Rheumatoid arthritis (update)
Consultation on draft guideline - Stakeholder comments table
18/01/18 to 01/03/18
Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

ID	Type	Organisation name	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
1	[office use only]	AbbVie Ltd	Full	6	1-7	Recommendations 1.2.2 abd 1.23: AbbVie welcomes the treat to target recommendations of remission or low disease activity (LDA). The timings on achieving this target are currently unclear. It would be useful for patients and clinicians to have an objective timeline to work towards for achievement of this target.	Thank you for your comment. The committee agree that additional information on how long to try one step of the strategy would be useful, however the evidence review was unable to inform the timings for the treat to target strategy. The committee considered this would have to be an individualised decision according to clinical judgement because of variability in response between individuals.
2	[office use only]	AbbVie Ltd.	Full	7	5-6	Recommendation 1.4.2: AbbVie welcomes the use of glucocorticoids as a short-term bridging treatment alongside the initiation of a new cDMARD. However AbbVie is concerned that this may translate into glucocorticoids being used as maintenance treatment in clinical practice and the implications this will have for patients. The use of glucocorticoids as a short-term bridging treatment should be limited to the treatment initiation phase only.	Thank you for your comment. Within the recommendation we have stated this is specifically for *short term* bridge therapy when starting new DMARD.
3	[office use only]	AbbVie Ltd.	Full	7	8-11	Recommendation 1.4.3: AbbVie understands that the majority of patients do not achieve an adequate response with this treatment choice. In order to fully encompass the treat-to-target strategy, it would be more appropriate to treat patients aggressively (by using biologic treatments earlier) which can result in improved long-term outcomes for patients.[1,2,3] [1] Raza K, Buckley CE, Salmon M, & Buckley CD (2006). Treating very early rheumatoid arthritis. Best Pract Res Clin Rheumatol; 20(5): 849–863. [1] Van Tuyl et al. (2008). Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission	Thank you for your comment. The technology appraisals for the biologic treatments include the criteria for initiation biologic therapy. Editing these criteria is beyond the remit of the guideline update, and they will be linked to as appropriate within the NICE pathway.

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						in a pilot trial. Ann Rheum; 67(11):1574-7. [1] Goekoop-Ruiterman YP et al. (2007). Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med; 146(6):406-15.	
4	[office use only]	AbbVie Ltd.	Full	8	15-16	Recommendation 1.5.5, second bullet point: AbbVie is concerned that this may translate into glucocorticoids being used as maintenance treatment in clinical practice and the implications this will have for patients. The use of glucocorticoids as a short-term bridging treatment should be limited to the treatment initiation phase only.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
5	[office use only]	AbbVie Ltd.	Full	8	26	Abbvie is of the position that if patients are treated with oral NSAIDs, the use of PPIs should also be reviewed regularly as part of the review of risk factors for adverse events	Thank you for your comment. We agree that this should be reviewed regularly. The third bullet point in recommendation 1.6.2 is intended to highlight this. Medicine review is covered in the Medicines adherence guideline CG76 and the medicines optimisation guideline NG5.
6	[office use only]	AbbVie Ltd.	Full	11	24-25	Recommendation 1.9.3: The assessment and recording of DAS-28 scores should also be considered during the annual review	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
7	[office use only]	AbbVie Ltd.	Full	12	5-6	It is unclear how "the effect the disease is having on a person's life" would be assessed. How would it be ensured that this aspect of the disease is being discussed during the annual review?	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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8	[office use only]	AbbVie Ltd.	Full	12	7-11	Recommendation 1.9.4: It is important that any step-down strategy is based on careful consultation with the patient and extensive consideration of the implications this approach could have. A recent meta-analysis (Henaux et al., 2017)[4] demonstrated that discontinuation of bDMARDs leads to an increased risk of losing remission or LDA and radiographic progression, while tapering doses of bDMARDs does not increase the risk of relapse (LDA) or radiographic progression, even though there is an increased risk of losing remission. It is also unclear how patients who lose remission or LDA while they are undergoing treatment tapering or have stopped treatment will be treated? Would these patients be treated as a patient who is initiating RA treatment again? [4] Henaux S et al. (2017). Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. Ann Rheum;0:1–8.	Thank you for your comment. We agree that any change in treatment should be done in consultation with the patient, who should be give appropriate information to make an informed choice on these decisions. This is part of the guidance provided by NICE clinical guideline 138: Patient experience in adult NHS services: improving the experience of care for people using adult NHS services. Shared decision making and medication review is also covered by the NICE medicines optimisation and adherence guidelines. Biological DMARDs are beyond the remit of this guideline. Guidance provided by the relevant technology appraisals are cross-referred to for recommendations on these treatments. In the last paragraph of this recommendation, it states that people should return promptly to the previous DMIARD regimen if the treatment target is no longer met.
9	[office use only]	AbbVie Ltd.	Full	12	12-13	Recommendation 1.9.5: AbbVie is concerned that this recommendation would mean that radiographic progression of disease would not be detected. Ultrasound monitoring should continue to take place during annual review.	Thank you for your comment. An evidence review was undertaken for the added value of ultrasound in monitoring of people with rheumatoid arthritis. This did not demonstrate any added value from the use of ultrasound for routine monitoring, including in terms of

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							radiological progression where there was considerable uncertainty in the effect. The committee's experience suggested that there may be circumstances in which monitoring with ultrasound may be useful, for example when clinical examination was uncertain or inconsistent with other signs of disease activity. As the current evidence base was unable to inform a recommendation in this group, a research recommendation was prioritised by the committee in this area to inform future updates of the guideline.
10	[office use only]	AbbVie Ltd.	Full	23	28-29	AbbVie believes that this is not in line with the treat-to-target approach recommended in this guideline update. Further clarification of what an "Inadequate response" encompasses is required.	Thank you for your comment. Inadequate response is defined by the targets set out in recommendation 1.2.1 (remission or low disease activity). In the committee's discussion of the evidence in Evidence reviews C and D (section headed 'Benefits and harms') there is further clarification provided regarding possible definitions of remission, noting that various composite scoring measures can be used, and therefore a definition is not given within the recommendation.
11	[office use only]	Bristol-Myers Squibb Pharmaceuticals Ltd.	Short	4	18-19	Measuring anti-CCP is best practice and should be used as a diagnostic tool rather than following diagnosis of RA. About 40% of patients will be RF-negative, but still have RA: delay to measuring anti-CCP could delay the most effective treatment and disease control.	Thank you for your comment. This topic was not included in the scope for the update of this guideline. However within the updated reviews, a recommendation was added to state that anti-CCP measurement should be carried out if not already measured at diagnosis, to identify those at increased risk of radiological progression and encourage self-monitoring of their condition (recommendation 1.1.5). We agree that the focus should be to not delay referral for diagnosis.
12	[office use only]	Bristol-Myers Squibb Pharmaceuticals Ltd.	Short	5	16-17	The guideline could state 'Advise the person…' rather than 'Tell the person…', to more effectively build a therapeutic relationship with patients suffering from RA.	Thank you for your comment. We agree that this is better wording and have changed this as suggested.

