial hypertrophy vs. pain (1 study) [208]	r 0.68-0.74		
US HIP vs. CE **5 studies** [198,200,215-217]		**MRI HIP vs. CE** **5 studies** [198,212,218-220]		**CR HIP vs. CE** **1 study** [212]	
Synovitis/effusion (5 studies) [198,200,215-217]	0.85-fold (0.13-1.39-fold)	**MRI inflammation** (4 studies) [198,212,218,219]	0.88-fold (0.50-1.78-fold)	**Joint distension vs. clinical effusion** (1 study) [212]	0.80-fold
Synovitis/effusion vs. LOM (1 study) [217]	Association p 0.006				
Synovitis/effusion vs. pain (1 study) [217]	Association p 0.103	**Synovial enhancement** (1 study) [219]	0.94-fold		

US HANDS/WRISTS vs. CE **4 studies** [197,221-223]		**MRI HANDS/WRISTS vs. CE** **2 studies** [224,225]		**CR HANDS/WRISTS vs. CE** **1 study** [221]	
Synovitis/effusion (3 studies) [197,221,222]	0.93-fold (0.47-1.33-fold)	**Synovitis volume vs. total hand swelling score** (1 study) [224]	r 0.52-0.72 p<0.05	**Joint distension vs. clinical effusion** (1 study) [221]	0.63-fold
PD vascularity (2 studies) [197,223]	0.96-fold GS synovitis had weaker correlation with clinical disease activity than PD	**Synovitis volume vs. LOM** (1 study) [224]	r 0.76 p<0.05		
Flexor/extensor tenosynovitis (1 study) [223]	Significant association with clinical disease activity	**Synovitis score vs. wrist swelling score** (1 study) [225]	MRI score significantly higher with higher swelling score p<0.00001		
US ANKLES/FEET vs. CE **5 studies** [197,201,226-228]		**MRI ANKLES/FEET vs. CE** **1 study** [229]			
Synovitis/effusion (3 studies) [197,201,226]	1.30-fold (0.86-1.04-fold)	**Tibiotalar synovitis** (1 study) [229]	1.00-fold		
PD vascularity (1 study) [197]	0.57-fold	**Subtalar synovitis** (1 study) [229]	3.33-fold		
US TMJ vs. CE **3 studies** [230-232]		**MRI TMJ vs. CE** **8 studies** [231,233-239]			
Synovitis/effusion (2 studies) [230,231]	11.7-fold (0.35-23.0-fold)	**Synovitis** (6 studies) [231,235-239]	2.46-fold (1.10-5.91-fold)		
		Synovitis vs. reduced MIO (4 studies) [231,233,234,237]	Significantly correlated Reduced MIO best predictor of active MRI changes		
		Acute changes (1 study) [238]	71% asymptomatic 63% normal CE		
US enthesitis vs. CE **3 studies** [240-242]		**MRI enthesitis vs. CE** **1 study** [243]			
Enthesitis (3 studies) [240-242]	0.79-fold (0.53-1.09-fold)	**Enthesitis** (1 study) [243]	0.50-fold		
US VARIOUS MULTIPLE JOINTS vs. CE **9 studies** [244-253]		**MRI VARIOUS MULTIPLE JOINTS vs. CE** **1 study** [243]		**CR VARIOUS MULTIPLE JOINTS vs. CE** **1 study** [254]	
Synovitis/effusion (6 studies) [245,247-250,252]	1.85-fold (1.00-3.33-fold)	**Synovitis/effusion** (1 study) [243]	1.08-fold	**Soft tissue swelling vs.**	1.05-fold

Association US changes vs. swelling (1 study) [249]	SH: r 0.63 Effusion: r 0.66 PD: r 0.50			**clinical swelling** (1 study) [254]	
Association synovitis vs. CE (2 studies) [244,253]	Swelling: r 0.50 LOM: r 0.40 Pain: r 0.21 CE missed inflammation in 25.2% jt				
		MRI cervical spine vs. CE 1 study [255]			
		Synovitis/SH (1 study) [255]	4.25-fold		
		MRI SIJ vs. CE 2 studies [256,257]			
		Sacroiliitis (2 studies) [256,257]	0.93-fold CE was normal in 22.9% pt with MRI sacroiliitis		

CE, clinical examination; CR, conventional radiography; PD, power Doppler; LOM, limitation of movement; MIO, maximal incisional opening; SIJ, sacroiliac joint

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Thirty-seven studies compared joint damage (erosions, JSN, deformity) detected by imaging with clinical findings suggestive of underlying damage, such as tenderness, limitation of movement (LOM) and crepitus. In general, all imaging modalities appeared to detect less joint damage than suggested by clinical examination; for example the mean (range) detection rate for cartilage loss at the knee was 0.32-fold for US, 0.63-fold (0.20-1.0-fold) for MRI, and 0.46-fold (0.23-0.71-fold) for CR when compared with pain[198,258,259]. This reflects the poor sensitivity of pain as an indicator of underlying damage.

When the imaging modalities are directly compared MRI and US detected more joint damage than CR, particularly at the hip (MRI vs. CR detection rate, mean (range) 1.54-fold (1.08-2.0-fold); US vs. CR detection rate, mean 2.29-fold), and at the wrist (MRI vs. CR detection rate, 1.36-fold (1.0-2.0-fold)[198,215,225,259-261].

Imaging specific joints

> *PTC 4: In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the TMJ and axial involvement.*

Cervical spine MRI performs better at detecting inflammation than clinical examination; one study showed 20% of patients had pain and/or LOM whereas 85% had MRI inflammatory changes suggesting that cervical spine involvement in JIA is often clinically silent[262]. MRI and CR have shown better detection rates than clinical examination for structural changes in the cervical spine (4.5-fold and mean, range 2.29 (1.58-3.0-fold) respectively[263,264]. Abnormal sacroiliac joint (SIJ) imaging is also seen despite a high rate of normal examination; for example normal SIJ examination in 42.9% and 22.9% in patients with CR and MRI sacroiliitis respectively[265,266].

Muller at al compared temporomandibular joint (TMJ) clinical examination and US with MRI changes, and found that examination correctly identified 58% patients with active MRI TMJ arthritis compared with 33% for US, and missed inflammation in 42% and 67% respectively[231]. They described reduced maximal incisal opening (MIO) to be the best predictor of active MRI changes[267]. Full data comparing the various imaging modalities with clinical examination of the TMJ is given in appendix J.

Prognosis

PTC 5: Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.

Thirteen observational studies examined the relationship between baseline imaging and subsequent radiographic and clinical outcome; 11 with CR and 2 with MRI at baseline. The statement on US inflammation is therefore based on expert opinion; the findings are given in full in table 14. In general, CR damage in the first year has a moderate correlation with functional deterioration according to Steinbocker class, Childhood Health Assessment Questionnaire (CHAQ) and physician/parent disability scores at 5 years, as well as with CR progression at 5 years[268-270]. A baseline CR wrist adapted Sharp van der Heijde score >1 was shown to be predictive of CR progression at 5 years (OR, 8.2), and patients with erosions and/or JSN in the first 6 months of the study spent more time with clinically active disease and were less likely to achieve clinical remission on medication[271,272]. Just one study described the correlation of baseline MRI wrist synovial volume with MRI erosive progression at 1 year; this found a moderate correlation, and all patients with high synovial volume at baseline had erosive progression[273].

Monitoring inflammation

PTC 6: In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.

Data comparing imaging with clinical examination in detecting joint inflammation is discussed in PTC 1, and specific information on imaging the TMJ and for axial involvement is summarised in PTC 4. This section will consider the comparison of the ability of imaging to detect inflammation, responsiveness of imaging to change in inflammation, and which joints should be assessed.

Table 14. JIA imaging point to consider 5: Summary of included studies describing the prognostic value of the imaging modalities

Baseline CR predictive factors:						
Reference	**No. of subjects**	**Duration of follow-up (months)**	**Radiological or clinical assessment**	**Outcome assessed**	**Correlation**	
Susic 2011[274]	87	48	Wrist involvement	CHAQ DI	Significant correlation p<0.01	
			Hip involvement		Significant correlation p<0.001	
			JADI-A		Significant correlation p<0.01	
Ravelli 2007[270]	96	min. 60	CR wrist changes at: baseline in 1st year in 1st 5 years	No. jt with LOM	Baseline: low r 0.16 1st yr: low r 0.35 1st 5 yr: moderate r 0.59	
				JADI-A	Baseline: low r 0.21 1st yr: moderate r 0.53 1st 5 yr: moderate r 0.60	
				Steinbocker functional class	Baseline: low r 0.21 1st yr: moderate r 0.48 1st 5 yr: moderate r 0.55	
				CR progression at 5 years	Baseline: low r 0.38 1st yr: moderate r 0.61 1st 5 yr: high r 0.89	
Pederzoli 2011[271]	130	min. 60	CR wrist aSH score > 1	CR progression at 5 years	Significant predictor OR 8.2	
Magni-Manzoni 2003[269]	94	54			Baseline Poznanski score	CR progression in 1st yr
			Baseline Poznanski score	Yearly CR progression	r 0.88 p 0.47	r 0.62, p<0.001 OR 14.32, p<0.0001

			CR wrist progression in 1st year	Final Poznanski score	r 0.58 p<0.0001	r 0.59, p<0.0001 OR 6.49, p 0.0006
				CHAQ	r 0.20 p 0.14	r 0.39, p 0.003 OR 8.42, p 0.002
Bertamino 2010[268]	148	max. 132	CR hip progression in 1st year	CHAQ	r 0.24, p 0.1	
				SJC	r 0.03, p 0.86	
				TJC	r 0.06, p 0.65	
				No. jt. with LOM	r 0.46, p 0.0005	
				Steinbocker functional class	r 0.50, p 0.005	
				JADI-A	r 0.45, p 0.01	
				Physician disability score	r 0.40, p 0.05	
				Parent disability score	r 0.53, p 0.007	
Oen 2003[275]	136	min. 60	Early (< 2 years) erosions/JSN	CHAQ	No correlation	
Selvaag 2006[276]	197	36	Baseline swelling/osteopenia	CR erosive progression	OR 7.95, p<0.001	
					Less patients with CR progression had CHAQ of 0, p 0.045	
Ringold 2009[272]	104	29.9	Early (< 6 months) erosions/JSN vs. normal	Time with active disease	More time with active disease p<0.001 Less chance of CRM, RR 0.34, p<0.001	
			RF +ve vs. -ve	CRM	More time with active disease p 0.07	
Oen 2003[277]	88	Early (<2 years) Late (1-20.8 years)	Late vs. early JSN	CHAQ	Significant correlation Explains 17.7% of variation in CHAQ	
			Joint pain		Explains 32.4% of variation in CHAQ	
Habib 2008[278]	68	-	ACPA	CR erosions	Significant correlation p 0.004	

Arvidsson 2010[279]	103	324	Baseline/early TMJ involvement	Micrognathia	66.7% pt with micrognathia had baseline TMJ involvement; 33.3% had CR TMJ involvement within 2 years
Baseline MRI predictive factors:					
Malattia 2012[273]	58	12	Baseline wrist synovial volume	MRI erosive progression	Correlation r 0.42 p<0.02 All pt with high synovial volume had erosive progression
			Baseline CRP		Correlation r 0.40 p<0.02
Gardner-Medwin 2006[280]	10	12	Baseline synovial hypertrophy in a clinically normal joint	Disease extension from monoarthritis	100% pt developed clinical arthritis in other joints

CHAQ- DI, Childhood Health Assessment Questionnaire disability index; JADI-A, Juvenile Arthritis Damage Index for articular damage; LOM, limitation of movement; aSH, adapted Sharp van der Heijde score; OR, odds ratio; SJC, swollen joint count; TJC, tender joint count; JSN, joint space narrowing; RF, rheumatoid factor; CRM, clinical remission on medication; RR, relative risk; ACPA, anti- cyclic citrullinated peptide antibody; CRP, C-reactive protein

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Comparison of the ability of imaging to detect inflammation

Several studies compared US with MRI in the detection of inflammation, particularly at the knee[198,258,281,282]. These studies have shown MRI to be better at detecting knee inflammation than US (mean detection rate 1.20-fold, range 0.63-1.56-fold) and in particular MRI was better than US in differentiating pannus from effusion. Contrast enhanced knee MRI was more reliable at localising and differentiating SH from synovial fluid particularly when there was <5mm of SH, but the addition of contrast did not provide additional information in the assessment of inflammatory bone marrow lesions[211,283,284]. Comparison of PD with grey-scale wrist US have produced conflicting results, whereas the use of contrast significantly increased knee US synovial pixel intensity in those with symptomatic disease (p 0.004) and asymptomatic disease (p 0.0001), but not in those in clinical remission[285-287].

Studies comparing TMJ US with MRI have shown a poor correlation between these modalities, with US missing 67-75% of TMJ MRI inflammation[231,288]. The use of MRI contrast enhancement improved the detection of MRI TMJ inflammation from 35.7% to 86.7%[236]. One study examined CR findings in patients with TMJ MRI synovitis and found significant correlation with abnormal condyle morphology and accentuated antegonial notching on CR, and joints with both of these changes on CR were 7.5 times more likely to have MRI synovitis (OR 7.55, 95% CI 1.66- 34.4, p 0.009)[289].

Responsiveness of imaging to change in inflammation

US and MRI have both been shown to have good responsiveness to change in inflammation, as measured by SRM (≥0.20 small change, ≥0.50 moderate, ≥0.80 good). The mean (range) SRM for MRI wrist synovitis was good at 1.27 (0.51-1.69) and demonstrated ability to discriminate between different levels of clinical responder categories, whereas the SRM for MRI wrist bone marrow oedema was small at 0.22[225,273,290]. Similar levels of SRM have been described for MRI knee SH (0.68-0.70) and BM oedema (0.15)[291,292]. A comparison of MRI wrist synovitis score with US showed higher MRI responsiveness (1.61) when compared with US grey-scale (0.87) and US PD (0.71)[293].

Which joints to assess

Studies describing the frequency of US joint inflammation in JIA have shown these changes to be most common in the knee (~30%) and wrist (~20%), then ankle, proximal interphalangeal joint (PIPJ) and metatarsophalangeal joint (MTPJ) (~10% each)[294,295]. US PD activity was most common in the wrist (~35%)[294,295]. One study examined the frequency of US peripheral synovitis and found changes more commonly in the MTPJ (61.9%) than in the metacarpophalangeal joint (MCPJ) (39%), with the first MTPJ and second MCPJ most frequently affected (20% and 13% respectively)[296].

Monitoring damage

> *PTC 7: The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.*

As for PTC 6, this section will compare the ability of imaging to detect damage, responsiveness of imaging to change in damage, and which joints should be assessed. Data comparing imaging with clinical examination in detecting joint damage and comparing CR with MRI and US in detecting damage is discussed in part in PTC 3.