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13	[office use only]	Bristol-Myers Squibb Pharmaceuticals Ltd.	Short	6	1-3	We suggest that targets should be individualised to patients. Some patients will be unable to achieve remission and physicians need to be aware of patient beliefs about medication, medication burden to the patient, and what the patient and clinician agree together is an appropriate target.	Thank you for your comment. We agree that targets should be individualised to people with RA. The aim should be remission, but low disease activity was included as an option for people who cannot achieve remission. This can be measured using various composite scoring measures and the definitions will vary for each.
14	[office use only]	Bristol-Myers Squibb Pharmaceuticals Ltd.	Short	5	5-7	We suggest a note about the potential masking of infection and the need to consult with the patient about carrying an alert card when they are being treated with ANY disease-modifying drug.	Thank you for your comment. The responsibility of the prescriber is to provide full patient information as part of safe prescribing practice. Providing further detail on this here is beyond the remit of this guideline.
15	[office use only]	Bristol-Myers Squibb Pharmaceuticals Ltd.	Short	21	11-16	We suggest the importance is emphasised of monthly monitoring of disease activity/biomarkers, and clarifying the difference between validated markers of disease compared to CRP monitoring (which is a marker of inflammation)	Thank you for your comment, we agree and have included a recommendation (number. 1.2.3) regarding monthly monitoring of CRP and disease activity.
16	[office	Bristol-Myers	Short	30	13-15	It would be informative to link the statement that 'Approximately one-	Thank you for your comment. This section is

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	use only]	Squibb Pharmaceuticals Ltd.				third of people stop work because of the disease within 2 years of onset' to the median age for disease onset. This will emphasise the high number of productive working years lost due to RA, and the clear need to intervene more aggressively at early stages of disease to slow or prevent progression.	included to provide some current context to the recommendations. The guideline recommends referring people early and treating until remission or low disease activity is achieved. Therefore we believe the focus of the guideline is as you suggest (emphasising intervening early with aggressive treatment) without the need to edit this statement.
17	[office use only]	British Society for Rheumatology	Guideline	3 4?	10	I don't agree we this comment. I think all patients who fulfil the aforementioned criteria should be referred urgently. I think this last criteria should be removed	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
18	[office use only]	British Society for Rheumatology	Guideline	6	22	I feel that there should be a comment about methotrexate being used specifically first line in those patients with poor prognostic signs – anti-CCP positive, erosions….	Thank you for your comment. An evidence review was undertaken for the DMARDS including reviewing as a separate stratum those with poor prognostic signs. No evidence was identified to support that a different treatment strategy should be recommended for this group, and therefore the guideline committee do not agree that methotrexate should be recommended specifically as the first line option for this group. A research recommendation has been prioritised by the committee to determine the effectiveness of managing RA with a poor prognosis with a different strategy from that used for standard management of RA.
19	[office use only]	British Society for Rheumatology	Guideline	7	8	No mention of s/c methotrexate here. This is commonly used and is worth a comment	Thank you for your comment. Subcutaneous methotrexate was included as an intervention within the protocol for this evidence review,

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							however no relevant evidence was identified. The committee agreed that evidence comparing subcutaneous methotrexate to oral preparations was an important area to prioritise for research to inform future updates of the guideline and have included a research recommendation within the guideline to highlight this.
20	[office use only]	British Society for Rheumatology	Guideline	12	12	I feel this comment is discouraging the use of ultrasound. MSK ultrasound can be useful in detecting ongoing disease activity, and I agree it doesn't need to be used for all, but can have a place in certain patients. Could the wording of this point be softened?	Thank you for your comment. An evidence review was undertaken for the added value of ultrasound in monitoring of people with rheumatoid arthritis. This did not demonstrate any added value from the use of ultrasound for routine monitoring. The committee's experience suggested that there may be circumstances in which monitoring with ultrasound may be useful, for example when clinical examination was uncertain or inconsistent with other signs of disease activity. As the current evidence base was unable to inform a recommendation in this group, a research recommendation was prioritised by the committee in this area to inform future updates of the guideline. This is also discussed in the rational and impact section on page 26.
21	[office use only]	Eli Lilly and Company Limited		General		Thank you for the opportunity to feedback on the draft consultation of Update of the Rheumatoid Arthritis NICE Guideline. Overall, we are in agreement with the document and only have one minor comment to make.	Thank you for your comment.
22	[office use only]	Eli Lilly and Company Limited	Full	18	20-30	Functional ability should also be assessed at regular intervals. T2T is a useful approach however; DAS28 does not give the complete picture. If HAQ is a poor tool, a user-friendly PRO tool/outcome	Thank you for your comment. We agree functional ability should be measured at regular intervals and have recommended that

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						measure should be integrated as part of regular assessments particularly with respect to fatigue and pain.	it should be measured at baseline and at least annually. HAQ is given as one example of a measure that can be used, other validated measures could also be considered.
23	[office use only]	Gilead Sciences	Draft consultation	General – throughout document		Given the mechanism of action for other interventions is clearly defined earlier in the clinical guideline (e.g.[tumour necrosis factor-α (TNF-α) inhibitor], we believe it should be made clear that 'targeted synthetic DMARDs' refers to Janus Kinase (JAK) inhibitors consistent with the terminology used in EULAR guidelines.	Thank you for your comment. JAK inhibitors were beyond the remit for this guideline; however we have used the terminology consistently with EULAR where appropriate.
24	[office use only]	Gilead Sciences	Draft consultation	4	15-17	We believe blood tests should investigate other indicators of Rheumatoid Arthritis (RA) beyond rheumatoid factor (RF) (e.g. erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]).	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
25	[office use only]	Gilead Sciences	Draft consultation	5	12-13	Health Assessment Questionnaire (HAQ) measure of physical functioning should be defined in full – Health Assessment Questionnaire-Disability Index (HAQ-DI).	Thank you for your comment. The abbreviation HAQ is commonly used to refer to this questionnaire. This is the preferred abbreviation that has been used throughout the guideline.

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26	[office use only]	Gilead Sciences	Draft consultation	5	12-14	Other Patient Reported Outcomes (PROs) should be considered in addition to HAQ-DI to fully assess the impact of disease on patients' Quality of Life (QoL) and the impact which new treatments may have. For example, **fatigue** (Functional Assessment Chronic Illness Therapy-Fatigue [FACIT-F]), **pain intensity and duration** (Visual Analogue Scales [VAS]).	Thank you for your comment. HAQ was given as an example of a measure that is used to assess functional ability as it was agreed by the committee to be widely used. Recommendation 1.1.5 specifically relates to investigations and assessments that should be carried out to inform prognosis and monitoring of progression. Although we note the importance of these other factors to patients, no evidence was reviewed to suggest that additional outcomes should be recommended as essential to assess.
27	[office use only]	Gilead Sciences	Draft consultation	6	1-3	We believe other patient sub groups should be considered within this treat-to-target strategy e.g. those at risk of rapid disease progression.	Thank you for your comment. We reviewed the evidence for people at risk of rapid progression but found no evidence that a separate recommendation should be made for this subgroup. Evidence did suggest that those with anti-CCP antibodies or erosions on X-ray at baseline were at increased risk of radiological progression and therefore suggested that for those people in particular remission should be considered rather than low disease activity.
28	[office use only]	Gilead Sciences	Draft consultation	6	9-12	We believe patient preference should be a key factor in deciding the most appropriate treatment option; this may include factors such as method of administration, which is an important factor considering the chronic nature of the condition.	Thank you for your comment. We agree that patient preference is an important factor in all treatment decisions. This area was not updated, however the principles covered in the NICE guideline on patient experience in adult NHS services (CG138) should apply across all guidelines. Involving patients in decision-making, medication review, supporting adherence and self-management plans are all covered in the NICE medicines optimisation (NG5) and medicines adherence (CG76) guidelines.
29	[office use only]	Gilead Sciences	Draft consultation	8	15-16	Given the mechanism of action for other interventions is clearly defined earlier in the clinical guideline (e.g.[tumour necrosis factor-α (TNF-α) inhibitor], we believe it should be made clear that 'targeted	Thank you for your comment. JAK inhibitors were beyond the remit for this guideline; however we have used the terminology

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						synthetic DMARDs' refers to Janus Kinase (JAK) inhibitors consistent with the terminology used in EULAR guidelines.	consistently with EULAR where appropriate.
30	[office use only]	Gilead Sciences	Draft consultation	8	18-28	We believe that consideration should be given to DMARDs which are also able to provide symptom control as a treatment option – many new interventions have demonstrated efficacy in the alleviation of severity and duration of joint pain.	Thank you for your comment. The recommendations for symptom control are to be considered in tandem with the recommendations for DMARD treatment and state that they can be considered when control of pain or stiffness is inadequate – acknowledging these may be controlled by the DMARD treatment. Disease activity measures include symptoms which are the target of treatment.
31	[office use only]	Gilead Sciences	Draft consultation	11	25	We believe consideration should be given to the assessment of other PROs during these annual reviews.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
32	[office use only]	Gilead Sciences	Draft consultation	13	26	Given the mechanism of other interventions is clearly defined earlier in the clinical guideline (e.g.[tumour necrosis factor-α (TNF-α) inhibitor], we believe it should be made clear that 'targeted synthetic DMARDs' refers to Janus Kinase (JAK) inhibitors consistent with the terminology used in EULAR guidelines.	Thank you for your comment. JAK inhibitors were beyond the remit for this guideline; however we have used the terminology consistently with EULAR where appropriate.