Comparison of the ability of imaging to detect damage

El-Miedany et al examined the role of MRI, US and CR in the detection of knee JSN and described a 3.14-fold detection rate of MRI compared with US, 4.40-fold for MRI compared with CR, and 1.4-fold for US compared with CR[258]. The addition of contrast to MRI enhanced the appreciation of depth of cartilage involvement by 1.42-fold. Data describing the detection of wrist erosive changes have shown a detection rate for MRI compared with US of 1.92-fold, MRI compared with CR of 1.36-fold, and US compared with CR of 1.0-fold[225,260,261,287].

In terms of detecting TMJ damage, Muller et al showed that MRI condylar damage was detected in 25% of their cohort, whereas US detected only 17% (1.47-fold)[231]. Weiss et al also described a poor correlation between these modalities, with only 50% agreement (detection rate 2.44-fold)[288].

Responsiveness of imaging to change in damage

Several studies examined the responsiveness of imaging to detect change in damage at the wrist, particularly with CR and MRI. The rate of change in CR score (Larsen, Sharp, Poznanski) appears to be greatest in the first year, which is mainly due to progression in JSN[269,297]. This seems to slow after the first year, whereas the rate of erosive change is steady from baseline to year 3; the rate of progression overall slows after the third year. In general, the rate of JSN exceeds that of erosions and total score[270]. When compared with CR, Malattia et al described the relative efficacy of MRI compared with CR erosion score to be <1 at year 1; i.e. MRI was less responsive than CR in detecting erosive progression; the fact that cartilage assessment was not included in the MRI scoring systems might explain this result[290]. A study of TMJ condylar changes showed that MRI identified significantly more changes than CR ($p \leq 0.003$), and MRI was superior to CR in following condylar changes over time: MRI condylar changes at baseline were found in 58.6% compared with 80% at year 2; CR condylar changes were stable at baseline and year 2 at 30%[298].

Which joints to assess

Studies describing the distribution of CR changes in 'early' (within 2 years of disease onset) and 'late' (up to 20.8 years of follow-up) disease have shown JSN to be most common in early disease in the wrist (20%), hips (16%), cervical spine (5%), ankles (4%) and knees (3%) compared with 34%, 25%, 38%, 15% and 6% respectively in late disease[277,299]. Rostom et al observed CR hip disease to start after 4 years of disease, whereas 80% had developed hip disease at 6 years, and 100% after 14 years[300]. Other studies describing radiological features of JIA found most CR changes in the hands (57%), knees (47%), ankles (27%) and feet (36%), with erosions mainly in hands (18%) and feet (25%)[301]. The hands and feet were the areas most likely to show CR damage progression at 6 months and 5 years[302,303].

Guided treatment

PTC 8: US can be used for accurate placement of intra-articular injections.

Studies summarising the role of imaging for guiding intra-articular steroid injections are given in table 15, along with additional data on the use of imaging to assess and monitor efficacy of steroid injections. All studies used triamcinolone injections; doses and preparations varied according to the age of the patient and the joint being injected. Young et al used US to assess the accuracy of needle placement for steroid injections at various sites (joints and tendon sheaths), and described that US allowed accurate visualisation of the injection point in all 1,444 injections performed[304]. A study by Parra et al used CT to establish if US-guided TMJ injections had been accurately placed; needle placement was shown to be acceptable in 91% (75% required no needle adjustment, 16% required minor adjustment) and unacceptable in 9% where the needle required major readjustment[305]. A study of the efficacy of TMJ injections used MRI to assess needle placement accuracy according to the location (intra- or extra-articular) of the injected material on MRI acquired after injection; MRI confirmed that 65% of injections were accurately placed[306]. A similar study using MRI post SIJ injection described technical success in 100%[307].

Remission

PTC 9: US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.

Several studies addressed the discrepancy between clinical remission and inflammation seen on US and MRI; these are summarised in table 16. Evidence of ongoing US synovitis has been described in 56.1-94.1% of patients with clinically inactive joints, and 32% of patients with inactive disease showed US signs of SH, effusion and PD activity[308-310]. In clinical remission, US grey-scale synovitis was seen in up to 84.1% of joints, and PD activity in up to 48.6% of joints, with a non-significant trend to more US inflammation in clinical remission on medication compared with clinical remission off medication[286,311-316]. MRI knee inflammation has been demonstrated in up to 50% of patients in clinical remission and BM oedema in 33.3% patients with clinically inactive joints[317-319]. Recent pilot studies have demonstrated that patients with subclinical US or MRI inflammation are more likely to develop active disease and disease progression, even within 6 months of follow-up[309,316,319,320].

Table 15. JIA imaging point to consider 8: Summary of included studies describing the role of imaging for guided IA steroid injections

Reference	No. of subjects	Duration of follow-up (months)	Intervention	Imaging modality	Outcome assessed	Outcome
Young 2012[304]	198	Not specified	IA various joints	US-guided	Accuracy of needle placement	US allowed visualisation of point for injection for 1444 injections
Agarwal 2012[321]	23	30	IA hip	US-guided	Clinical response	Clinical response in 71% after 1 injection Mean duration of response (range): 7 (4-15) months
Boehnke 1994[322]	26	18	IA hip	US-guided	US remission	US remission in 32%
Neidel 2002[323]	48	24	IA hip	US-guided	Clinical remission MRI remission	Clinical remission in 76.1% MRI remission in 76.1%
Tynjala 2004[324]	13	12	IA hip	US	Clinical remission US remission	Clinical and US remission in 70% at 3 and 6 months, 50% at 12 months
Eich 1994[198]	10	1	IA hip and knee	US MRI	US inflammation MRI inflammation	US: Hips – 100% improved; knees – no change MRI: Hips - 75% improved; knees - 63.6% improved
Laurell 2012[325]	11	1	IA wrist	US-guided	Clinical response US response	Clinical response in 80%; US response in 91% US enabled precise location of inflamed compartment which could not be established clinically
Laurell 2011[326]	30	1	IA ankle	US-guided	US inflammation	Improvement in 87% (resolution in 55%, regression in 32%) US enabled precise location of inflamed compartment which could not be established clinically

Savage 2012[327]	20	3	IA ankle	US-guided	Clinical response US response	Clinical resolution in 81.6% US resolution in 92.1%
Parra 2010[305]	83	None	IA TMJ	US-guided	Accuracy of needle placement by CT	Acceptable needle placement in 91% (75% required no adjustment, 16% minor adjustment) Unacceptable needle placement in 9% (i.e. required major readjustment)
Habibi 2012[328]	39	2	IA TMJ	US-guided	Clinical response	Clinical response in 92.1%
Arabshahi 2005[329]	14	6-12	IA TMJ	CT-guided	Clinical response MRI inflammation	Improvement in pain (77%), jaw locking (67%), MIO 43% Resolution of effusion in 48%
Cahill 2007[330]	15	15	IA TMJ	CT-guided	Clinical response MRI inflammation	Clinical response in 58.3% MRI improvement in 73%, stable in 20%, worse in 6.7%
Lochbuler 2013[331]	33	6-12	IA vs. extra-articular TMJ	MRI	MRI inflammation	MRI improvement in 56% with IA injection, 17% with extra-articular injection
Saurenmann 2009[306]	33	3	IA vs. extra-articular TMJ	MRI	MRI accuracy of needle placement MRI inflammation	MRI confirmed injection accurately placed IA in 65% MRI improvement in 73% with IA injection, 15% with extra-articular injection
Stoll 2012[332]	31	5.3	IA TMJ	MRI	MRI response	MRI improvement in 38.7% (resolution in 14.5%), deterioration in 24.2%, stable changes 12.9%, stable normal 24.2%
Fritz 2011[307]	14	22	IA SIJ	MRI-guided	Clinical response MRI inflammation	100% of injections were accurately located Clinical response in 79% MRI improvement in 59%
Huppertz 1995[333]	21	13	IA knee, ankle, elbow	MRI	Clinical response MRI inflammation	At 7 weeks: clinical resolution in 76.2%, MRI improvement in 100%, resolution in 52.4% At 13 months: clinical resolution in 50%, MRI improvement in 100%

Beukelman 2006[334]	38	1.5	IA ankle	Fluoroscopy -guided	Clinical response	Clinical response in 89%
Cahill 2007[335]	38	1.5	IA ankle	Fluoroscopy -guided	Clinical response	Clinical response in 89%
Sparling 1990[336]	30	42	IA various joints	CR	Deterioration in damage	CR deterioration after IA steroid was unusual, but most common at the hip (deterioration in 33% by 2+ grades)

IA, intra-articular; MIO, maximal incisal opening

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Table 16. JIA imaging point to consider 9: Summary of included studies describing imaging findings in clinical remission

Reference	No. of subjects	Clinical assessment of remission	Imaging modality	Site	Outcome	
Collado 2012[312]	44	CRM CR	US synovitis (GS, PD)	44-joints	GS synovitis: 84.1% jt PD activity: 48.6% jt More in CRM than CR, p NS	
Erik Nielsen 2013[309]	62	Clinically inactive joints	US synovitis	Multiple	Subclinical synovitis: 56.1% pt	
Halbwachs 2012[310]	13	Clinically inactive joints	US synovitis	Multiple	Subclinical synovitis: 94.1% jt	
Magni-Manzoni 2013[295]	39	ID	US inflammation	Multiple	Synovial hyperplasia: 76.9% pt Effusion: 66.7% pt PD activity: 15.4% pt Tenosynovitis: 15.4% pt	
Donati 2012[308]	100	Wallace ID	US inflammation (SH, effusion, PD)	72-joints	US inflammation: 23% pt, 43/7200 (0.06%) jt All 3 US changes: 17/43 (32%) jt	
Silva 2013[316]	35	CRM CR	US synovitis (SH, PD)	17-joints	Subclinical US: 37.8% jt	
Rebollo-Pollo 2011[315]	28	Clinical remission	US synovitis (GS, PD)	Wrist	**Pt with prior jt disease (%)**	**Pt with no prior jt disease (%)**
					GS: 57.1	GS: 50.0
					PD: 21.4	PD: 0
				Ankle	GS: 40	GS: 12.5
					PD: 6.7	PD: 0
Bugni Miotto e Silva 2014[311]	36	Clinical remission	US synovitis (GS, PD)	Multiple	GS synovitis: 41.7% pt (3.1% jt) PD activity: 19.4% pt Subclinical synovitis more common with older disease onset (p 0.007), and in extended oligoarticular or pJIA (p 0.013)	
Parsa 2011[314]	35	ID, CRM, CR	US inflammation	Knee	Inflammation: 35% pt in ID, CRM or CR	
Molina 2011[313]	11	Clinical remission	US synovitis	Knee	Synovitis: 36% pt	

Doria 2001[286]	22	Clinical remission vs. active disease	US effusion	Knee	Effusion in remission: 20% jt Effusion in active disease: 77.8%
Hemke 2014[317]	146	Clinically inactive joints	MRI inflammation	Knee	Synovitis: 35.9% pt BM changes: 33.3% pt
Van Veenendaal 2012[319]	16	CRM CR	MRI synovitis	Knee	Synovitis: 50% pt
Van Veenendaal 2011[318]	30	CRM CR	MRI synovitis	Knee	Synovitis, CRM: 30% pt Synovitis, CR: 25% pt
Brown 2012[337]	11	CRM CR	MRI inflammation	Hand/ wrist	Any MRI inflammation: 63% pt Synovitis: 45.5% pt BM oedema: 27.3% pt Tenosynovitis: 54.5%
Zwir 2010[338]	93	Active disease vs. CRM and CR	MRI synovitis	TMJ	Synovitis, active disease: 80% pt Synovitis, CRM: 70% pt Synovitis, CR: 65.6%

CRM, clinical remission on medication; CR, clinical remission off medication; GS, grey scale; PD, power Doppler; NS, not significant; ID, inactive disease; SH, synovial hypertrophy; BM, bone marrow

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4.3.3 Feedback from the Patient and Public Involvement event

There were extensive discussions around differences in the experience of imaging for children with JIA. Although the patients involved were young adults, they had personal experience of JIA and of imaging from early childhood (4 years old in one case). One patient had just experienced CR and the other two had experienced CR, US and MRI. No specific comments were given on the PTC as they felt they were directed towards medical staff but 'thought they all sounded reasonable' and had no objections. However, they did make a number of overarching observations related to imaging in general, and on the individual imaging modalities (table 17). A lay summary of the PTC is given in appendix K.

Table 17. Summary of comments from the JIA imaging Patient and Public Involvement event

General comments:
Really important to be talked to and treated as an adult and as someone with understanding of their illness
Understanding how a machine works makes it less scary
One stop shop is best to reduce time wasted
Always good to be shown scans
Need scanning to show joint inflammation as when you have pain for a long time you get used to it and may not notice it anymore
Having contrast (injection and needle) can be frightening
Position for X-ray and MRI can be painful particularly if have to maintain in the same position for a long time
CR specific comments:
At least this is quick
Parents can be frightened by the risk of X-ray radiation
MRI specific comments:
Need clear information in advance about how long it will take, how noisy it is and what it looks like
Perceived high value of MRI for some joints (TMJ)
MRI is often in an environment used by adults and children and can look frightening
It can be difficult to get on and off the MRI 'bed', and they often don't have the right equipment to help you
US specific comments:
Good because they can show you what's going on at the time of the scan; you get instant feedback and they can show you the image and inflammation on the screen, even if that joint feels fine; it's very visual and instant
US made guided injections less worrying
US is easy to understand

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4.3.4 Research agenda

The group formulated a research agenda based on areas identified with a lack of currently available evidence, shown in table 18.

Table 18. JIA imaging research agenda

	Research agenda
1	What are the age-specific changes in imaging, including age-specific intervals for imaging, development of an atlas of age-specific normal images and a registry as mechanism for pooling of data
2	Development of validated scoring systems including pathology definition (for example differentiating reversible structural abnormalities from damage), imaging acquisition protocols and quantification
3	What are the imaging characteristics of the sub-types of JIA, and which target sites should be imaged?
4	What is the clinical significance of imaging-detected subclinical disease in diagnosis, monitoring and remission?
5	What is the usefulness of imaging-guided injection over non-imaging guided injection?
6	What is the prognostic value of specific imaging features, for example BM oedema?
7	Can imaging be used to assess and monitor response to treatment?
8	What are the feasibility, cost and appropriate training for using US and MRI in JIA in clinical practice?

JIA, juvenile idiopathic arthritis; BM, bone marrow; US, ultrasound; MRI, magnetic resonance imaging.

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4.4 Conclusion

These considerations for imaging provide important and novel advice for JIA in clinical practice. There is still significant research needed in this field, in particular consensus on understanding normative data to allow the interpretation of imaging abnormalities, agreement on appropriate MRI protocols and definitions of BM oedema, synovitis and erosions, and suitability of the imaging modalities for detecting changes at specific joints. Our data is limited by the lack of specific information for each JIA disease subtype; this is reflected in the research agenda.

The Patient and Public Involvement process provided invaluable insight into understanding the patient perspective of various aspects of imaging in JIA. It highlights the importance of involving patients as far as possible in the development of clinical recommendations. In particular, key concerns related to the environment in which the imaging takes place, the ease of positioning, the time taken, the importance of understanding the technology and having rapid access to a result. There are significant conceptual differences between imaging in adult and paediatric conditions, and consideration must be given to the appropriateness and feasibility of different imaging modalities which differs with age and developmental stage, as well as to economic issues such as the cost-effectiveness of the intervention. Repeated unnecessary exposure to radiation from imaging should also be considered.

We appreciate that access to individual imaging modalities may be insufficient to allow full implementation of these PTC; however most of the points include the use of US which is generally readily available. An economic evaluation was not included in the process as the primary aim was to discuss the clinical implications of imaging; the overall cost of implementing the PTC should be low.

After dissemination of the PTC by means of publication and presentation at European meetings, we would propose to perform a survey of awareness and their use, for example:

- Do you have access to musculoskeletal US and MRI routinely?
- Are you aware of and implementing the JIA imaging PTC?
- Have the PTC changed your clinical practice?

The task force agreed that it was not appropriate to create audit or implementation tools as the strength of data was only sufficient to develop PTC rather than recommendations.

In summary, we developed 9 PTC on the role of imaging in various clinical aspects in JIA which have now been published[188]. We would recommend that a similar rigorous process is followed to reassess the available data after an interval of 5 years.

Chapter 5: Ensuring the quality of rheumatology management recommendations

5.0 Chapter abstract

Objective:

To increase understanding of how to ensure the quality of rheumatology guidelines by reviewing EULAR management recommendations using the AGREE II instrument, ten years after publication of the EULAR SOP for the production of recommendations. It was hoped that this work could help inform improvements in guideline development by other societies and organisations.

Methods:

The SOP were published in 2004 to ensure the quality of EULAR endorsed recommendations. We reviewed 27 published EULAR recommendations for management using the AGREE II tool. This provides a framework to assess the quality of guidelines across 6 broad domains using 23 specific questions.

Results:

Overall the EULAR recommendations reviewed were performed to a high standard. There were particular strengths in the methodology and presentation of the guidelines; however the results show areas for development in future recommendations, in particular stakeholder involvement and applicability of the recommendations. Improvements in quality were evident in more recent years with patient representation in 9 of 15 (60.0%) recommendations published 2010-2014 compared to 4 of 12 (33.3%) published 2000-2009.

Conclusions:

The overall quality of recommendations was good with standards improving over the decade following publication of the SOP. However, this review process has identified potential areas for improvement especially in patient representation and provision of implementation tools. The lessons from this work can be applied

to the development of rheumatology guidelines by other societies and organisations.

5.1 Introduction

Ensuring the quality of rheumatology management guidelines by using robust and reliable methodology is vital to maintain the confidence of clinicians. The EULAR executive committee published their SOP for the 'elaboration, evaluation, dissemination, and implementation of recommendations' in 2004 to provide a formal structure to ensure the quality of EULAR endorsed recommendations[60]. The SOP describes in detail methodological aspects to consider when producing recommendations including a clear statement of the objectives, target population and appropriate steering group members, use of a vigorous evidence based approach to review and assess the quality of the literature including a description of categories of evidence and strength of the recommendations. It also describes the subsequent presentation of the recommendations, assessment of their relevance and the process for dissemination, implementation and updating of such recommendations.

On the back of the last two chapters and a decade after the publication of the SOP for the production of recommendations, we assessed the quality of existing EULAR management recommendations according to the AGREE II tool[47]. The original AGREE instrument was published in 2003 by a group of international guideline developers and researchers, the AGREE collaboration, to provide a standardised structure for guidelines in development in order to improve consistency in quality, and provide a framework to assess the quality of published guidelines. The AGREE instrument was updated on its 10th anniversary in 2013, funded by a grant from the Canadian Institute of Health Research, and includes 6 quality domains using 23 specific questions. The domains cover the scope and purpose; the extent of stakeholder involvement; rigour of the methodology and development process; clarity of presentation of the guideline; consideration of applicability, including barriers and facilitators to guideline implementation and resource implications; and editorial independence (table 19). We were interested to learn lessons from this review that would be useful in raising standards of rheumatology guidelines developed by other international societies and organisations.

5.2 Methods

Published EULAR management recommendations were identified through the EULAR website[339]. Supporting publications describing the SLR process were also accessed where necessary. Each recommendation was assessed according to the AGREE II tool using the AGREE guideline online appraisal system[53]. The recommendations were scored on each question using the 7-point response scale from 7, strongly agree, to 1, strongly disagree, which results in a score for each domain. The recommendations were given an overall quality score and statement on whether the use of the recommendation could be supported. A summary of the areas assessed by each domain is given in table 19 with full details given on the AGREE enterprise website[53].

Table 19. Summary of the AGREE II domains

Domain 1. Scope and Purpose (Q1-3)	Overall aim of guideline, specific health questions, target population
Domain 2. Stakeholder Involvement (Q4-6)	Extent guideline developed by appropriate stakeholders and represents views of intended users
Domain 3. Rigour of Development (Q7-14)	Process used to gather and synthesize the evidence, formulate recommendations and update them
Domain 4. Clarity of Presentation (Q15-17)	Language, structure and format of the guideline
Domain 5. Applicability (Q18-21)	Consideration of barriers and facilitators to implementation, improvement strategies and resource implications
Domain 6. Editorial Independence (Q22-23)	Potential impact of bias from competing interests
Overall assessment	Overall quality rating and statement of recommendation for use in practice

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5.3 Results

There were 30 documents listed on the 'EULAR management recommendations' section of the EULAR website when accessed in May 2014, of which 27 met our criteria and were included for evaluation. The three documents that were excluded were a description of perspectives among patients and rheumatologists rather than management recommendations, a patient version of a recommendation and a systematic review for a recommendation. The 27 EULAR recommendations for management that were published between 2000-2014 were on diverse topics ranging from the inflammatory arthropathies and osteoarthritis to recommendations on vaccination and the management of fibromyalgia syndrome and Behçet's disease[339]. A full reference list for the included recommendations is given in appendix L.

Overall the EULAR recommendations reviewed scored highly using the AGREE II tool, thereby supporting their ongoing use. The mean and range scores for each domain and overall scores are given in table 20, and the trend in changes in the domain scores, as a percentage of the total possible score, is shown in figure 9a, with a summary of scores for each recommendation in appendix M. This highlights the improvement in these areas following the publication of the SOP in 2004, and in particular the strengths in the areas of scope and purpose, rigour of development and clarity of presentation of the guidelines. The scores also show areas for development in future recommendations, with potential to improve stakeholder involvement, transparency of editorial independence and applicability of the recommendations. However, improvements in quality were evident over latter years with patient representation in 9 of 15 (60.0%) recommendations published 2010-2014 compared with 4 of 12 (33.3%) published 2000-2009 (figure 9b).

Table 20. Mean and range for each AGREE domain and overall score

	Domain 1. Scope and Purpose (0-21)	Domain 2. Stakeholder Involvement (0-21)	Domain 3. Rigour of Development (0-56)	Domain 4. Clarity of Presentation (0-21)	Domain 5. Applicability (0-28)	Domain 6. Editorial Independence (0-14)	Overall score (1-7)
Mean score, (range)	16.8 (11-21)	13.9 (6-21)	42.5 (32-54)	20.4 (15-21)	8.4 (4-24)	8.0 (2-12)	4.9 (4-7)

Reprinted from Colebatch-Bourn AN, Conaghan PG, Arden NK, et al, Raising the quality of rheumatology management recommendations: lessons from the EULAR process 10 years after provision of standard operating procedures, Rheumatology (Oxford), 2015, 54(8), 1392-6, by permission of the British Society for Rheumatology[340].

Figure 9a.

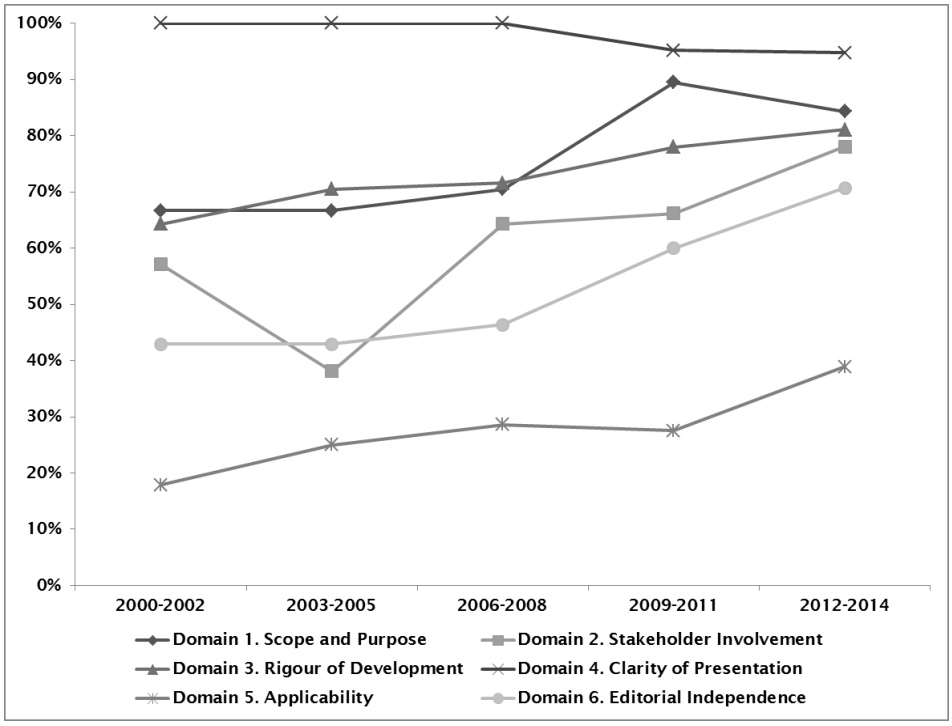

Figure 9b.

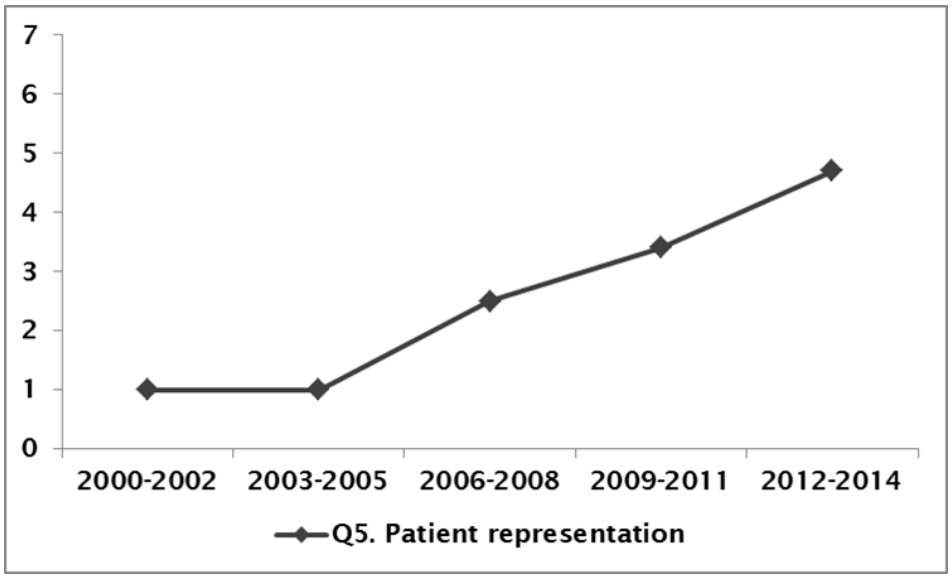

Figure 9. Line chart illustrating the trend in changes in AGREE scores.

(a) Changes in domain scores. Scores are given as % of possible scores for each domain.
(b) Changes in patient representation. Possible score range, 1-7.

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5.4 Conclusion

The publication of the EULAR SOP in 2004 provided a framework for the production of high quality recommendations, written in a consistent format. This study has assessed the quality of all EULAR management recommendations published between 2000 (including recommendations published before the SOP in 2004) and 2014. It has demonstrated that the overall quality of recommendations has been good during these 10 years, with standards improving over the decade. However, the review process has also identified potential areas for improvement especially in applicability, editorial independence and stakeholder involvement. The recommendation publications assessed consistently scored low on all four of the questions addressing applicability which specifically deals with the description of facilitators and barriers to application of the recommendation, inclusion of tools to put the recommendation into practice, consideration of the potential resource implications of the recommendation, and the inclusion of monitoring or audit criteria. These areas should be given more attention in future recommendation publications. We also suggest more transparency in the declaration of editorial independence, which should include a statement of the source of funding (EULAR in this case) as well as their influence on the content of the recommendation, and a detailed description of competing interests of all co-authors, and how these may have influenced the development of the recommendations. There is also potential for improvement in stakeholder involvement, although there was a trend towards improvement in this domain over the latter five years. This has mainly been as a result of an increase in patient involvement in the recommendation development process, and future recommendation publications should be encouraged to describe how patients have been involved and how their input informed the recommendation development process. Finally, although the recommendation publications tended to score quite highly in the rigour of development domain, it is important to ensure that the strengths and limitations of the evidence considered are clearly described, which should include quality and risk of bias assessments.

Clinical guidelines are used across the world to inform and optimise patient care, but there have been concerns raised about their quality and structure[341]. Appraisal systems such as the AGREE tools help to guide the methodological standards framework and quality assessment. The AGREE instruments are widely accepted

as validated assessment tools by various organizations; it has been endorsed by NICE in the United Kingdom[342] and is now used by the 2017 BSR Creating Clinical Guideline Protocol[52]. There have been a number of publications that have used the AGREE tools to assess the quality of existing guidelines, but to date none of the major rheumatology societies have assessed the quality of all of their own guidelines using this or another tool. They have performed a few appraisals of condition-specific guidelines, for example Nuki assessed the quality of the 2012 ACR guidelines on the management of gout using AGREE II, and Zhang et al performed a critical appraisal of existing guidelines on the management of hip and knee osteoarthritis using AGREE, in preparation for the production of new guidelines in these conditions for the Osteoarthritis Research Society International (OARSI)[343,344]. There are also a number of other rheumatological guidelines that have been quality assessed using an AGREE tool[345-353]. The tools are widely used across all specialties; for example Hu et al used AGREE to assess the quality of all Chinese clinical practice guidelines published between 2006 and 2010[354].

The EULAR recommendations are divided into three broad categories, those on conducting and reporting clinical studies, those on classification and diagnostic/response criteria and those on management. We have only included the latter group in this review process as the AGREE II tool includes questions that are not applicable to the other categories, for example, 'the different options for management of the condition or health issue are clearly described'. There does not seem to be an alternative tool that could be used for the other categories; however it is possible that the existing AGREE II tool could be modified in order to better accommodate them.