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33	[office use only]	Gilead Sciences	Draft consultation	17	13-15	We believe other patient sub groups should be considered for further research e.g. those at risk of rapid disease progression.	Thank you for your comment. This research recommendation relates specifically to the population for which evidence was searched, and found to be absent. Specific details of subgroups that may also be studied within this may be defined by researchers if the research is carried out.
34	[office use only]	GreenVits	Full	General	General	Rheumatoid Arthritis is not caused by the absence of a drug – ***it is caused by wrong diet*** The current advice about diet in CG79 (1.7) is totally inadequate, as there is lack of suitable guidance about the management of diet and lifestyle Suggest add advice that GP should refer patient to a Dietitian or Nutritional Therapist on first presentation The purpose of this is to evaluate current diet and lifestyle and to recommend improvements This should include advice about anti-inflammatory diets There is very good evidence that diet contributes to the Inflammation that presents as Rheumatoid Arthritis Sources: http://www.ncbi.nlm.nih.gov/pubmed/16194694 http://rheumatology.oxfordjournals.org/content/38/11/1039.full http://www.semarthritisrheumatism.com/article/S0049-0172(05)00087-9/abstract	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
35	[office use only]	GreenVits	Full	General	General	There is very good evidence that increasing Vitamin D levels of 25(OH)D to 100-150 nmol/L helps to prevent and treat Rheumatoid Arthritis - in the early stages - and helps to reduce Inflammation Suggest GP to test 25(OH)D and prescribe Vitamin D to adjust level to 100-150 nmol/L and review after 3 months This is not general advice to "get more sunshine" but a medical	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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						procedure to test and adjust the level of Vitamin D The current referral to diet in CG79 (1.7) is totally inadequate, as there is lack of suitable guidance about Vitamin D To make long-term improvements, the patient must make changes in both diet and lifestyle Making these changes does not need drugs, but requires advice about nutrition, healthy eating plus adequate and safe exposure to sunshine Source: http://www.vitamindwiki.com/Overview+Rheumatoid+Arthritis+and+vitamin+D http://www.ncbi.nlm.nih.gov/pubmed/24907153	
36	[office use only]	GreenVits	Full	General	General	There is very good evidence that adjusting Omega-3 and Omega-6 levels helps to both prevent and treat Rheumatoid Arthritis - in the early stages - and helps to reduce Inflammation **Key Indicators**……**Target**…**Comments** **Omega-3 Index**…..>8%.....Is the Omega-3 level high enough ? **Omega-6/3 Ratio** <3:1……Is the Inflammation low enough ? Increasing Omega-3 to these levels may need 2-5 grams of Omega-3 per day. Reducing Omega-6 needs advice about diet and lifestyle from a Dietitian or Nutritional Therapist Making these changes does not need drugs, but requires advice about nutrition and healthy eating This is not general advice to "eat more fish" but a medical procedure to test and adjust the level of Omega-3 and 6 There is very good evidence from thousands of patients in Germany that measuring and adjusting these 2 Indicators helps to make major improvements in the Inflammation that presents at Rheumatoid Arthritis The current referral to diet in CG79 (1.7) is totally inadequate, as there is lack of suitable guidance about Fatty Acids	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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						Source: http://www.expertomega3.com/omega-3-studies/inflammatory-diseases http://www.ncbi.nlm.nih.gov/pubmed/12442909 http://www.ncbi.nlm.nih.gov/pubmed/22765297 https://www.norsan-omega.com/does-omega-3-really-help/ http://www.greenvits.eu/pages/omega-3	
37	[office use only]	GreenVits	Full	General	General	Investigate biomarkers for the Inflammation that is the basis for Rheumatoid Arthritis Source: http://www.greenvits.eu/blogs/news/90038403-what-to-do-about-inflammation http://www.expertomega3.com/omega-3-studies/inflammatory-diseases http://www.ncbi.nlm.nih.gov/pubmed/22765297 http://www.greenvits.eu/pages/omega-3	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
38	[office use only]	GreenVits	Full	-	1.8.8	The guidance given in Section 1.8.8 about Diet and complementary therapies is totally unsatisfactory Rheumatoid Arthritis is not caused by absence of a drug, but by diet that causes Inflammation Suggest GP refers patient to a Dietitian who can assess existing diet and suggest an "Anti-Inflammatory Diet"	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
39	[office use only]	GreenVits	Full	-	1.8.8	The guidance given in Section 1.8.8 about Diet and complementary therapies is totally unsatisfactory Where is the detailed evidence for: "a Mediterranean diet that includes more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils" ? Where is the evidence that bread is of benefit ? Where is the evidence that ***all*** meat causes Rheumatoid Arthritis ?	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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						Which meat is good and which meat is bad ? Which fruit and vegetables are good and which are bad ? Which fish are good and which fish are bad ? Where is the evidence that butter and cheese ***cause*** Rheumatoid Arthritis ? Where is the evidence that vegetable and plant oils ***help*** Rheumatoid Arthritis ? There is evidence that processed vegetable and plant oils contribute to the excess of Omega-6 that contributes to the Inflammation that presents as Rheumatoid Arthritis – ie: ***they help to cause Rheumatoid Arthritis*** Source: http://www.fatsoflife.com/health-effects-of-fats-rheumatoid-arthritis/	
40	[office use only]	Keele University	Draft, full	4	5	The referral guidelines are different from that being assessed as part of the HQUIP audit, firstly the definition of adult should be specified (as I suspect it should be age ≥ 16 years not 18 years). The HQUIP guidance talks about referring persistent synovitis (not any synovitis).	Thank you for your comment. An update of the quality standard will follow the update of this guidance. The recommendations for referral were not included in the scope for the update of this guideline. The term 'persistent' has now been reinstated, however we are unable to alter the definition of adults which has not been specifically stated in the guideline due to variation across the country in the age at which transition to adult services occurs.
41	[office use only]	Keele University	Draft, full	5	18	The comment about CCP and erosions driving management is not helpful- all patients need to be have self monitoring and access to specialist care in the event of a flare, not just those who are CCP positive or have erosions on XR	Thank you for your comment. We agree that this applies to all people with rheumatoid arthritis, and state this in recommendation 1.9.1. Recommendation 1.1.6 highlights that people with anti-CCP antibodies or erosions on X-ray at baseline assessment are at an increased risk of radiological progression and therefore emphasises to them the importance of monitoring their own condition.
42	[office use only]	Keele University	Draft, full	6	5	Monthly DAS28 measuring is reasonable, however if this is measured using DAS28 ESR then CRP may not be required	Thank you for your comment. We have not specified which disease activity measure to use as a number are available. This would be informed by the healthcare professional's judgement.