The 2004 SOP provided a robust framework resulting in well-designed recommendations, but this review has identified that there is potential for further improvement. Since this review was performed and published, EULAR have updated the SOP using the AGREE II tool as a framework[48,340]. This is an approach that is already used by other European rheumatology societies, such as the French Society for Rheumatology[355-358]. Our work shows how the use of a standard approach and quality framework can lead to improvements in the production of guidelines. This knowledge can be widely applied to other organisations tasked with similar work.

Chapter 6: Discussion, conclusions & future research

6.0 Introduction

The preceding chapters have presented data from two SLR used to develop guidelines on the role of imaging in the management of IA, and discusses the existing recommendations against validated assessment tools. This chapter summarises the key findings of these chapters, including the significance for clinical practice, limitations of the findings and the implications for future research are considered.

6.1 Imaging in inflammatory arthritis: Summary of advancement of knowledge and implications for clinical practice

This thesis has provided a review of the use of SLR to develop guidelines for the management of IA, the process of producing guidelines and assessing their quality. It includes a review of the literature on the role of imaging in the management of patients with RA and JIA, and evidence based recommendations to be used in clinical practice. It also considers the quality of EULAR management recommendations and areas where improvements could be made.

The recommendations produced from the SLR on imaging in RA were:

- When there is diagnostic doubt, conventional radiography, US or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.
- The presence of inflammation seen with US or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.
- US and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation.
- Conventional radiography of the hands and feet should be used as the initial imaging technique to detect damage. However, US and/or MRI

should be considered if conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA).

- MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or US as well as joint damage detected by conventional radiographs, MRI or US can also be considered for the prediction of further joint damage.
- Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.
- Given the improved detection of inflammation by MRI and US than by clinical examination, they may be useful in monitoring disease activity.
- The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly US) is more responsive to change in joint damage and can be used to monitor disease progression.
- Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed.
- MRI and US can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation.

These recommendations have highlighted the importance of particular imaging modalities in various aspects of the management of RA, for example CR in the detection and monitoring of damage, and US and MRI in the detection and monitoring of inflammation, which is of particular importance given the role of subclinical inflammation in causing ongoing joint damage. It has also demonstrated where gaps exist in the current knowledge and stressed the need for further trials. This will be discussed further later in the chapter.

Data was found to be lacking during the SLR process on imaging in JIA. As a result, PTC were developed as follows:

- US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, both in diagnosis and assessing extent of joint involvement.
- When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.
- If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.
- In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the TMJ and axial involvement.
- Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.
- In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.
- The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.
- US can be used for accurate placement of intra-articular injections.
- US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.

This SLR was an important step in identifying what data already exists on imaging in JIA and highlights the key role of imaging in JIA, with emphasis on using newer imaging techniques such as US and MRI to detect early or subclinical disease, or for imaging specific joints, for example the TMJ or axial spine. This review has demonstrated the paucity of data related to imaging in JIA, which leads to important research recommendations.

These recommendations have important strengths including the composition of the expert committee which involved a wide range of specialists from a number of European countries. Quality assessment and risk of bias was performed on all included studies, and an overall level of evidence, grade of recommendation and level of agreement was scored for each recommendation. The recommendations

were based on the most recent evidence and on expert opinion; the level of agreement with each recommendation was generally high (score range 7.80-9.64), suggesting good validity and relevance of the recommendations.

The process of performing these SLR stimulated a review of the quality of EULAR recommendations, using the AGREE-II tool as a framework. The key messages from this review were:

- Publication of standardised operating procedures has raised standards of recommendations and provided consistency in quality.
- There are potential areas for improvement especially in patient representation and provision of implementation tools.
- Updated standardised operating procedures with the use of AGREE II could raise the quality of guidelines for other organisations.

This review helped to identify potential areas for improvement for producing clinical guidelines, and established a need to update the existing SOP using AGREE II which has since been published[48].

6.2 Limitations

The main limitation of these reviews resulted from the lack of relevant studies specific to each research question. However it does demonstrate where gaps in the knowledge base exist so that this can be considered in future research, and will be discussed later. The search strategies used did identify an abundance of literature so it is unlikely that relevant data was not identified through the search process. The electronic search was supplemented with hand searching to ensure confidence that all relevant research was identified and included in the reviews. Systematic reviews of clinical effectiveness of healthcare interventions often only consider evidence from RCTs for inclusion, however no RCTs were identified during the search process. These reviews did not exclude data on the basis of study design, and quality assessment of the included studies was made using the appropriate tool.

In both reviews abstracts of all potential articles were screened for inclusion irrespective of the publication language of the full text article however non-English language publications were not included thereafter. This resulted in the exclusion of 44 articles in the RA SLR, and 200 articles in the JIA SLR. This

decision was made following discussion with the task force involved in both reviews, with specific consideration made to the articles that would be excluded on this basis; the quality of the data from the non-English language articles identified was felt not to be sufficient to warrant inclusion in the reviews.

The main limitation of the data was the heterogeneity of the populations of the included studies in both reviews, but in particular in the JIA imaging review given the nature of the condition and lack of specific data for each JIA disease subtype. As a result of patient heterogeneity and general differences between the trials including quality of the study reports, study protocols and reported outcomes it was inappropriate to combine the results of studies in order to perform a meta-analysis.

Although only one person undertook the data extraction in both of the reviews presented here, this researcher was very experienced in the SLR process and any uncertainty was discussed with the task force epidemiologist.

6.3 Implications for future research

These review processes have summarised the available data, resulting in recommendations and highlighting areas where more research is required. Both reviews included future research agendas which are summarised here.

Suggested research agenda following the imaging in RA SLR:

- Further evaluation of the specific joints to be assessed, timing of assessment(s) and the evaluation system to be employed in order to optimise the role of modern imaging modalities in diagnosis, prognosis and outcome measurement of RA.
- To assess algorithms using established and modern imaging modalities to examine their cost-effectiveness in clinical practice diagnosis, prognosis and outcome measurement of RA.
- To further elucidate the importance of subclinical inflammation, including synovitis, BM oedema and tenosynovitis, especially in low disease activity states and to define key thresholds to guide intervention.
- To further assess the importance of imaging, in particular MRI and US, in the evaluation of damage, including JSN and cartilage loss.

- To assess the feasibility, costs and appropriate training required to use US and MRI in clinical practice.

Proposed research agenda following the imaging in JIA SLR:

- What are the age-specific changes in imaging including age-specific intervals for imaging, and development of an atlas of age-specific normal images and a registry as mechanism for pooling of data?
- Development of validated scoring systems including pathology definition (for example differentiating reversible structural abnormalities from damage), imaging acquisition protocols and quantification.
- What are the imaging characteristics of the sub-types of JIA, and which target sites should be imaged?
- What is the clinical significance of imaging-detected subclinical disease in diagnosis, monitoring and remission?
- What is the usefulness of imaging-guided injection over non-imaging guided injection?
- What is the prognostic value of specific imaging features, for example BM oedema?
- Can imaging be used to assess and monitor response to treatment?
- What are the feasibility, cost and appropriate training for using US and MRI in JIA in clinical practice?

Before further progress can be made with imaging in JIA, there must be agreement of the normative imaging findings in children. Once this has been described more informative studies can be performed to document pathological changes, with particular need to describe specific changes in each JIA disease subtype.

The number of guidelines published has risen recently, with an estimate from a selection of prominent societies suggesting that more than 120 clinical rheumatology guidelines have been produced in just 15 years, with a significant increase since 2006-7 (figure 10)[359]. This may not be very useful though, as multiple guidelines on the same topic may provide conflicting advice, and clinicians may be unsure of the best source to identify relevant guidelines. This rate of growth in the number of recommendations produced is not sustainable;

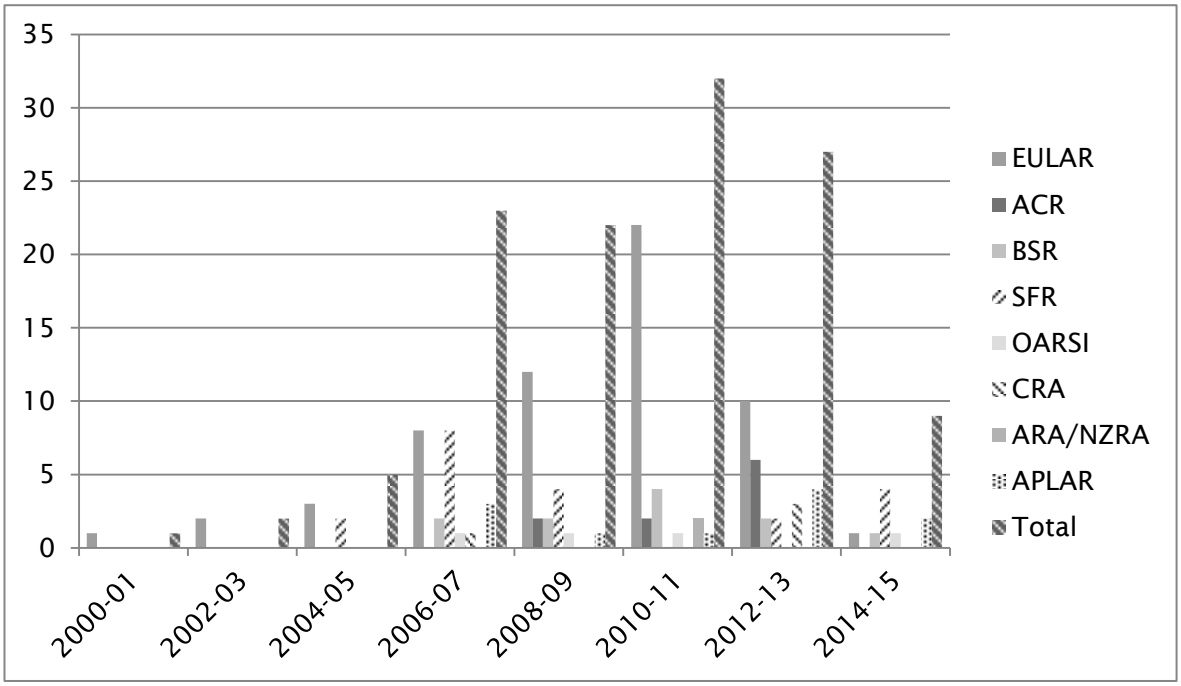

Figure 10. Summary of the number of guidelines produced by a selection of major rheumatology societies, 2000-2015

EULAR, European League Against Rheumatism; ACR, American College of Rheumatology; BSR, British Society for Rheumatology; SFR, Société Française de Rhumatologie; OARSI; Osteoarthritis Research Society International; CRA, Canadian Rheumatology Association; ARA, Australian Rheumatology Association; NZRA, New Zealand Rheumatology Association; APLAR, Asia Pacific League of Associations for Rheumatology

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ideally societies would work together more to produce joint guidelines in the future.

The review of EULAR management recommendations identified that these were generally performed to a high level, but by using the AGREE II tool areas for potential improvement were identified. The use of this tool was included in the updated EULAR SOP which was published following this review[48].

As well as ensuring guidelines are of a high quality it is essential to consider the role and worth of guidelines. The main aim of recommendations is to translate findings from health research into clinical practice, with successful implementation leading to an improvement in quality of care and improved health outcomes[360]. This can be limited by a lack of high quality data to inform the recommendations, poor methodology used to create the recommendation, and an inadequate dissemination process. The Cochrane Musculoskeletal Group has described 10 different strategies to disseminate Cochrane reviews to the most relevant groups including patients, clinicians and policy makers; for example patient decision aids, summary of findings tables, podcasts and other social media messaging including Twitter[361].

Clinicians then need to implement the recommendation which relies on it to be clinically relevant and have external validity. There is some limited evidence that guidelines lead to improvements in patient care and outcome, for example the BSR guidelines for the management of early RA published in 2006 appear to have been associated with an increase in the prescription of methotrexate in the first year after diagnosis[362]. Adherence to the EULAR treatment guidelines in early arthritis has been assessed in terms of patient outcome, including radiographic progression and disability[363]. Adherence rates for the three recommendations included in the study ranged from 51.8-78.3%, but only 22.8% adhered to all three recommendations. The study showed that adherence to the recommendations improved outcomes; patients whose treatment did not follow the guidelines were at increased risk of radiographic progression at one year (OR 1.98, 95% CI 1.08-2.62) and of functional impairment at two years (OR 2.36, 95% CI 1.17-4.67). This study developed a propensity score to assess adherence to the guidelines which is an interesting concept to use when considering the impact of following treatment recommendations.

May et al developed the Normalization Process Theory (NPT) to provide a framework for understanding how a new intervention becomes part of normal practice in order to improve implementation outcomes in healthcare[364]. This involves four core constructs including coherence, which refers to the process of understanding the clinical problem; cognitive participation, which describes commitment to a process; collective action, which is the operational work to implement a new intervention; and reflexive monitoring, which is the appraisal process used to assess the effects of an intervention. This has resulted in a 16-point interactive toolkit for working through an implementation issue[365]. The developers have also proposed a role for NPT in SLR, particularly for reviews addressing implementation processes[366]:

- To support the development of research questions and overall design of a systematic review.
- To serve as a framework for data analysis within a systematic review.
- To support the interpretation of a systematic review's results.

In summary, in order for new interventions to successful it must be disseminated and adopted, but importantly there needs to be continued investment in it for it to be integrated fully into what is considered to be normal practice.

6.4 Summary

This thesis has reviewed the process involved in performing SLR and in producing guidelines. It has produced the first evidence-based recommendations on imaging in RA and JIA for use in clinical practice. Overall, the process of performing these SLR and guideline production has been successful. We aimed to produce guidelines for EULAR, which have been published and disseminated by the organisation, for use in clinical practice. The RA guidelines have been particularly successful in this respect, with 42 currently recorded PubMed Central article citations[367], and discussion of the recommendations included in presentation on treat-to-target in RA at the EULAR Annual Congress of Rheumatology in Paris in 2014. The JIA SLR has only 7 Pubmed Central article citations at present[368], however this SLR was performed more recently and JIA tends to receive less

research attention than RA. However, data was lacking for all of the research questions, which has generated extensive research recommendations.

The recommendations were performed with input from experienced committees who used their expertise to help produce recommendations based on expert opinion where data was lacking. This has resulted in recommendations that are clinically relevant that can be practically implemented into clinical practice. The recommendations have been published in a peer review journal and presented at European conferences to ensure optimal dissemination of the recommendations[58,188]. No audit or implementation tools were produced due to the low quality of data identified through the search processes; however, it would be interesting to assess awareness of the recommendations and to update them once there has been sufficient time for the proposed research agenda to be addressed.

The process of developing guidelines in IA presents unique difficulties compared with other disease entities given the complexity of the condition, the vast spectrum of tests used for diagnosis and monitoring, and the significant heterogeneity of IA, particularly JIA. These factors make it harder to pull information together in order to produce guidelines. However, in general the process was relatively straightforward, aided by clear guidelines and pathways for performing SLR and producing recommendations, as described earlier. It has resulted in an increased understanding and appreciation of the processes involved and the effort needed to produce guidelines, as well as experience in managing groups of people.

It is difficult to measure the value of the recommendations, as high quality guidelines seem to increase clinical outcomes. RA is a high cost condition as a result of the chronicity of the condition, high treatment costs, in particular medication, and high work disability. The total costs of RA in the UK have been estimated between £3.8 and £4.75 billion per year[369]. However, guideline development consumes large amounts of resource that can be measured in time given by experts, assembling the required clinical expertise, clinical fellows, task force meetings, time taken to go through the rigorous process involved and the necessary financial support by rheumatology organisations. It is likely that guidelines can reduce the overall cost of RA in the long-term.

The thesis has also included a review of the quality of existing EULAR management guidelines, and identified potential areas where these could be improved[340]. The SOP used to advise the EULAR recommendation process has been updated as a result of this review[48], so a future review of the quality of EULAR guidelines published since the updated SOP would be very interesting.

Appendices

Appendix A RA imaging systematic review protocol

Proposed Title

European League Against Rheumatism (EULAR) points to consider on the use of imaging in the diagnosis and management of rheumatoid arthritis

Contact author name

Alexandra Colebatch

Christopher Edwards

Description of proposal

Objective

The aim of this review is:

- To propose EULAR points to consider on the use of traditional and modern imaging modalities in the diagnosis and management of rheumatoid arthritis (RA) for all health professionals who care for patients with inflammatory arthritis
- To review the evidence for the value and added value above clinical evaluation (history, examination, conventional laboratory) for each imaging modality in the diagnosis, prognostication and monitoring of RA, at the joint and patient level (activity and damage measures)

There are 13 specific questions, pre-defined by EULAR, to be addressed in this review:

Q1- What is the evidence for the added value (sensitivity , specificity etc.) of individual imaging modalities in detecting inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical evaluation?

Q2- What is the evidence of the added value above clinical examination for the comparative value (sensitivity, specificity etc.) of individual imaging modalities in detecting tissue damage (bone, cartilage, tendons, ligaments)?

Q3- What is the evidence for the differential diagnostic value of individual imaging modalities for RA?

Q4- What is the evidence for the diagnostic value above clinical criteria of individual imaging modalities for RA?

Q5- What is the evidence for the prognostic (prediction of outcome) value of individual imaging modalities for RA?

Q6- What is the evidence for the prognostic (prediction of therapeutic response) value of individual imaging modalities for RA?

Q7- What is the evidence for the prognostic (prediction of outcome) value above other known prognostic markers of individual imaging modalities for RA?

(Outcome=activity, damage, Qol, HAQ, mortality, surgery, HE, cumulative/AUC/temporal change)

Q8- What is the evidence for the prognostic (prediction of therapeutic response) value above other known prognostic markers of individual imaging modalities for RA?

(Outcome=activity, damage, Qol, HAQ, mortality, surgery, HE, cumulative/AUC/temporal change)

Q9- When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease inflammation?

Q10- When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease damage?

Q11- What is the relationship between individual imaging modalities and clinical remission in RA?

Q12- What is the impact with respect to outcome of imaging-detected inflammation /damage in the patient in clinical remission?

Q13- When (time and under what clinical circumstances), where (which joints), how (modality specifics) how often, and with what imaging modality do we need to image the spine in RA?

Study inclusion criteria

Types of study

We will include papers with English abstracts that report data on individuals. Non-human studies will therefore be excluded.

Study designs that may be included are:

- Systematic literature reviews
- Randomised control trials or other experimental studies
- Cohort (prospective or retrospective)
- Case-control studies
- Cross-sectional studies

Participants

We will be including studies based on adult participants, aged 18 years and over with a diagnosis of RA, as defined by the American College of Rheumatologists (ACR) criteria. The criteria and methods used in studies to define cases of RA will be considered when assessing study quality.

Interventions

Due to the highly overlapping nature of the questions, we propose to perform one search that encompasses all of the questions listed above.

Studies that report the relationship between a given diagnostic intervention and one of the outcomes of the review will be included in the review.

The diagnostic interventions are:

- Conventional radiographs
- Ultrasound
- Magnetic resonance imaging (MRI)
- Computed tomography (CT)
- Dual-emission X-ray absorptiometry (DXA) and digital X-ray radiogrammetry (DXR)
- Scintigraphy
- Positron emission tomography (PET)

Outcomes and comparisons

Q1- Detection of inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical evaluation

Q2- Detection of tissue damage (bone, cartilage, tendons, ligaments) above clinical examination

Q3- Differential diagnostic value of individual imaging modalities

Q4- Diagnostic value above clinical criteria

Q5- Prognostic (prediction of outcome) value

Q6- Prognostic (prediction of therapeutic response) value

Q7- Prognostic (prediction of outcome) value above other known prognostic markers

(Outcome=activity, damage, Qol, HAQ, mortality, surgery, HE, cumulative/AUC/temporal change)

Q8- Prognostic (prediction of therapeutic response) value above other known prognostic markers

(Outcome=activity, damage, Qol, HAQ, mortality, surgery, HE, cumulative/AUC/temporal change)

Q9- When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease inflammation?

Q10- When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease damage?

Q11- Relationship between individual imaging modalities and clinical remission in RA

Q12- Impact with respect to outcome of imaging-detected inflammation /damage in the patient in clinical remission

Q13- When (time and under what clinical circumstances), where (which joints), how (modality specifics) how often, and with what imaging modality do we need to image the spine in RA?

Exclusion criteria

The following studies will be excluded:

- Case reports
- Descriptive reviews

Study settings and timing

We plan to include all studies that contribute relevant information, regardless of the setting. The study setting will be noted as part of the data extraction process and the degree to which its findings can be applied in normal clinic practise will be considered when assessing the study quality.

Search strategy for identification of studies

Search strategy

Our search strategy will aim to identify studies that satisfy our stated inclusion criteria, and describe the use of the imaging techniques listed above in the diagnosis and management of RA.

The following resources will be searched:

- Electronic databases – Medline, Embase, Cochrane database of systematic reviews, Cochrane library
- Bibliographies of selected papers

The years of search to be included are 1948 to the present day.

Search terms

Search terms will be developed with the input of an information specialist. We will use a combination of MeSH terms and free text. Combinations of search terms will be selected to ensure that studies relating imaging in RA are retrieved. The combination of search terms used will also include a study design facet.

Methods of the review

Screening of abstracts

When applying selection criteria, all abstracts will be independently assessed by one reviewer. Indecision will be resolved by discussion with the principal investigator.

Data extraction

Data will be extracted by one reviewer, and separate data extraction forms will be used to mark or correct errors or disagreements and for use in future methodological work.

Data will be extracted onto an electronic form containing the following items:

General information (date of extraction; reviewer details); study information (type of study; inclusion/exclusion criteria); study population characteristics; baseline data (age, sex, ethnicity); methods of assessment of disease activity; diagnostic criteria adhered to; quality criteria; outcomes (what they were and how they were obtained); confounding factors (see below); analysis (statistical techniques, sample size based on power calculation, adjustment for confounding, losses to follow up); results (direction of relationship, size of effect and measure of precision of effect estimate such as 95% confidence interval or standard error).

Confounding factors

It will be important to assess whether or not studies have adequately controlled for important variables that could act as potential modifying or confounding factors. The following are considered to be important potential confounding factors in the assessment of a diagnostic intervention in inflammatory arthritis: sex, smoking status, socio-economic status, family history of RA, presence of the shared epitope (SE), age, time duration of symptoms prior to seeking medical attention, rheumatoid factor (RhF) positivity at baseline, anti-cyclic citrullinated peptide antibody (anti-CCP) positivity at baseline, adverse events occurring as a consequence of the diagnostic intervention being used in the study.

For each study included in the review, we will record whether important confounding variables have been assessed and whether or not they have been adjusted for the in statistical analysis. This information will be then be used in the quality assessment.

Appendix B Details of RA imaging search strategy

Search strategy, MEDLINE

1. exp arthritis, rheumatoid/

2. ((rheumat$ or reumat$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. 1 or 2

4. Diagnostic Imaging/

5. Radiography/

6. exp Magnetic Resonance Imaging/

7. magnetic resonance.tw.

8. mri$.tw.

9. exp Ultrasonography/

10. (ultrasonic adj (diagnos$ or tomography or imaging$)).tw.

11. echotomograph$.tw.

12. echograph$.tw.

13. ultrasonography$.tw.

14. ultrasound.tw.

15. sonograph$.tw.

16. exp Tomography, X-Ray Computed/

17. exp Contrast Media/

18. computed adj2 tomography.tw.

19. cat scan$.tw.

20. ct.tw.

21. X-Rays/

22. xray$.tw.

23. (roentgen adj ray$).tw.

24. Absorptiometry, Photon/

25. Absorptiometr$.tw.

26. ((dxa or dexa) adj scan$).tw.

27. radiogram$.tw.
28. dxr.tw.
29. Radionuclide Imaging/
30. (Scintigraph$ or scintiphotograph$).tw.
31. ((gamma camera or radionuclide) adj imag$).tw.
32. radioisotope scan$.tw.
33. Positron-Emission Tomography/
34. Positron emission tomograp$.tw.
35. pet scan$.tw.
36. or/4-35
37. 3 and 36
38. randomized controlled trial.pt.
39. controlled clinical trial.pt.
40. randomized.ab.
41. placebo.ab.
42. drug therapy.fs.
43. randomly.ab.
44. trial.ab.
45. groups.ab.
46. or/38-45
47. (animals not (humans and animals)).sh.
48. 46 not 47
49. 37 and 48
50. exp cohort studies/
51. cohort$.tw.
52. controlled clinical trial.pt.
53. epidemiologic methods/
54. limit 53 to yr=1966-1989
55. exp case-control studies/
56. (case$ and control$).tw.
57. or/50-52,54-56

58. 37 and 57

59. ("review" or "review academic" or "review tutorial").pt.

60. (medline or medlars or embase or pubmed).tw,sh.

61. (scisearch or psychinfo or psycinfo).tw,sh.

62. (psychlit or psyclit).tw,sh.

63. cinahl.tw,sh.

64. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.

65. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.

66. (pooling or pooled or mantel haenszel).tw,sh.

67. (retraction of publication or retracted publication).pt.

68. (peto or dersimonian or der simonian or fixed effect).tw,sh.

69. or/60-68

70. 59 and 69

71. meta-analysis.pt.

72. meta-analysis.sh.

73. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.

74. (systematic$ adj5 review$).tw,sh.

75. (systematic$ adj5 overview$).tw,sh.

76. (quantitativ$ adj5 review$).tw,sh.

77. (quantitativ$ adj5 overview$).tw,sh.

78. (quantitativ$ adj5 synthesis$).tw,sh.

79. (methodologic$ adj5 review$).tw,sh.

80. (methodologic$ adj5 overview$).tw,sh.

81. (integrative research review$ or research integration).tw.

82. or/71-81

83. 37 and 82

84. limit 37 to "diagnosis (best balance of sensitivity and specificity)"

85. or/49,58,83-84

Search strategy, EMBASE

1. exp rheumatoid arthritis/

2. ((rheumat$ or reumat$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. 1 or 2

4. diagnostic imaging/

5. radiography/

6. exp nuclear magnetic resonance imaging/

7. magnetic resonance.tw.

8. mri$.tw.

9. exp echography/

10. (ultrasonic adj (diagnos$ or tomography or imaging$)).tw.

11. echotomograph$.tw.

12. echograph$.tw.

13. ultrasonography$.tw.

14. ultrasound.tw.

15. sonograph$.tw.

16. exp computer assisted tomography/

17. exp contrast medium/

18. (computed adj2 tomography).tw.

19. cat scan$.tw.

20. ct.tw.

21. X ray/

22. xray$.tw.

23. (roentgen adj ray$).tw.

24. photon absorptiometry/

25. Absorptiometr$.tw.

26. ((dxa or dexa) adj scan$).tw.

27. radiogram$.tw.

28. dxr.tw.

29. scintiscanning/

30. (Scintigraph$ or scintiphotograph$).tw.

31. ((gamma camera or radionuclide) adj imag$).tw.

32. radioisotope scan$.tw.

33. positron emission tomography/

34. Positron emission tomograp$.tw.

35. pet scan$.tw.

36. or/4-35

37. 3 and 36

38. (random$ or placebo$).ti,ab.

39. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.

40. controlled clinical trial$.ti,ab.

41. RETRACTED ARTICLE/

42. or/38-41

43. (animal$ not human$).sh,hw.

44. 42 not 43

45. 37 and 44

46. exp cohort analysis/

47. exp longitudinal study/

48. exp prospective study/

49. exp follow up/

50. cohort$.tw.

51. exp case control study/

52. (case$ and control$).tw.

53. or/46-52

54. 37 and 53

55. exp review/

56. (literature adj3 review$).ti,ab.

57. exp meta analysis/

58. exp "Systematic Review"/

59. or/55-58

60. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.

61. RETRACTED ARTICLE/

62. 60 or 61

63. 59 and 62

64. (systematic$ adj2 (review$ or overview)).ti,ab.

65. (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.

66. or/63-65

67. 37 and 66

68. limit 37 to "diagnosis (best balance of sensitivity and specificity)"

69. or/45,54,67-68

Search strategy, The Cochrane Library

#1 MeSH descriptor Arthritis, Rheumatoid explode all trees

#2 ((rheumat* or reumat*) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab

#3 (#1 OR #2)

#4 MeSH descriptor Diagnostic Imaging, this term only

#5 MeSH descriptor Radiography, this term only

#6 MeSH descriptor Magnetic Resonance Imaging explode all trees

#7 "magnetic resonance":ti,ab

#8 mri*:ti,ab

#9 MeSH descriptor Ultrasonography explode all trees

#10 (ultrasonic next (diagnos* or tomography or imaging*)):ti,ab

#11 echotomograph*:ti,ab

#12 echograph*:ti,ab

#13 ultrasonography:ti,ab

#14 ultrasound:ti,ab

#15 sonograph*:ti,ab

#16 MeSH descriptor Tomography, X-Ray Computed explode all trees

#17 MeSH descriptor Contrast Media explode all trees

#18 "computed tomography":ti,ab

#19 "Cat scan*":ti,ab

#20 ct:ti,ab

#21 MeSH descriptor X-Rays, this term only

#22 xray*:ti,ab

#23 (roentgen next ray*):ti,ab

#24 MeSH descriptor Absorptiometry, Photon, this term only

#25 Absorptiometr*:ti,ab

#26 ((dxa or dexa) next scan*):ti,ab

#27 radiogram*:ti,ab

#28 dxr:ti,ab

#29 MeSH descriptor Radionuclide Imaging, this term only

#30 (Scintigraph* or scintiphotograph*):ti,ab

#31 ((gamma camera or radionuclide) next imag*):ti,ab

#32 "radioisotope scan*":ti,ab

#33 MeSH descriptor Positron-Emission Tomography, this term only

#34 "Positron emission tomograp*":ti,ab

#35 "pet scan*":ti,ab

#36 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)

#37 (#3 AND #36)

Appendix C Number of included articles per RA imaging review question

	Number of included articles
Q1- What is the evidence for the differential diagnostic value of individual imaging modalities for RA?	3
Q2- What is the evidence for the diagnostic value above clinical criteria of individual imaging modalities for RA?	15
Q3- What is the evidence for the added value (sensitivity , specificity etc) of individual imaging modalities in detecting inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical evaluation?	51
Q4- What is the evidence of the added value above clinical examination for the comparative value (sensitivity, specificity etc) of individual imaging modalities in detecting tissue damage (bone, cartilage, tendons, ligaments)?	3
Q5- What is the evidence for the prognostic (prediction of outcome) value of individual imaging modalities for RA?	12
Q6- What is the evidence for the prognostic (prediction of outcome) value above other known prognostic markers of individual imaging modalities for RA?	38
Q7- What is the evidence for the prognostic (prediction of therapeutic response) value of individual imaging modalities for RA?	0

Q8- What is the evidence for the prognostic (prediction of therapeutic response) value above other known prognostic markers of individual imaging modalities for RA?	2
Q9- When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease inflammation?	23
Q10- When (time and under what clinical circumstances), where (which joints), how (modality specifics) and how often, and with what imaging modality should we monitor RA disease damage?	55
Q11- When (time and under what clinical circumstances), where (which joints), how (modality specifics) how often, and with what imaging modality do we need to image the spine in RA?	13
Q12- What is the relationship between individual imaging modalities and clinical remission in RA?	7
Q13- What is the impact with respect to outcome of imaging-detected inflammation /damage in the patient in clinical remission?	7

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Appendix D Reference list of included articles per RA imaging recommendation

Recommendation 1. (in patients with at least one joint with definite clinical synovitis)

When there is diagnostic doubt, conventional radiography, US or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.