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							CRP is a better guide to disease activity because the ESR may be raised from causes other than inflammation therefore the committee do not agree that the recommendation should suggest CRP is not always necessary.
43	[office use only]	Keele University	Draft, full	7	2	It is appropriate to use HCQ for palindromic disease, however mild disease may need further definition as HCQ is not actually disease modifying and this seems a shift in practice without much evidence	Thank you for your comment. The recommendations for hydroxychloroquine are for it to be considered as an option for these groups. The other conventional DMARDs are also an option. The committee do not agree that considering hydroxychloroquine for mild disease is a shift in practice, as hydroxychloroquine was also an option in the previous guideline. These recommendations clarify when it might be most appropriate to consider hydroxychloroquine. The committee's discussion of the evidence in evidence review F explains that the discretion of the treating clinician and the person with rheumatoid arthritis should inform the choice of DMARD and therefore a specific definition of mild disease is not included in the recommendation. The treat to target strategy should be followed for all people with RA and therefore if they do not respond, the treatment should be altered.
44	[office use only]	Keele University	Draft, full	7	14	More links to biologics need to be provided otherwise this reads as an odd jump to anakinra	Thank you for your comment. The NICE pathway will link to all relevant technology appraisal guidance for rheumatoid arthritis (including the biologics). The technology appraisal for anakinra was replaced by this guidance, and therefore those recommendations remain within this guideline.
45	[office use	Keele University	Draft, full	8	16	"all other treatment options (including biological and targeted	Thank you for your comment. This topic was not included in the scope for the update of this

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	only]					synthetic 15 DMARDs) have been offered"- should include unless contraindicated as therapies may not have been offered entirely appropriately	guideline.
46	[office use only]	Keele University	Draft, full	8	26	Add a space between events and regularly	Thank you for your comment, this has been amended.
47	[office use only]	Keele University	Draft, full	11	26	More detail needs to be included for what should be included in an annual review- it is reasonable to measure disease activity and damage and for example hypertension. However, there is no evidence that full CVD risk assessment should be performed annually- indeed EULAR guidelines on CVD risk management suggest that "CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy"(Agca 2016 ARD)	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
48	[office use only]	Keele University		12	12	Whilst I agree with the wording that ultrasound should not be used for routine monitoring, my concern is that commissioners/managers will read that it shouldn't be used-leading to disinvestment in ultrasound services- I would support adding a qualifying statement after eg: "should not be used for routine management, but may be useful if clinical examination is inconclusive or is inconsistent with other signs of disease activity"	Thank you for your comment. We agree that there may be some circumstances in which the use of ultrasound may be of benefit and worded the recommendation as 'routine monitoring' to indicate this. In the rationale and impact section on pages 26 and 27, and in the full evidence review, the committee's considerations of this are discussed. A research recommendation was also prioritised

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							by the committee to identify whether ultrasound is useful to monitor disease in adults with RA when clinical examination is inconclusive or inconsistent with other signs of disease activity.
49	[office use only]	medac Pharma (formerly medac GmbH)	Full	5	22	We agree on the implementation of a treat-to-target strategy as this is generally in line with global evidence based recommendations (Smolen et al. 2017, Singh et al. 2016). We are concerned that these guidelines do not entirely reflect current knowledge on the available treatments within a treat-to-target approach and even contradict evidence-based recommendations (Smolen et al. 2017, Singh et al. 2016). In particular, the NICE recommendations do not elaborate on the optimal use of methotrexate as first line therapy in rheumatoid arthritis as part of a treat-to-target strategy. *Singh JA et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research 2016; 68(1): 1–25* *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76(6): 960-977*	Thank you for your comment. The committee were aware of the EULAR and ACR guidelines, but do not agree that this guideline is inconsistent with the evidence base. The evidence for DMARDs was reviewed by the committee. There was no evidence to support that methotrexate should be specifically recommended as the first line. The choice of first line DMARD should be made on an individualised basis.
50	[office use only]	medac Pharma (formerly medac GmbH)	Full	6	22	This statement clearly contradicts current evidence-based recommendations. According to EULAR (European League Against Rheumatism) guidelines, methotrexate (MTX) should be part of the first treatment strategy based on its efficacy, safety, the option to individualise dose range and route of administration and relatively low cost. Moreover, MTX appears to reduce comorbidities and mortality in rheumatoid arthritis. Only in patients with a contraindication to MTX or early intolerance, should leflunomide or sulfasalazine be considered (Smolen et al. 2017). *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying*	Thank you for your comment. The committee were aware of the EULAR guidelines, but do not agree that this guideline is inconsistent with the evidence base. The evidence for DMARDs was reviewed by the committee. There was no evidence to support that methotrexate should be specifically recommended as the first line. The choice of first line DMARD should be made on an individualised basis.

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						antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76(6): 960-977	
51	[office use only]	medac Pharma (formerly medac GmbH)	Full	6	22	We are concerned about the guidelines being limited to the sole use of oral methotrexate (oral MTX). Current evidence suggests that the route of administration of MTX is a fundamental parameter for optimising rheumatoid arthritis (RA) treatment and for delaying the use of more cost intensive therapies (Vena et al. 2018, Yadlapati et al. 2016, Bianchi et al. 2016, Li et al. 2016, Jay 2015, Keystone et al. 2014, Cipriani et al. 2014a, Cipriani et al. 2014b, Yazici et al. 2013, Mainman et al. 2010). Therefore in line with current EULAR (European League Against Rheumatism) guidelines, the most cost effective treatment strategy should be used as long as safety and outcomes are similar to more costly treatments (Smolen et al. 2017). The benefits of subcutaneous methotrexate (SC MTX) over oral methotrexate (oral MTX) have been summarised in a recently published study by Yadlapati and Efthimiou. They concluded that SC MTX is the drug of choice for the treatment of RA due to its reliable efficacy, predictable bioavailability, sustained clinical outcomes, minimal gastrointestinal (GI) adverse effects, its usefulness either singularly or in combination therapy and its favourable cost to efficacy ratio compared with biologics (Yadlapati et al. 2016). Hazlewood et al. compared the overall effectiveness of oral MTX with SC MTX as initial therapy in 666 patients with early RA. After 1 year of treatment, a significantly higher proportion of patients initially treated with oral MTX (n = 417) had treatment failure compared with those who received SC MTX (n = 249; 77% vs. 49%, respectively) mostly due to lack of efficacy rather than toxicity or intolerance to therapy. Patients treated with SC MTX showed a more significant reduction in mean DAS28 (Disease activity score) values at 3, 6, and 9 months after the beginning of treatment compared with patients treated with oral MTX. This study demonstrated a significant association between initial administration of SC MTX and improved treatment continuation over the first year of treatment in patients with early RA compared with oral administration, and further	Thank you for your comment. The evidence review for conventional DMARDs included searching for the evidence for subcutaneous methotrexate compared to other conventional DMARDs. No evidence was identified relevant to the review protocol (comparing subcutaneous methotrexate to oral methotrexate, or other oral conventional DMARDs) to inform a recommendation on the use of subcutaneous methotrexate. We have reviewed the references you have provided; however none would be included within our review due to comparing to DMARDs with those that are outside the scope of this guideline, being narrative reviews only, retrospective observational studies or open label cohort studies. The committee agree that subcutaneous methotrexate may be an option for some people with RA; however in the absence of evidence to support this, a research recommendation was prioritised to inform future updates of the guideline.

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						supports the use of SC MTX as the preferred route of MTX administration (Hazlewood et al. 2016). A recent observational study by O'Connor et al. whose objective was to determine rapidity of response of SC MTX in early RA, has shown that optimal usage of MTX from the onset can induce remission or low disease activity state for 59% of patients within 6 weeks. In this study, 103 patients were included from a single site between 2008 and 2014. All received MTX (98.0% SC MTX, 25mg/week). There were no dropouts. A significantly greater early change in DAS28 (−1.9 vs. −0.2, $p < 0.00$) and for several outcome measures, was seen. By 6 weeks, 59% had achieved either DAS28 remission or low disease activity state, with 74% achieving either state by 12 weeks (O'Connor et al. 2016). In a Canadian study published by Harris et al. eight centres across Canada compared the outcomes of early RA patients following a variety of treatment options. One site followed the treatment strategy by O'Connor as discussed above. This site had the highest proportion of patients in remission at 6 months (64.5%) and at 12 months (74.5%). Only 12% of patients had their medication changed and 8.9% had their medication increased in the first 12 months, the lowest across all the sites. No patients went on to receive biologic treatment. The authors concluded that early RA patients with initial treatment of SC MTX had better outcomes. A strong treatment predictor of good outcomes was less changes and fewer increases in medication after their initial visit (Harris et al. 2013). Bianchi et al. summarised the scientific evidence currently available on comparing SC MTX with oral MTX routes of administration in optimising the therapeutic strategy in RA in a real life setting. They concluded that both randomised double-blind clinical studies and retrospective or longitudinal analyses in real life settings, demonstrated that SC MTX is more effective than oral MTX in terms of DAS28 and American College of Rheumatology (ACR) criteria, either as first line therapy in MTX naive patients, or in oral MTX experienced patients as switch therapy. SC MTX also showed a better tolerability profile with respect to gastrointestinal (GI) side effects. By switching from oral MTX to SC MTX in non-responders the use of more expensive biological therapies could be delayed	

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						and thus, might provide cost savings (Bianchi et al. 2016). In a retrospective evaluation of continuation rates following a switch from oral MTX to SC MTX by Scott, Clayon and Ellis, it was shown that a switch to SC MTX in patients who fail to respond to or tolerate oral MTX, provided a good long term survival on therapy (retention rates of 83% at 1 year, 75% at 2 years, and 47% at 5 years) and a minimal need for further treatment with biological disease modifying anti-rheumatic drugs (bDMARDS).The authors concluded that management guidelines should be adapted to include advice that SC MTX should be used before biologic therapy and that MTX failure is defined as failure only when use of SC MTX has failed (Scott et al. 2014). A recently published review by Bello et al. summarised best practices for MTX use in RA patients. Based on current evidence, the author concluded that although treatment guidelines clearly support the use of MTX in patients with RA, a paradigm shift for more effective MTX usage should be considered. This includes administration of a high initial dose of MTX, switching to SC MTX in cases of intolerability or inadequate efficacy to oral MTX and consideration of starting treatment with SC MTX due to its favourable bioavailability and pharmacodynamics profile. Moreover, several other conventional disease modifying anti-rheumatic drugs (DMARDs) appear to be less effective than MTX, thereby invalidating a switch in treatment (Bello et al. 2017). Mainman et al. advocated consideration of parenteral MTX in all RA patients unresponsive to oral therapy prior to treatment with anti-TNF therapy based on the results of their retrospective data analysis. Among patients commencing parenteral MTX, 60 (76%) had a stable baseline DAS28 >5.1 and would have qualified for anti-TNF therapy on this basis, having failed a trial of at least 6 months of oral therapy. After 6 months of parenteral therapy, DAS scores fell by at least 1.2 in 59 patients (74%), equivalent to a response to treatment with biological agents in three quarters of patients. Furthermore, DAS scores fell to <3.2 (low disease activity) in 27 patients (29%) on parenteral therapy, compared to 12 (16%) on oral MTX (p=0.02). Parenteral MTX was well tolerated. This equates to a considerable cost saving and further supports the use of parenteral	

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						MTX prior to anti-TNF therapy in RA patients who fail to respond to oral MTX (Mainman et al. 2010). The potential economic impact of SC MTX or a biologic over a 12 month period was analysed by Fitzpatrick, Scott and Keary, as RA has a substantial impact on patients and the economy, costing the NHS an estimated £689 million annually. In this study, a decision based model was developed taking various management options at each decision point requiring drug switches based on NICE guidance and their estimated costs into account. By using a hypothetical population of patients who have failed to tolerate or respond to oral MTX and published data on continuation rates of SC MTX and biologics, the costs of the two treatment options were compared. The results of this study suggest that routine use of SC MTX following oral MTX failure has the potential to reduce the cost of treatment of around £7,000 per patient or £9 million across the cohort of RA patients by reducing the need for biologic therapy. In the context of the BSR/BHPR guidelines, recommending the availability of TNF inhibitors for RA patients with a DAS28 >3.2 and specific features of active disease, this is particularly important. A decrease in the threshold in the UK for the introduction of biologics will increase biologic use from 6 to 8-12 % leading to a doubling of current costs (Fitzpatrick et al. 2013). The cost of subcutaneous methotrexate has reduced by 60% of list price in England, as of July 2017 for hospitals & homecare, making SC MTX a more affordable option. (English National Contract) The above listed studies demonstrate the important role of SC MTX in the treatment of RA. Overall, SC MTX is characterised by higher bioavailability (Schiff et al. 2017, Schiff et al. 2014, Pichlmeier et al. 2014, Kremer et al. 2004, Hoekstra et al. 2004, Alsufyani et al. 2004), greater clinical efficacy (O'Connor et al. 2016, Islam et al. 2013, Bakker et al. 2010, Braun et al. 2008, Verstappen et al. 2007, Rozin et al. 2002), better tolerability (Kromann et al. 2015, Rutkowska-Sak et al. 2009) and risk:benefit profile than oral MTX. Switching from oral to SC MTX in non-responders may provide cost savings due to delaying the use of more aggressive and more expensive therapies, such as bDMARDs (Fitzpatrick et al. 2013). Moreover, fewer changes in the treatment of the patient might also	

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						results in less patient visits to hospital resulting in time and cost savings as well as improved adherence (Hazlewood et al. 2016, Branco et al. 2016, Scott et al. 2014, Hazlewood et al. 2013). We would therefore suggest removing the limitation to treat solely with oral MTX and would propose the following change to the recommendation: Offer first-line treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs) as soon as possible and ideally within 3 months of the onset of persistent symptoms. Methotrexate should be part of a first-line treatment strategy. In patients with a contraindication or early intolerance to MTX, leflunomide or sulfasalazine should then be considered. *Alsufyani K et al. The Role of Subcutaneous Administration of Methotrexate in Children with Juvenile Idiopathic Arthritis Who Have Failed Oral Methotrexate. J Rheumatol 2004; 31: 179–82* *Bakker MF et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Ann Rheum Dis 2010 ;69: 1849–1852* *Bello AE et al. Open Access Rheumatology: Research and Reviews 2017: 9: 67–79* *Bianchi G. Methotrexate and Rheumatoid Arthritis: Current Evidence Regarding Subcutaneous Versus Oral Routes of Administration. Adv Ther 2016; 33: 369–378* *Branco JC et al. Utilization of Subcutaneous Methotrexate in Rheumatoid Arthritis Patients After Failure or Intolerance to Oral Methotrexate: A Multicenter Cohort Study. Adv Ther 2016; 33 :46–57* *Braun J et al. Comparison of the Clinical Efficacy and Safety of Subcutaneous Versus Oral Administration of methotrexate in Patients With Active Rheumatoid Arthritis. ARTHRITIS & RHEUMATISM 2008; 58(1): 73-81* *Cipriani P et al. Methotrexate in rheumatoid arthritis: Optimising therapy among different formulations. Current and emerging paradigms. Clinical Therapeutics 2014a; 36(3)*	

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						Cipriani P et al. Methotrexate: an old new drug in autoimmune diseases. Expert Rev Clin Immunol. 2014b; 10(11) *Fitzpatrick R, Scott DGI and Keary I. Cost minimisation analysis of subcutaneous methotrexate versus biologic therapy for the treatment of patients with rheumatoid arthritis who have had an insufficient response or intolerance to oral methotrexate. Clin Rheumatol 2013* *Harris J et al. Determining best practices in early rheumatoid arthritis by comparing difference in treatment at sites in the Canadian Early Arthritis Cohort. The Journal of Rheumatology 2013; 40: 11* *Hazlewood GS et al. The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis. Ann Rheum Dis 2016; 75: 1003–1008* *Hoekstra M et al. Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients with Rheumatoid Arthritis. J Rheumatol 2004 ;31: 645–8* *Islam MS et al. Comparative Efficacy of Subcutaneous Versus Oral Methotrexate in Active Rheumatoid Arthritis. Mymensingh Med J 2013 Jul; 22 (3): 483-488* *Jay R. Methotrexate revisited: considerations for subcutaneous administration in RA. Clin Rheumatol 2015; 34: 201-205* *Keystone E and Freundlich B. Methotrexate in rheumatoid arthritis: benefits, limitations and the emerging value of subcutaneous administration. Int. J. Clin. Rheumatol 2014; 9(4): 345-351* *Kremer JM, Toward a better understanding of methotrexate, Arthritis Rheum 2004; 50 (5): 1370-82* *Kroman CB et al. Does switching from oral to subcutaneous administration of methotrexate influence on patient reported gastro-intestinal adverse effects? J Dermatolog Treat 2015; 26(2): 188-190* *Li et al. Subcutaneous administration of methotrexate at high doses makes a better performance in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: A systematic review and meta-analysis. Sem Arthritis Rheumatism 2016; 45: 656-662* *Mainman H et al. When should we use parenteral methotrexate? Clin Rheumatol 2010; 29: 1093–1098* *O'Connor A et al. The rapid kinetics of optimal treatment with subcutaneous methotrexate in early inflammatory arthritis: an observational study. O'Connor et al. BMC Musculoskeletal*	