1. Agrawal S, Bhagat SS, Dasgupta B. Improvement in diagnosis and management of musculoskeletal conditions with one-stop clinic-based ultrasonography. *Mod Rheumatol* 2009;19:53-56.

2. Matsos MP, Khalidi N, Zia P, et al. Ultrasound of the hands and feet for rheumatological disorders: influence on clinical diagnostic confidence and patient management. *Skeletal Radiol* 2009;38:1049–1054.

3. Narváez J, Sirvent E, Narváez JA, et al. Usefulness of magnetic resonance imaging of the hand versus anticyclic citrullinated peptide antibody testing to confirm the diagnosis of clinically suspected early rheumatoid arthritis in the absence of rheumatoid factor and radiographic erosions. *Semin Arthritis Rheum* 2008;38:101-109.

4. Sugimoto H, Takeda A, Masuyama J, et al. Early-stage rheumatoid arthritis: diagnostic accuracy of MR imaging. *Radiology* 1996;198:185-192.

5. Sugimoto H, Takeda A, Hyodoh K. Early-stage rheumatoid arthritis: Prospective study of the effectiveness of MR imaging for diagnosis. *Radiology* 2000;216:569-575.

Recommendation 2. The presence of inflammation seen with US or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis

1. de Bois MHW, Arndt JW, Speyer I, et al. Technetium-99m labelled human immunoglobulin scintigraphy predicts rheumatoid arthritis in patients with arthralgia. *Scand J Rheumatol* 1996;25:155-158.

2. Duer A, Østergaard M, Hørslev-Petersen K, et al. Magnetic resonance imaging and bone scintigraphy in the differential diagnosis of unclassified arthritis. *Ann Rheum Dis* 2008;67;48-51.

3. Duer-Jensen A, Horslev-Petersen K, Hetland ML, et al. MRI bone edema is an independent predictor of development of rheumatoid arthritis in patients with early undifferentiated arthritis. *Arthritis Rheum* 2011;63:2192–2202.

4. Eshed I, Feist E, Althoff CE, et al. Tenosynovitis of the flexor tendons of the hand detected by MRI: an early indicator of rheumatoid arthritis *Rheumatology (Oxford)* 2009;48:887-891.

5. Filer A, De Pablo P, Allen G, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis* 2011;70:500-507.

6. Mori G, Tokunaga D, Takahashi KA, et al. Maximum intensity projection as a tool to diagnose early rheumatoid arthritis. *Mod Rheumatol* 2008;18:247–251.

7. Ozgul A, Yasar E, Arslan N, et al. The comparison of ultrasonographic and scintigraphic findings of early arthritis in revealing rheumatoid arthritis according to criteria of American College of Rheumatology. *Rheumatol Int* 2009;29:765–768.

8. Petre MA, Cheng CK, Boire G, et al. Prognostic value of patient history, radiography and serology on poor outcomes in undifferentiated inflammatory arthritis patients (abstract). *Arthritis Rheum* 2009;60 Suppl 10:1191.

9. Salaffi F, Ciapetti A, Gasparini S, et al. A clinical prediction rule combining routine assessment and power Doppler ultrasonography for predicting progression to rheumatoid arthritis from early-onset undifferentiated arthritis. *Clin Exp Rheumatol* 2010;28: 686-694.

10. Solou-Gervais E, Legrand J-L, Cortet B, et al. Magnetic resonance imaging of the hand for the diagnosis of rheumatoid arthritis in the absence of anti-cyclic citrullinated peptide antibodies: a prospective study. *J Rheumatol* 2006;33:1760–1765.

11. Tamai M, Kawakami A, Uetani M, et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of

the wrists and finger joints and serologic autoantibodies. *Arthritis Rheum* 2009:61, No. 6;772–778.

12. Zhang L, Li J, He W, et al. The prediction and evaluation of the progression to rheumatoid arthritis in 157 patients with undifferentiated arthritis (abstract). *Int J Rheum Dis* 2010;13 Suppl 1:0908.

Recommendation 3. US and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation

1. Andonopoulos AP, Yarmenitis S, Sfountouris H, et al. Baker's cyst in rheumatoid arthritis: an ultrasonographic study with a high resolution technique. *Clin Exp Rheumatol* 1995;13:633-636.

2. Bajaj S, Lopez-Ben R, Oster R, Alarcón GS. Ultrasound detects rapid progression of erosive disease in early rheumatoid arthritis: a prospective longitudinal study. *Skeletal Radiol* 2007;36:123–128.

3. Batalov A, Kuzmanova S, Atanasov. Ultrasound follow-up study of arthroscoped patients with gonitis. *Folia Medica* 1999;41:63-70.

4. Beckers C, Ribbens C, André B, et al. Assessment of disease activity in rheumatoid arthritis with ^{18}F-FDG PET. *J Nucl Med* 2004;45:956-964.

5. Calisir C, Murat Aynaci AI, Korkmaz C. The accuracy of magnetic resonance imaging of the hands and feet in the diagnosis of early rheumatoid arthritis. *Joint Bone Spine* 2007;74:362-7.

6. Carotti M, Salaffi F, Manganelli P, et al. Power Doppler sonography in the assessment of synovial tissue of the knee joint in rheumatoid arthritis: a preliminary experience. *Ann Rheum Dis* 2002;61:877-882.

7. Chávez-López MA, Naredo E, Acebes-Cachafeiro JC, et al. Diagnostic accuracy of physical examination of the knee in rheumatoid arthritis: Clinical and ultrasonographic study of joint effusion and Baker's cyst. *Reumatol Clin* 2007;3:98-100.

8. Cheung PP, Ruyssen-Witrand A, Gossec L, et al. Reliability of patient self-evaluation of swollen and tender joints in rheumatoid arthritis: a comparison study with ultrasonography, physician, and nurse assessments. *Arthritis Care Res* 2010;62:1112-1119.

9. Cindaş A, Gökçe-Kutsal Y, Özgen Kirth P, et al. Scintigraphic evaluation of synovial inflammation in rheumatoid arthritis with ^{99m}technetium-labelled human polyclonal immunoglobulin G. *Rheumatol Int* 2001;20:71-77.

10. Damjanov N, Radunović G, Prodanović S, et al. Construct validity and reliability of ultrasound disease activity score in assessing joint inflammation in RA: comparison with DAS-28. *Rheumatology (Oxford)* 2012;51:120-128.

11. de Bois MH, Tak PP, Arndt JW, et al. Joint scintigraphy for quantification of synovitis with ^{99m}Tc-labelled human immunoglobulin G compared to histological examination. *Clin Exp Rheumatol* 1995;13:155-159.

12. Emery P, van der Heijde D, Østergaard M, et al. Exploratory analyses of the association of MRI with clinical, laboratory and radiographic findings in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:2126–2130.

13. Filippucci E, Iagnocco A, Salaffi F, et al. Power Doppler sonography monitoring of synovial perfusion at the wrist joints in patients with rheumatoid arthritis treated with adalimumab. *Ann Rheum Dis* 2006;65:1433-1437.

14. Forslind K, Johanson A, Larsson EM et al. Magnetic resonance imaging of the fifth metatarsophalangeal joint compared with conventional radiography in patients with early rheumatoid arthritis. *Scand J Rheumatol* 2003;32:131-137.

15. Forslind K, Larsson EM, Eberhardt K, et al. Magnetic resonance imaging of the knee: a tool for prediction of joint damage in early rheumatoid arthritis? *Scand J Rheumatol* 2004;33:154–161.

16. Goerres GW, Forster A, Uebelhart D, et al. F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. *Clin Nucl Med* 2006;31: 386–390.

17. Goupille P, Roulot B, Akoka S, et al. Magnetic resonance imaging: a valuable method for the detection of synovial inflammation in rheumatoid arthritis. *J Rheumatol* 2001;28:35-40.

18. Haavardsholm EA, Ostergaard M, Hammer HB, et al. Monitoring anti-TNF alpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. *Ann Rheum Dis* 2009;68:1572-1579.

19. Hammer HB, Sveinsson M, Kongtorp AK, et al. A 78-joints ultrasonographic assessment is associated with clinical assessments and is highly responsive to improvement in a longitudinal study of patients with rheumatoid arthritis starting adalimumab treatment. *Ann Rheum Dis* 2010;69:1349–1351.

20. Hmamouchi I, Bahiri R, Srifi N, et al. A comparison of ultrasound and clinical examination in the detection of flexor tenosynovitis in early arthritis. *BMC Musculoskelet Disord* 2011;12:91.

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Recommendation 4. Conventional radiography of the hands and feet should be used as the initial imaging technique to detect damage. However, US and/or MRI should be considered if conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA)

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Recommendation 5. MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by

MRI or US as well as joint damage detected by conventional radiographs, MRI or US can also be considered for the prediction of further joint damage

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Recommendation 6. Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment

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Recommendation 7. Given the improved detection of inflammation by MRI and US than by clinical examination, they may be useful in monitoring disease activity

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Recommendation 8. The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly US) is more responsive to change in joint damage and can be used to monitor disease progression

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Appendix E JIA imaging systematic review protocol according to AGREE II

Proposed Title

EULAR-PReS Points to Consider for the Use of Imaging in the Diagnosis and Management of Juvenile Idiopathic Arthritis in Clinical Practice

Contact author name

Alexandra Colebatch

Christopher Edwards

Domain 1. Scope and Purpose

1. Overall objective: to produce validated, evidence and consensus-based recommendations for the use of conventional radiography (CR), ultrasonography (US), magnetic resonance imaging (MRI), scintigraphy, computerised tomography (CT) and positron emission tomography (PET) in the diagnosis, monitoring and management of patients with JIA.

2. Description of specific health question: which imaging modality should be used in the diagnosis, monitoring and management of patients with JIA?

Clinical questions:

Agreed by a process of discussion and consensus.

i. What is the evidence for the added value (sensitivity, specificity etc) of individual modalities in detecting inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical examination according to age?

ii. What is the evidence for the added value above clinical evaluation and the comparative value (sensitivity, specificity etc) of individual imaging modalities in detecting age-related structural abnormalities and damage in JIA (bone, cartilage, tendons, ligaments)?

- ROM, deformity

- “reference standard” vs “gold standard”

– Use of x-fold detection rate

iii. What is the evidence for the differential diagnostic value of individual imaging modalities for JIA?

- Consideration of disease subtypes will come after literature review

iv. What is the evidence for the diagnostic value above clinical criteria of individual imaging modalities for JIA?

v. What is the evidence for the prognostic (prediction of therapeutic response) value of individual imaging modalities for JIA?

– Definition of outcome:

· clinical (ACR Pedi, JADAS, joint count, CHAQ, JADI, health related QoL, clinically inactive disease, remission, time to flare)

· Imaging – structural damage

(Outcome = activity, damage, QoL, HAQ, mortality, surgery, HE, cumulative/AUC/temporal change)

vi. What is the evidence for the prognostic (prediction of outcome) value of individual imaging modalities for JIA?

– Definition of outcome:

· clinical (CHAQ, JADI, health related QoL, clinically inactive disease, remission)

· Imaging – structural damage

(Outcome = activity, damage, QoL, HAQ, mortality, surgery, HE, cumulative/AUC/temporal change)

vii. When (time), where (which joints), how often and with what imaging modality should we monitor JIA disease inflammation?

- Target joints - TMJ and spine

viii. When (time), where (which joints), how often and with what imaging modality should we monitor age-related structural abnormalities and damage in JIA?

- Target joints - TMJ and spine

ix. What is the relationship between individual imaging modalities and clinical remission in JIA?

- Definition of clinical remission:

· Remission on treatment

· Remission off treatment

· Low disease activity

x. What is the impact with respect to outcome of imaging-detected inflammation/damage in the patient in clinical remission?

- To include patient outcomes and treatment

3. Population: all patients with JIA, diagnosis confirmed aged <16 (no exclusions)

Domain 2. Stakeholder Involvement

4. Professional groups of the guideline development group: need speciality, hospital and role in group

i. Prof Alberto Martini, paediatric rheumatologist (Genoa, Italy)

ii. Dr Marion van Rossum, paediatric rheumatologist (Amsterdam, The Netherlands)

iii. Dr Paz Collado, paediatric rheumatologist (Madrid, Spain)

iv. Dr Esperanza Naredo, rheumatologist (Madrid, Spain)

v. Dr Sandrine Jousse-Joulin, rheumatologist (Brest, France)

vi. Dr Madeleine Rooney, paediatric rheumatologist (Belfast, Northern Ireland)

vii. Dr Nikolay Tzaribachev, paediatric rheumatologist (Bad Bramstedt, Germany)

viii. Prof Mikkel Østergaard, rheumatologist (Copenhagen,Denmark)

ix. Prof Maria Antonietta D'Agostino, rheumatologist (Paris, France)

x. Jelena Vojinovic, paediatric rheumatologist (Nis, Serbia)

xi. Robert Hemke, radiologist (Amsterdam, The Netherlands)

xii. Prof Philip Conagham, co-convenor and rheumatologist (Leeds, UK)

xiii. Dr Clara Malattia, co-convenor and paediatric rheumatologist (Genoa, Italy)

xiv. Dr Christopher Edwards, clinical epidemiologist and rheumatologist (Southampton, UK)

xv. Dr Alexandra Bourn, clinical fellow and rheumatologist (Southampton, UK)

xvi. Louise Falzon, Information Specialist, Center for Behavioral Cardiovascular Health, Columbia University Medical Center

5. Views of target population

6. Target users of the guideline: All secondary care professionals involved in the care of people with JIA including rheumatologists, paediatricians and radiologists to inform clinical decisions on appropriate imaging in patients with JIA

Domain 3. Rigour of Development

7. Search methodology:

i. Search resources: Electronic databases – Medline, Embase, Cochrane database of systematic reviews, Cochrane library; bibliographies of selected papers

ii. Search period: 1948 to the present day

iii. Search terms: to be written in conjunction with the expert help of an experienced information specialist, using a combination of specific medical subject headings (MeSH) and free text. Combinations of search terms will be selected to ensure that studies relating imaging in JIA are retrieved. The full search strategy will be included in the appendix.

8. Selection inclusion criteria:

i. Population: patients with JIA diagnosed aged <16

ii. Intervention: imaging modality (CR, US, MRI, scintigraphy, CT, PET)

iii. Comparison: other imaging modalities (CR, US, MRI, scintigraphy, CT, PET) and clinical features

iv. Outcome: diagnosis, monitoring, management of JIA – to be agreed and finalised by the expert panel

v. Study design: systematic literature reviews (SLR), randomised control trials (RCT) or other experimental studies, cohort (prospective or retrospective) and case-control studies, case series/reports n>10

vi. Included languages: English only abstracts with any language full text

vii. Context: not relevant

Selection exclusion criteria: case series/reports n<10, descriptive reviews

9. Evaluation for bias and quality: all included studies will be assessed for bias as appropriate to the study technique, e.g. risk of bias for RCT, and for level of evidence according to BMJ classification schemes in “Developing Guidelines”, *BMJ* 1999;318:594-6.

10. Recommendation development process: following presentation of the data from the literature review, the experts will produce recommendations with final agreement by a process of discussion and consensus, employing the well-described Delphi techniques as employed by previous EULAR recommendation task forces. The experts will score the perceived level of agreement for each proposition using a 0–10 visual analogue scale.

11. Consequences of the recommendations: provision of clinical implication recommendations for the use of CR, US, MRI, scintigraphy, CT and PET in patients with JIA as none exists currently. The elaboration of the evidence for all three imaging modalities in JIA will result in the production of a set of evidence based recommendations for their use in daily practice. There are no risks involved in the review process or the production of these recommendations. The

recommendations will actually ensure that any radiation exposure resulting from imaging is clinically indicated and appropriate.

12. Link between the supporting evidence and recommendations: each recommendation will be informed and supported by the evidence obtained by the systematic literature review. This will be summarised after each recommendation with the aid of evidence tables and references.

13. External review of the guideline: the guideline will be subject to review by the EULAR committee. It will then be submitted for comments to a peer reviewed journal and modified accordingly before publication and dissemination.

14. Updating the guideline: a statement of recommendation to update the guidelines after a specific interval (5 years), and using a similar vigorous technique will be included.

Domain 4. Clarity of Presentation

15. Clarity of recommendations: each recommendation will include the overall statement, the purpose of the recommendation, a description of the relevant population and any caveats.

16. Consideration of different possible options for screening, diagnosis and monitoring of JIA: specifically when different imaging modalities should be used will be considered.

17. Identification of recommendations: these will be included in a separate box, and highlighted in the main text using italic text.

Domain 5. Applicability

18. Facilitators and barriers to application: there may be insufficient access to individual imaging modalities restricting application of the recommendations. This will be considered in the formulation of the recommendations and discussed in the manuscript.

19. Implementation of the recommendations in practice: the recommendations will be disseminated by means of presentation at European meetings and publication in a peer reviewed journal.

20. Resource implications of the recommendations: some consideration of the cost implication of the recommendations will be made, but the primary aim is to discuss clinical implications.

21. Monitoring/audit criteria: it may not be possible to produce clear monitoring or audit criteria but these will be considered where possible. Possible areas to audit include the availability of imaging and assessment of adherence to the recommendations.

Domain 6. Editorial Independence

22. Influence of funding body: We would like to thank EULAR for financial support for this work. The funding body did not influence the content of these recommendations.

23. Completing interests: declared by all members of the guideline development group.

Appendix F Details of JIA imaging search strategy

Search Strategy, MEDLINE

1. exp Arthritis, Juvenile Rheumatoid/
2. (juvenile$ adj3 arthrit$).tw.
3. jia.tw.
4. or/1-3
5. exp ARTHRITIS/
6. arthrit$.tw.
7. (still$ adj disease).tw.
8. Oligoarthrit$.tw.
9. Polyarthrit$.tw.
10. or/5-9
11. exp Child/
12. Adolescent/
13. child$.tw.
14. adolesc$.tw.
15. juvenile$.tw.
16. teenage$.tw.
17. youth$.tw.
18. or/11-17
19. 10 and 18
20. 4 or 19
21. exp Diagnostic Imaging/
22. magnetic resonance.tw.
23. mri$.tw.
24. (ultrasonic adj (diagnos$ or tomography or imaging$)).tw.
25. echotomograph$.tw.
26. echograph$.tw.

27. ultrasonograph$.tw.
28. ultrasound.tw.
29. sonograph$.tw.
30. exp Contrast Media/
31. (computed adj2 tomography).tw.
32. cat scan$.tw.
33. ct.tw.
34. X-Rays/
35. (xray$ or x-ray$).tw.
36. Arthrograph$.tw.
37. radiograph$.tw.
38. radiolog$.tw.
39. (roentgen adj ray$).tw.
40. (Scintigraph$ or scintiphotograph$).tw.
41. ((gamma camera or radionuclide) adj imag$).tw.
42. radioisotope scan$.tw.
43. Positron emission tomograp$.tw.
44. (pet scan$ or pet-scan$).tw.
45. or/21-44
46. 20 and 45

Search Strategy, EMBASE

1. juvenile rheumatoid arthritis/
2. (juvenile$ adj3 arthrit$).tw.
3. jia.tw.
4. or/1-3
5. exp arthritis/
6. arthrit$.tw.
7. (still$ adj disease).tw.
8. Oligoarthrit$.tw.
9. Polyarthrit$.tw.

10. or/5-9
11. child/
12. adolescent/
13. child$.tw.
14. adolesc$.tw.
15. juvenile$.tw.
16. teenage$.tw.
17. youth$.tw.
18. or/11-17
19. 10 and 18
20. 4 or 19
21. exp diagnostic imaging/
22. exp joint radiography/
23. exp nuclear magnetic resonance imaging/
24. magnetic resonance.tw.
25. mri$.tw.
26. exp echography/
27. (ultrasonic adj (diagnos$ or tomography or imaging$)).tw.
28. echotomograph$.tw.
29. echograph$.tw.
30. ultrasonograph$.tw.
31. ultrasound.tw.
32. sonograph$.tw.
33. exp computer assisted tomography/
34. exp contrast medium/
35. (computed adj2 tomography).tw.
36. cat scan$.tw.
37. ct.tw.
38. X ray/
39. (xray$ or x-ray$).tw.
40. Arthrograph$.tw.

41. radiograph$.tw.
42. radiolog$.tw.
43. (roentgen adj ray$).tw.
44. scintiscanning/
45. (Scintigraph$ or scintiphotograph$).tw.
46. ((gamma camera or radionuclide) adj imag$).tw.
47. radioisotope scan$.tw.
48. positron emission tomography/
49. Positron emission tomograp$.tw.
50. (pet scan$ or pet-scan$).tw.
51. or/21-50
52. 20 and 51

Search Strategy, The Cochrane Library

#1 MeSH descriptor: [Arthritis, Juvenile Rheumatoid] this term only
#2 juvenile* near/3 arthrit*:ti,ab
#3 jia:ti,ab
#4 #1 or #2 or #3
#5 MeSH descriptor: [Arthritis] explode all trees
#6 arthrit*:ti,ab
#7 "still* disease":ti,ab
#8 Oligoarthrit*:ti,ab
#9 Polyarthrit*:ti,ab
#10 #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Child] explode all trees
#12 MeSH descriptor: [Adolescent] this term only
#13 child*:ti,ab
#14 adolesc*:ti,ab
#15 juvenile:ti,ab
#16 teenage*:ti,ab
#17 youth*:ti,ab

#18 #11 or #12 or #13 or #14 or #15 or #16 or #17

#19 #10 and #18

#20 #4 or #19

#21 MeSH descriptor: [Diagnostic Imaging] explode all trees

#22 "magnetic resonance":ti,ab

#23 mri*:ti,ab

#24 (ultrasonic next (diagnos* or tomography or imaging*)):ti,ab

#25 echotomograph*:ti,ab

#26 echograph*:ti,ab

#27 ultrasonograph*:ti,ab

#28 ultrasound:ti,ab

#29 sonograph*:ti,ab

#30 MeSH descriptor: [Contrast Media] explode all trees

#31 computed near/2 tomography:ti,ab

#32 "cat scan*":ti,ab or cat-scan*:ti,ab

#33 ct:ti,ab

#34 MeSH descriptor: [X-Rays] this term only

#35 xray*:ti,ab or x-ray*:ti,ab

#36 Arthrograph*:ti,ab

#37 radiograph*:ti,ab

#38 radiolog*:ti,ab

#39 "roentgen ray*":ti,ab

#40 (Scintigraph* or scintiphotograph*):ti,ab

#41 (("gamma camera" or radionuclide) next imag*):ti,ab

#42 "radioisotope scan*":ti,ab

#43 "Positron emission tomograp*":ti,ab

#44 ("pet scan*" or pet-scan*):ti,ab

#45 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44

#46 #20 and #45

Appendix G Number of included articles per JIA imaging review question

	No. of included articles
Q1 - What is the evidence for the differential diagnostic value of individual imaging modalities for JIA?	4
Q2 - What is the evidence for the diagnostic value above clinical criteria of individual imaging modalities for JIA?	2
Q3 - What is the evidence for the added value (sensitivity, specificity etc) of individual imaging modalities in detecting inflammation (synovitis, tenosynovitis, osteitis, bursitis, enthesitis) above clinical evaluation according to age?	65
Q4 - What is the evidence for the added value above clinical examination for the comparative value (sensitivity, specificity etc) of individual imaging modalities in detecting age-related structural abnormalities and damage in JIA (bone, cartilage, tendons, ligaments)?	37
Q5 - What is the evidence for the prognostic (prediction of therapeutic response) value of individual imaging modalities for JIA?	1
Q6 - What is the evidence for the prognostic (prediction of outcome) value of individual imaging modalities for JIA?	13
Q7 - When (time), where (which joints), how often and with what imaging modality should we monitor JIA disease inflammation?	39
Q8 - When (time), where (which joints), how often and with what imaging modality should we monitor age-related structural abnormalities and damage in JIA?	57

Q9 - What is the role of imaging for the monitoring of systemic treatment (corticosteroids, synthetic and biological DMARDs) and the targeted delivery of local treatments such as intra-articular injections?	40
Q10- What is the relationship between individual imaging modalities and clinical remission in JIA?	16
Q11- What is the impact with respect to outcome of imaging-detected inflammation /damage in the patient in clinical remission?	5

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Appendix H Scores for risk of bias and applicability of the JIA imaging studies included according to QUADAS-2

Point to consider			RoB				Applicability		
			Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1	US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, both in diagnosis and assessing extent of joint involvement.	Low (%)	43	41.5	95.4	53.8	97	92.3	92.3
		High (%)	0	6.2	1.5	0	0	0	4.6
		Unclear (%)	56.9	52.3	3.1	46.2	3.1	7.7	3.1
2	When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.	Low (%)	50	50	50	50	66.7	66.7	66.7
		High (%)	0	0	16.7	0	0	0	0
		Unclear (%)	50	50	33.3	50	33.3	33.3	33.3
3	If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.	Low (%)	46.8	41.5	85.1	43.6	96.8	93.6	93.6
		High (%)	0	0	1.1	0	0	1.1	2.1
		Unclear (%)	53.2	56.4	13.8	56.4	3.2	5.3	4.3
4	In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the TMJ and axial involvement	Low (%)	36.8	39.5	89.5	26.3	89.5	89.5	94.7
		High (%)	0	2.6	2.6	0	0	0	0
		Unclear (%)	63.2	57.9	7.9	73.7	10.5	10.5	5.3

5	**Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.**	Low (%)	46.2	46.2	76.9	61.5	92.3	100	100
		High (%)	0	7.7	0	0	0	0	0
		Unclear (%)	53.8	46.2	23.1	3.8	7.7	0	0
6	**In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.**	Low (%)	43.6	33.3	89.7	69.2	100	89.7	84.6
		High (%)	0	12.8	0	0	0	0	7.7
		Unclear (%)	56.4	53.4	10.3	30.8	0	10.3	7.7
7	**The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.**	Low (%)	49.1	45.6	78.9	54.4	98.2	93.0	91.2
		High (%)	0	3.5	1.8	0	0	1.8	3.5
		Unclear (%)	50.9	50.9	19.3	45.6	1.8	5.3	5.3
8	**US can be used for accurate placement of intra-articular injections.**	Low (%)	47.6	19.0	23.9	85.7	85.7	90.5	90.5
		High (%)	0	14.3	14.3	0	0	0	0
		Unclear (%)	52.4	66.7	61.9	14.3	14.3	9.5	9.5
9	**US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.**	Low (%)	29.4	58.9	100	35.3	100	100	100
		High (%)	0	5.9	0	0	0	0	0
		Unclear (%)	70.6	35.3	0	64.7	0	0	0

RoB, risk of bias. *Reproduced from Ann Rheum Dis, Colebatch-Bourn AN, Edwards CJ, Collado P, et al, 74, 1946-57, 2015 with permission from BMJ Publishing Group Ltd*[188].

Appendix I Reference list of included articles per JIA imaging point to consider

PTC 1. US and MRI are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, both in diagnosis and assessing extent of joint involvement.

1. Abdul-Aziez OA, Saber NZ, El-Bakry SA, et al. Serum S100A12 and temporomandibular joint magnetic resonance imaging in juvenile idiopathic arthritis Egyptian patients: a case control study. *Pak J Biol Sci* 2010;13:101-13.

2. Abramowicz S, Susarla HK, Kim S, et al. Physical findings associated with active temporomandibular joint inflammation in children with juvenile idiopathic arthritis. *J Oral Maxillofac Surg* 2013;71:1683-7.

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PTC 3. If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.

1. Abdul-Aziez OA, Saber NZ, El-Bakry SA, et al. Serum S100A12 and temporomandibular joint magnetic resonance imaging in juvenile idiopathic arthritis Egyptian patients: a case control study. *Pak J Biol Sci* 2010;13:101-13.

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PTC 5. Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.

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PTC 7. The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.