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						Disorders 2016; 17: 364-371 *Pichlmeier U and Heuer KU. Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate. Clin Exp Rheumatol 2014; 32: 563-71* *Rozin A et al. Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate. Ann Rheum Dis 2002; 61: 756–757* *Rutkowska-Sak L, Rell-Bakalarska M and Lisowska B. Oral vs. subcutaneous low-dose methotrexate treatment in reducing gastrointestinal side effects. Reumatologia 2009; 47, 4: 207–211* *Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomized, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. Ann Rheum Dis 2014; 73 (8): 1549-51* *Schiff M H et al. Oral to subcutaneous methotrexate dose-conversion strategy in the treatment of rheumatoid arthritis. Rheumatol Int 2017; 37: 213-218* *Scott DG, Clayon P and Ellis C. Retrospective evaluation of continuation rates following a switch to subcutaneous methotrexate in rheumatoid arthritis patients failing to respond to or tolerate oral methotrexate: the MENTOR study. Scand J Rheumatol 2014; 43(6): 470-6* *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76(6): 960-977* *Vena GA, Cassano N and Iannone F. Update on subcutaneous methotrexate for inflammatory arthritis and psoriasis. Ther Clin Risk Mang 2018; 9(14): 105-116* *Verstappen SMM et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007; 66: 1443–1449* *Yadlapati S and Efthimiou P. Inadequate response or intolerability to oral methotrexate: Is it optimal to switch to subcutaneous methotrexate prior to considering therapy with biologics? Rheumatol Int 2016; 36: 627-633* *Yazici Y and Bata Y. Parenteral Methotrexate for the Treatment of*	

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						Rheumatoid Arthritis. Bulletin of the Hospital for Joint Diseases 2013; 71(Suppl 1): S46-8 English National Contract for National Proprietary Pharmaceuticals ; reference CM/PHR/14/5445/01	
52	[office use only]	medac Pharma (formerly medac GmbH)	Full	7	4	We agree with including dose escalation into the NICE recommendations as this is in line with current evidence based guidelines. However, we are concerned that again the use of methotrexate (MTX) is not adequately reflected. According to the present EULAR (European League Against Rheumatism) guidelines, dose optimisation should be an important aspect of first-line DMARD strategy. MTX should be titrated rapidly to 20–30mg/week, depending on clinical response and tolerability; parenteral administration should be considered in case of inadequate clinical response or intolerance (Combe et al. 2016, Smolen et al. 2017). Portuguese recommendations for the use of MTX in rheumatic diseases published the best dosing strategy and route of administration of MTX in patients with rheumatoid arthritis (RA) to optimise an early response and minimise toxicity. The guidelines recommend that oral MTX should be started at 10–15mg/week, with an escalation of 5mg every two to four weeks up to 25mg/week, depending on clinical response and tolerability. Parenteral administration should be considered in the case of inadequate clinical response or intolerance. They concluded that starting MTX therapy by the parenteral route may be an option (Duarte et al. 2017). The Spanish recommendations for the use of MTX in patients with RA suggested that patients should start treatment with MTX, preferably via an oral route. However, they stated that consideration should be given to subcutaneous (SC) or intramuscular routes in patients with poor compliance, insufficient effectiveness or gastrointestinal (GI) side effects. In RA patients treated with oral MTX, available evidence justified the change to SC route of administration when a lack of therapeutic response was expressed against the activity of the disease, or GI toxicity or therapeutic failure were present, since the SC route is associated with better treatment	Thank you for your comment. The dose of the DMARD to be used can be found in the BNF. A recommendation for subcutaneous methotrexate could not be made for a specific group due to an absence of evidence. The committee agree that this may be an option and therefore have prioritised a research recommendation to inform future updates of the guideline. We have reviewed the references you have provided; however none would be included within our review due to comparing to DMARDs with those that are outside the scope of this guideline, being narrative reviews only, retrospective observational studies or open label cohort studies. The guidelines you reference are also developed following a different process to the NICE guidelines and therefore differences in the protocols and levels of evidence used to inform recommendations (including consensus opinion) lead to different recommendations being made. The level of evidence and criteria for evidence informing this guideline is detailed in the protocols of the relevant evidence review chapters – for this recommendation; Evidence review F.

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						response. Its better cost effectiveness in studies suggest the suitability of changing from oral administration to parenteral MTX in patients with an inadequate response, as the evidence shows that this prevents or delays subsequent therapy with biological agents (Molina et al. 2015). Studies on the bioavailability of MTX have shown that even at a relatively low dose, less MTX is absorbed by the body when administered orally compared to parenterally (Kremer et al. 2004). In a randomised open-label, cross-over study in 48 patients with RA published by Schiff et al., bioavailability, safety and tolerability of oral MTX and SC MTX administered via an autoinjector were compared. When given orally, the ingested MTX reaches a plateau at doses higher than 15mg while the bioavailability of subcutaneously administered MTX increases linearly. In this context, better MTX bioavailability was not associated with poorer tolerability. The authors concluded that patients with an inadequate clinical response to oral MTX may benefit from higher drug exposure by switching to SC MTX (Schiff et al. 2014). An effective dose conversing strategy by comparing the bioavailability from oral and subcutaneous administration based on data from an 8 week, open-label, randomised, cross-over study in adult RA patients was developed by Schiff et al. This study was designed to compare MTX pharmacokinetic profiles as a result of different MTX treatment administrations. Compared to oral MTX, SC MTX demonstrated a greater bioequivalence and a dose proportional increase. No exposure limitations were seen and enhanced bioequivalence may increase the efficacy of the drug. Based on these results, a convenient dose conversing strategy was established that can easily be applied into practice (Schiff et al. 2017). As outlined above, EULAR and several national guidelines recommend MTX as the first-line non biologic disease modifying anti-rheumatic drug (DMARD) treatment in RA. All guidelines stress the need to optimise MTX therapy before giving patients combination therapy with another synthetic DMARD or a biologic agent (Smolen et al. 2017, Duarte et al. 2017, Molina et al. 2015).	

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						Another goal of RA therapy is to avoid unnecessary patient harm from other therapies (Schiff et al. 2017). Therefore, optimising MTX dosing is key. (Smolen et al. 2017, Duarte et al. 2017, Molina et al. 2015, Schiff et al. 2017). Unlike the exposure limitations of oral MTX, dose proportional exposure concomitant with an enhanced bioavailability and increased efficacy was demonstrated with SC MTX, especially at doses above 15mg (Schiff et al. 2017, Schiff et al. 2014, Braun et al. 2008, Kremer 2004). The risk of sub-optimal dosing of MTX may be avoided by switching from oral to SC MTX. We therefore suggest adjusting the NICE recommendation as follows: Escalate dose as tolerated. MTX should be rapidly escalated, usually to 25–30mg/week. If tolerated, the maximum MTX dose should be sustained for approximately 8–12 weeks to assess efficacy. For doses higher than 15mg/week, subcutaneous administration should be considered. *Braun J et al. Comparison of the Clinical Efficacy and Safety of Subcutaneous Versus Oral Administration of methotrexate in Patients With Active Rheumatoid Arthritis. ARTHRITIS & RHEUMATISM 2008; 58(1): 73-81* *Combe B et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis 2016;0:1–12* *Duarte A C et al. Portuguese recommendations for the use of methotrexate in rheumatic diseases – 2016 update. Acta Reumatol Port 2017; 42: 127-140* *Kremer JM, Toward a better understanding of methotrexate, Arthritis Rheum 2004; 50 (5): 1370-82* *Molina J T et al. Recommendations for the use of methotrexate in rheumatoid arthritis: Up and down scaling of the dose and administration routes. Reumatol Clin 2015; 11: 3–8* *Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomized, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. Ann Rheum Dis 2014; 73 (8): 1549-51* *Schiff M H et al. Oral to subcutaneous methotrexate dose-conversion strategy in the treatment of rheumatoid arthritis.*	

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						Rheumatol Int 2017; 37: 213-218 *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76(6): 960-977*	
53	[office use only]	medac Pharma (formerly medac GmbH)	Full	7	8	In general we agree on the implementation of a disease modifying anti-rheumatic drug (DMARD) combination as part of a step up strategy aiming for remission. Research suggests that an initial use of combination DMARDs is associated with an increased likelihood of remission, especially in early rheumatoid arthritis (RA) patients. Combination DMARDs can provide equivalent outcomes at lower costs than biologic DMARDs (Gottheil et al. 2016). Gottheil et al. published data from the Canadian Early Arthritis Cohort (CATCH), a prospective cohort study of patients with early RA. The objective of this study was to compare effects of initial treatment with oral methotrexate (oral MTX) monotherapy, subcutaneous methotrexate (SC MTX) monotherapy and methotrexate (MTX) combination therapy on time to first use of biologic DMARDs. Oral MTX monotherapy was used as initial treatment in 230 (20%) patients, SC MTX monotherapy in 226 (20%) and MTX combination therapy in 664 (60%). In fully adjusted Cox regression models, patients treated with SC MTX monotherapy had a significantly delayed time to first biologic use (HR = 0.53, p = 0.02). There was no difference between MTX combination therapy and oral MTX monotherapy (HR = 0.95). In conclusion, early use of SC MTX can potentially delay the need for more expensive biologic treatments (Gottheil et al. 2016). We are concerned that this recommendation is restricted to the use of oral MTX as outlined in comment 2 above. MTX should be the first conventional disease modifying anti-rheumatic drug (cDMARD) to be used in a step up strategy, the dose and route of administration should be optimised prior to adding the next DMARD. This strategy is strongly supported by current knowledge (Vena et al. 2018, Yadlapati et al. 2016, Bianchi et al. 2016, Li et al. 2016, Jay 2015, Keystone et al. 2014, Cipriani et al. 2014a, Cipriani et al.	Thank you for your comment. The evidence for initiating treatment with a single DMARD compared to a combination was reviewed within the update, but combinations were not found to be superior to starting with one drug. The recommendation therefore states the initial treatment should be with one drug, due to this also having a reduced side-effect profile to two medications. A treat-to-target strategy following a step-up strategy is then recommended. The reference you provide (Gottheil et al. 201) is an abstract only and therefore was not included within this guideline's review. As per our above replies, no evidence was identified for subcutaneous methotrexate that is relevant to this review protocol, and therefore a research recommendation was prioritised by the committee to inform future updates of the guideline.

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						2014b, Yazici et al. 2013, Mainman et al. 2010) and evidence based guidelines for RA (Smolen et al. 2017, Singh et al. 2016). We would therefore propose removing the limitation to treating solely with oral methotrexate and would suggest the following change to the recommendation: Offer additional cDMARDs (leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step up strategy when the treatment target (remission or low disease activity) has not been achieved despite the optimisation of MTX (or other cDMARDs) via dose and subcutaneous administration. *Bianchi G. Methotrexate and Rheumatoid Arthritis: Current Evidence Regarding Subcutaneous Versus Oral Routes of Administration. Adv Ther 2016; 33: 369–378* *Cipriani P et al. Methotrexate in rheumatoid arthritis: Optimising therapy among different formulations. Current and emerging paradigms. Clinical Therapeutics 2014a; 36(3)* *Cipriani P et al. Methotrexate: an old new drug in autoimmune diseases. Expert Rev Clin Immunol. 2014b; 10(11)* *Gottheil S, Thorne JC, Schieir O, Boire G, Haraoui B, Hitchon C, Tin D, Barnabe C, Hazlewood G, Keystone E, Bykerk VP, Pope JE, Bartlett SJ. "Early Use of Subcutaneous MTX Monotherapy Vs. MTX Oral or Combination Therapy Significantly Delays Time to Initiating Biologics in Early RA [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10).* *Jay R. Methotrexate revisited: considerations for subcutaneous administration in RA. Clin Rheumatol 2015; 34: 201-205* *Keystone E and Freundlich B. Methotrexate in rheumatoid arthritis: benefits, limitations and the emerging value of subcutaneous administration. Int. J. Clin. Rheumatol 2014; 9(4): 345-351* *Li et al. Subcutaneous administration of methotrexate at high doses makes a better performance in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: A systematic review and meta-analysis. Sem Arthritis Rheumatism 2016; 45: 656-662* *Mainman H et al. When should we use parenteral methotrexate? Clin Rheumatol 2010; 29: 1093–1098* *Singh JA et al. 2015 American College of Rheumatology Guideline*	

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						for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research 2016; 68(1): 1–25 *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76(6): 960-977* *Vena GA, Cassano N and Iannone F. Update on subcutaneous methotrexate for inflammatory arthritis and psoriasis. Ther Clin Risk Mang 2018; 9(14): 105-116* *Yadlapati S and Efthimiou P. Inadequate response or intolerability to oral methotrexate: Is it optimal to switch to subcutaneous methotrexate prior to considering therapy with biologics? Rheumatol Int 2016; 36: 627-633* *Yazici Y and Bata Y. Parenteral Methotrexate for the Treatment of Rheumatoid Arthritis. Bulletin of the Hospital for Joint Diseases 2013; 71(Suppl 1): S46-8*	
54	[office use only]	NHS England	Full	4	1.1.2 and 1.1.3	Draft guideline seems to suggest RF and Anti CCP Antibody are secondary care investigations, while these are undertaken routinely now in Primary Care	Thank you for your comment. The committee are aware these may be done in primary care – as implied in recommendation 1.1.1 but had wanted to highlight that results of these tests should not delay referral for further investigation, diagnosis and rapid treatment as appropriate. The line 'these recommendations on investigations are for specialist care' has been edited to say 'If the following investigations are ordered in primary care, they should not delay referral for specialist opinion (see recommendation 1.1.1)' to clarify that they may be done in primary care.
55	[office use only]	NHS England	Full	4	5-11	The guideline recommendation would mean OA, Gout and other conditions which can cause synovitis would end up being referred to Secondary Care, which are currently managed in Primary care in many instances.	Thank you for your comment. This section has not been prioritised for update. The heading was amended slightly from the 2009 wording 'referral for specialist treatment' to 'Referral from primary care'. Recommendation 1.1.1 now states that this is for adults with *persistent* synovitis 'of undetermined cause'. The word 'persistent' was deleted in error in the consultation

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							version of the guideline and has now been reinstated. The committee considered that this wording should not lead to the referral of people with conditions such as OA and gout.
56	[office use only]	NHS England	Full	9	Sec 1.8	The referral to Specialist Physiotherapy/Occupational Therapy/Hand exercises Programmes/Podiatry and periodic review does not specify where the responsibility for referral and ongoing monitoring of outcomes lies	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
57	[office use only]	NHS England	Full	20	Lines 15-24	Guideline does not specify where the responsibility of monitoring of active disease lies, as it this is passed to Primary care - it has potential for increasing the work load caused by the need to liaise on a monthly basis with Secondary care.	Thank you for your comment. The initial recommendation of the guideline is under the subheading of 'Referral from primary care'. Following referral, diagnosis, management and monitoring would be in secondary care.
58	[office use only]	Pfizer Ltd	Full	8	15 & 16	It is stated that "all other treatments (including biological and targeted synthetic DMARDs) have been offered.", however, targeted synthetic DMARDs were not available in 2009; therefore, this amend should be noted as a 2018 update.	Thank you for your comment. This text was highlighted in yellow in the consultation version of the short guideline to indicate that it had been altered since 2009, consistent with NICE's approach for editorial changes only to recommendations.
59	[office use only]	Pfizer Ltd	Full	13	17-26	Under the "Terms used in this guideline", only conventional disease-modifying anti-rheumatic drugs are outlined for the reader; Pfizer would recommend that both biological DMARDs and targeted	Thank you for your comment. The 'terms used in this guideline' section in the short version is intended to just refer to key terms used in the