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Appendix J JIA imaging PTC 4: Summary of the included studies comparing imaging and CE in the detection of TMJ damage and inflammation

TMJ damage:							
US TMJ vs. CE **3 studies [21, 24, 30]**		**MRI TMJ vs. CE** **10 studies [1, 6, 9, 11, 12, 13, 20, 21, 23, 30]**		**CR TMJ vs. CE** **11 studies [3, 13-15, 17, 19, 23, 26-28, 31]**		**CT TMJ vs. CE** **3 studies [8, 10, 25]**	
	Detection rate, mean (range) **US vs. CE**		**Detection rate, mean (range)** **MRI vs. CE**		**Detection rate, mean (range)** **CR vs. CE**		**Detection rate, mean (range)** **CT vs. CE**
Bony changes vs. abnormal CE (2 studies) [21, 30]	0.52-fold (0.35-0.69-fold)	**Bony changes vs. abnormal CE** (3 studies) [9, 21, 30]	1.26-fold (0.41-1.69-fold) Condylar damage in 81.6% asymptomatic jt	**Bony changes vs. abnormal CE** (4 studies) [3, 14, 27, 31]	1.54-fold (1.13-1.78-fold)	**Bony changes vs. abnormal CE** (2 studies) [8, 25]	0.86-fold (0.72-1.0-fold) Increase in % pt with symptoms with increasing severity of CT changes
		Abnormal translation vs. facial asymmetry (1 study) [6]	1.20-fold All pt with asymmetry/micrognathia had abnormal MRI translation	**Bony vs. functional changes** (1 study) [19]	1.0-fold No significant correlation		
				Bony changes vs. chin deviation (2 studies) [26, 28]	1.71-fold (1.58-1.83) OR 4.9, p 0.002		
				Bony changes vs. pain on movement (1 study) [28]	4.89-fold OR 5.2, p 0.04		
				Bony changes vs. absence of translation (1 study) [28]	2.0-fold OR 4.9, p 0.002		
				Bony changes vs. crepitation (1 study) [28]	5.5-fold OR 10.1, p 0.011		

		Bony changes vs. reduced MIO (2 studies) [11, 23]	5.63-fold p 0.002	**Bony changes vs. reduced MIO** (4 studies) [15, 19, 23, 27]	1.75-fold (1.39-2.40) r -0.46, p<0.001	**Bony changes vs. facial asymmetry** (1 study) [10]	Correlation: 0.303 p<0.05
				Bony changes vs. tenderness (1 study) [15]	1.07-fold No significant correlation		
Erosions vs. abnormal CE (1 study) [24]	Agreement: 81.9% kappa: 0.57	**Erosions vs. abnormal CE** (5 studies) [1, 12, 13, 20, 21, 30]	0.86-fold (0.63-1.0-fold) Erosions in 57.9% asymptomatic jt	**Erosions vs. abnormal CE** (2 studies) [13, 17]	1.71-fold (0.67-2.78-fold)		
				Clinical indicators of CR TMJ arthritis (1 study) [26]	reduced MIO, mandibular asymmetry, mandibular deviation: positive discriminator when all 3 factors combined in 86%		
TMJ inflammation:							
US TMJ vs. CE 3 studies [18, 21, 24]		**MRI TMJ vs. CE 8 studies [1, 2, 12, 13, 20, 21, 30, 32]**					
Synovitis/effusion (2 studies) [18, 21]	11.7-fold (0.35-23.0-fold)	**Synovitis** (6 studies) [12, 13, 20, 21, 30, 32]	2.46-fold (1.10-5.91-fold)				
		Synovitis vs. reduced MIO (4 studies) [1, 2, 20, 21]	Significantly correlated Reduced MIO best predictor of active MRI changes				
		Acute changes (1 study) [30]	71% asymptomatic 63% normal CE				

References in appendix I, PTC 4.

CE, clinical examination; CR, conventional radiography; MIO, maximal incisal opening; r, correlation coefficient. *Reproduced from Ann Rheum Dis, Colebatch-Bourn AN, Edwards CJ, Collado P, et al, 74, 1946-57, 2015 with permission from BMJ Publishing Group Ltd*[188].

Appendix K Lay summary of the JIA imaging points to consider

Imaging may be more important than clinical examination in JIA

A EULAR task force has developed nine key points to consider around the use of imaging children with JIA in clinical practice, and a research agenda to help further the evidence.

Introduction

Juvenile idiopathic arthritis is more commonly referred to as JIA, and includes most types of arthritis seen in children. JIA is an inflammatory arthritis that causes pain and swelling in one or more joints. Some children develop long-term joint damage from JIA, but most get better and are able to live close to normal lives.

Imaging techniques are a non-invasive way to be able to look inside the joint. There are several imaging techniques available, including MRI (magnetic resonance imaging), ultrasound and radiography (X-ray). These give doctors a picture of the inside of the joint and may be more accurate than clinical examination. But they involve inconvenience for children and we need to know how to use imaging in a way that most benefits children's care.

What did the authors hope to find?

The authors hoped to find evidence about the role of imaging in the diagnosis and treatment of JIA. This included seeing how well the imaging techniques could detect both potentially treatable inflammation and permanent damage in joints, and how imaging could help in monitoring response to treatment. The study also looked for information on the use of imaging to assess the amount of joint involvement and show whether children are really in remission despite how well they might appear.

Who was studied?

The authors looked at studies that had already been published. These all reported the use of imaging techniques in children with JIA.

How was the study conducted?

A systematic review aims to identify all the published evidence on a particular topic and draw it together into one summary.

The authors used major electronic databases and clinical trial registries to search for trials and studies that reported studies of imaging techniques in children with JIA. The search gave a long list of 13,277 articles. Of these, 204 had the correct type of information and were included in the review.

What were the main findings of the study?

The authors developed nine key points to consider for the role of imaging in JIA. The findings suggest that imaging techniques are better than simple clinical examinations in evaluating joint inflammation. In particular, the authors highlight the importance of newer techniques such as ultrasound and MRI.

1. MRI and ultrasound are better than clinical examination in detecting joint inflammation.
2. When there is doubt, X-ray, MRI or ultrasound can be used to confirm a diagnosis of JIA.
3. MRI or ultrasound may be able to detect damage to the joints sooner than can be seen on an X-ray.
4. Imaging may be more useful in certain joints, for example in the lower back and jaw.
5. Imaging may be used to predict what damage might occur in the future.
6. MRI and ultrasound can be useful to monitor disease activity.
7. Joint damage should be checked for periodically.
8. Ultrasound can be used to guide injections into the joints.
9. MRI and ultrasound can be used for monitoring when the disease shows no clinical symptoms.

The study also helped the authors to develop a research agenda for further studies that are needed in this area.

Are these findings new?

The findings from the individual studies are not new as this is a summary of the available data and evidence that has already been published elsewhere, but they provide an up to date summary of the available evidence in this area and this enabled the expert committee to make new recommendations for everyday care of JIA.

How reliable are the findings?

There were some limitations in the information available. JIA can be complex and not all patients have the same pattern of disease, so comparisons of existing data are not always straightforward.

What do the authors plan on doing with this information?

The authors have produced a research agenda based on the areas where information is currently lacking, and hope that this will encourage researchers to increase studies in this area. If more studies become available and the issues raised in the research agenda are addressed then it is hoped that this systematic review will be repeated in 5 years.

What does this mean for me?

The last decade has seen a major increase in the use of newer imaging (MRI and ultrasound) for adult arthritis and it is hoped that the new recommendations will provide encouragement and a sensible basis for their use in JIA.

There are differences in imaging for children and adults – for example, some techniques require the patient to lie very still for a long time, and this may not be practical for small children – but more research should help to develop better options. With better imaging techniques, children with JIA may receive better care and treatment that is tailored to their disease.

If you would like to know more about imaging and how it may help you or your child, you should talk to your doctor.

Date prepared: November 2015

Appendix L Full reference list for recommendations included in the quality assessment of EULAR management recommendations

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Appendix M Summary of AGREE scores for each EULAR management recommendation

Reference	Domain 1. Scope and Purpose				Domain 2. Stakeholder Involvement				Domain 3. Rigour of Development									Domain 4 . Clarity of Presentation				Domain 5. Applicability					Domain 6. Editorial Independence			Overall score (1-7)	Recommend guidelines?
	1	2	3	Total (/21)	4	5	6	Total (/21)	7	8	9	10	11	12	13	14	Total (/56)	15	16	17	Total (/21)	18	19	20	21	Total (/28)	22	23	Total (/14)		
Management of RA with synthetic and biological DMARDs, 2013 update, 2014 [1]	7	7	7	**21**	7	7	7	**21**	7	7	7	7	7	7	5	7	**54**	7	7	7	**21**	7	7	7	3	**24**	5	7	**12**	**7**	Yes
Steroids in rheumatic diseases, 2013 [2]	5	4	2	**11**	7	6	2	**15**	6	5	4	7	6	7	5	1	**48**	7	6	7	**20**	2	1	2	1	**6**	4	5	**9**	**5**	Yes
Non-pharmacological management of hip and knee OA, 2013 [3]	7	7	7	**21**	7	6	7	**20**	7	7	4	7	6	7	3	2	**43**	7	7	5	**19**	2	1	5	3	**11**	5	3	**11**	**5**	Yes
Imaging in RA, 2013 [4]	7	7	7	**21**	7	1	1	**9**	7	7	3	5	5	7	5	1	**40**	7	7	7	**21**	4	1	3	2	**10**	5	7	**12**	**5**	Yes

Management of adult and paediatric lupus nephritis, 2012 [5]	7	7	2	**16**	5	1	5	**11**	4	4	3	5	5	7	4	1	**47**	5	7	7	**19**	1	1	1	4	**7**	4	3	**7**	**4**	Yes
Management of PsA, 2012 [6]	7	5	5	**17**	6	6	7	**19**	6	6	6	5	6	6	5	5	**45**	7	7	6	**20**	2	7	1	3	**13**	4	5	**9**	**5**	Yes
Role of the nurse in the management of chronic inflammatory arthritis, 2012 [7]	7	4	6	**17**	7	6	7	**20**	7	7	4	5	5	7	5	1	**41**	7	5	7	**19**	2	1	1	1	**5**	5	4	**9**	**5**	Yes
Vaccination in paediatric patients with rheumatic diseases, 2011 [8]	7	7	5	**19**	7	1	1	**9**	6	7	3	6	7	7	5	2	**43**	7	7	7	**21**	1	1	1	1	**4**	5	4	**9**	**5**	Yes
2010 update on the management of AS, 2011 [9]	7	6	7	**20**	5	6	7	**18**	6	6	5	5	6	6	5	2	**41**	7	7	7	**21**	1	1	1	1	**4**	1	4	**5**	**5**	Yes
Management of calcium pyro-phosphate deposition, 2011 [10]	7	6	3	**16**	4	1	1	**6**	4	4	3	6	6	6	5	1	**35**	7	7	6	**20**	3	1	1	1	**6**	5	4	**9**	**4**	Yes

Vaccination in adults with autoimmune inflammatory rheumatic diseases, 2011 [11]	7	7	7	**21**	6	1	4	**14**	5	7	4	6	7	7	5	5	**46**	7	7	7	**21**	1	1	1	2	**5**	5	4	**9**	**5**	Yes
Management of SLE with neuro-psychiatric manifestation, 2010 [12]	7	7	4	**18**	5	5	4	**14**	4	5	4	6	5	7	5	5	**41**	6	6	7	**19**	1	1	1	1	**4**	5	1	**6**	**4**	Yes
Monitoring adverse events of low-dose glucocorticoid therapy, 2010 [13]	7	7	5	**19**	5	5	1	**11**	6	6	4	5	7	6	5	1	**40**	5	7	3	**15**	1	1	1	1	**4**	5	4	**9**	**4**	Yes
Management of RA with synthetic and biological DMARDs, 2010 [14]	7	7	6	**20**	7	6	7	**20**	7	7	6	6	7	7	5	6	**51**	7	7	7	**21**	7	7	7	1	**22**	5	7	**12**	**7**	Yes
CV risk management in patients with RA and other forms of IA, 2010 [15]	7	4	5	**16**	6	1	7	**14**	7	5	4	4	7	7	5	5	**44**	7	7	7	**21**	4	4	1	1	**10**	5	3	**8**	**5**	Yes
Treatment of systemic sclerosis, 2009 [16]	7	7	6	**20**	7	5	5	**19**	7	7	5	7	7	7	1	4	**52**	7	7	7	**21**	4	1	4	4	**10**	5	4	**9**	**6**	Yes

Management of SLE , 2008 [17]	7	7	6	**20**	5	1	6	**12**	4	7	4	7	7	7	5	7	**48**	7	7	7	**21**	1	3	1	3	**8**	5	1	**6**	**5**	Yes
Management of Behçet disease, 2008 [18]	7	2	4	**13**	7	5	7	**19**	4	1	4	7	5	7	1	3	**32**	7	7	7	**21**	1	1	1	1	**4**	5	4	**9**	**4**	Yes
Management of fibromyalgia syndrome, 2008 [19]	7	2	5	**14**	5	1	4	**10**	5	5	5	5	7	7	1	4	**39**	7	7	7	**21**	1	1	3	1	**6**	5	7	**12**	**5**	Yes
Management of systemic glucocorticoid therapy in rheumatic diseases, 2007 [20]	5	2	4	**11**	7	5	4	**16**	7	7	3	7	7	7	1	1	**40**	7	7	7	**21**	1	5	1	1	**8**	1	4	**5**	**5**	Yes
Management of hand OA, 2007 [21]	7	2	5	**14**	6	1	6	**13**	7	6	6	7	7	7	1	1	**42**	7	7	7	**21**	1	1	7	1	**10**	5	1	**6**	**5**	Yes
Management of early arthritis, 2007 [22]	7	7	3	**17**	5	1	7	**13**	4	2	5	7	7	7	1	4	**37**	7	7	7	**21**	1	1	1	1	**4**	1	1	**2**	**4**	Yes
Management of gout, 2006 [23]	7	2	5	**14**	6	1	6	**13**	7	6	6	7	7	7	1	1	**42**	7	7	7	**21**	1	1	7	1	**10**	5	1	**6**	**5**	Yes
Management of AS, 2006 [24]	7	2	6	**15**	6	5	1	**12**	6	5	6	6	7	7	1	3	**41**	7	7	7	**21**	1	5	7	1	**14**	5	1	**6**	**5**	Yes

Management of hip OA, 2005 [25]	7	2	5	**14**	5	1	2	**8**	6	6	6	6	7	7	1	1	**41**	7	7	7	**21**	1	1	7	1	**10**	5	1	**6**	**4**	Yes
Management of knee OA, 2003 [26]	7	2	5	**14**	5	1	2	**8**	5	6	7	5	6	7	1	1	**38**	7	7	7	**21**	1	1	1	1	**4**	5	1	6	**4**	Yes
Management of knee OA, 2000 [27]	7	2	5	**14**	6	1	5	**12**	5	6	7	5	4	7	1	1	**36**	7	7	7	**21**	1	1	1	1	**4**	5	1	6	**4**	Yes

References in Appendix L.

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