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						synthetic DMARDs are included in this list to inform the individuals utilising this guideline.	recommendations. Conventional DMARDs were the only DMARDs in the scope of this update and therefore the definition focusses on these, and does clarify that targeted synthetic DMARDs are not included within this group.
60	[office use only]	Podiatry Rheumatic Care Association	Full	page 36	section 5	The extension of the annual review to include those people who have achieved clinical targets is welcomed. From a podiatry perspective, there is a group of people who continue to experience active foot problems despite low DAS scores. This will help to support onward referral for lower limb problems.	Thank you for your comment.
61	[office use only]	Podiatry Rheumatic Care Association				Implementation issues: Examples that promote the impact of lower limb problems and their MDT management would help to promote this aspect of MDT care particularly to commissioning groups.	Thank you for your comment. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
62	[office use only]	[Primary Care Rheumatology Society]	Full	4	5,15,18	We recognise and support the need for early arthritis diagnosis and treatment but we wonder about the possibility of helping to streamline the referrals that are sent to secondary care. The guideline recommends that investigations should be done in specialist acre and we feels this may be ignoring a lot of good work and referral processes that already exists in primary and community care. We feel that primary care could initiate the investigations for inflame markers, rheumatoid factor, xrays etc at the point of referral so that the information is there for the specialist and will speed up diagnosis and management. We agree that anti –CCP antibodies is	Thank you for your comment. The committee are aware these tests may be done in primary care – as implied in recommendation 1.1.1 but had wanted to highlight that results of these tests should not delay referral for further investigation, diagnosis and rapid treatment as appropriate. The line 'these recommendations on investigations are for specialist care' has been edited to say 'If the following investigations are ordered in primary

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						best reserved to be implemented in specialist care if rheumatoid factor is negative and there is still strong clinical suspicion	care, they should not delay referral for specialist opinion (see recommendation 1.1.1)' to clarify that they may be done in primary care.
63	[office use only]	[Primary Care Rheumatology Society]	Full	8	13	We would recommend adding screening for osteoporosis in patients on long term glucocorticoids	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
64	[office use only]	[Primary Care Rheumatology Society]	Full	9	5,11	This would have significant resource implications as many rheumatology departments have a small number of staff. Majority of departments will rely on their rheumatologists or staff grade clinicians and rheumatology nurses predominantly. Some have access directly to allied health professionals but not all departments. Having a named person co-ordinating care for patients could necessitate an increase in staffing for these departments at significant cost. Also, rheumatology specialist nurses are in short supply and may departments around the country struggle to find people to recruit.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
65	[office use only]	[Primary Care Rheumatology Society]	Full	9	16	Specialist physiotherapy for rheumatoid arthritis is not always available in local departments. This could have cost implications for implementation.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
66	[office use only]	[Primary Care Rheumatology Society]	Full	10	22	Psychological interventions for people with RA are not currently provided routinely. We agree with the guideline statement as best practice but are aware there could be cost implications for	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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						implementation.	
67	[office use only]	[Primary Care Rheumatology Society]	Full	11	16	There are pressures on many rheumatology departments and so ensuring rapid access for patients with flares could be quite difficult and can increase pressure on those departments.	Thank you for your comment. This recommendation is consistent with the 2009 guidance; the updated evidence review did not indicate that substantial changes to the recommendation were required. The committee considered that access may be by a telephone service; this has not been defined within the recommendation as the method of providing access may vary according to department.
68	[office use only]	Royal College of Anaesthetists	Full	25	9-27	The recommended pain armoury is limited and arguably too limited for those who have refractory pain and seek treatment. A more pragmatic approach could enable more effective treatment though if various recognised pain-killers are proven in the future not to work in this context then this would of course be wasteful.	Thank you for your comment. The evidence for analgesics was reviewed within the guideline; however the only available evidence identified was for NSAIDs. The committee agreed that there may be some benefit of analgesia other than NSAIDs and therefore have prioritised a research recommendation in this area.
69	[office use only]	Royal College of General Practitioners				Regarding the 'treat to target' section, I have met a number of patients in general practice who are under the care of rheumatologists for RA who continue to complain of significant joint pains. Their rheumatologists tell them that they should be pleased with their care as their RA is under control. I recall at least 1 patient with RA and another with psoriatic arthritis in this position, who, when I met them, clearly also had a co-existant connective tissue disease – either hEDS or HSD. This paper https://www.nature.com/articles/srep39636#s1 reviewed patients with hEDS and showed the prevalence of other rheumatological	Thank you for your comment. The guideline should be considered in tandem with clinical judgement, to consider the possibility of co-existing conditions.

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						conditions, trying to relate it to the degree of 'work-up' the patients had. I was not completely convinced by this argument, but found the tables in the supplementary information https://media.nature.com/original/nature-assets/srep/2017/170104/srep39636/extref/srep39636-s1.pdf highly illuminating, showing the significant increased prevalence of a number of conditions in hEDS patients. I would suggest therefore consideration of the possibility of a co-existing HCTD or specifically hEDS in patients with quiescent RA, but ongoing pain.	
70	[office use only]	Royal College of General Practitioners	Full	General	General	Overall, the guideline document is excellent; well-reasoned with a solid evidence base, achievable and likely to result in meaningful improvements in patient outcome.	Thank you for your comment and support of the guideline.
71	[office use only]	Royal College of General Practitioners	Full	4	1.1.1	This may result in referral of patients with short-lived reactive arthritis, whose symptoms may have resolved by the time of clinic review. However, that this should be balanced against the evidence-based need to ensure rapid assessment and treatment of patients with a new inflammatory arthritis. Whilst the recommendation may result in referral of patients with transitory self-limiting arthritis, on balance the benefits of urgent referral of all patients with small joint, persistent or polyarthritis outweighs this potential negative.	Thank you for your comment. The word 'persistent' was deleted in error in the consultation version of the guideline and has now been reinstated in recommendation 1.1.1. This should now not lead to referral of people with short-lived reactive arthritis.
72	[office use only]	Royal College of General Practitioners	Full	4	1.1.1	This recommendation may prove challenging in practice as it will result in an increase in urgent referrals to secondary care. This has implications for secondary care rheumatology departments, who may not have sufficient resources to assess patients within a reasonable timescale.	Thank you for your comment. This recommendation was not prioritised for update within the guideline; however an editorial change was made, removing the term 'persistent'. This has been reinstated so that the meaning remains the same as in the 2009 recommendations.

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73	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the United Kingdom. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this review of the Management of Rheumatoid Arthritis by NICE. It recognises that management protocols need to change with changes in the understanding of disease, its assessment and its treatment. Important changes have been made in this recommendation to reflect these.	Thank you for your comment.
74	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	5	8	It is important that the document stresses that anti CCP antibodies (and Rheumatoid factor) should not be used as a diagnostic test in patients with a new-onset inflammatory arthritis. As the whole document implies, this test determines prognosis. Patients can have negative tests (about one third) which denote a better prognosis but they do not exclude Rheumatoid Arthritis. Patients are frequently not referred to hospital because they have negative tests despite the right symptoms and signs.	Thank you for your comment. We agree and have implied that there should not be a delay in referral to secondary care in people even with negative blood tests. We have added anti CCP antibodies to recommendation 1.1.1 to clarify. Recommendation 1.1.5 is intended to inform prognosis and not as diagnosis. A line has been included to state that if the investigations are ordered in primary care, they should not delay referral for specialist opinion.
75	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	5	12	This is challenging in practice because it requires administration so that at outset the HAQ is documented. HAQ also was devised at a time when RA caused major disability whereas now with early intervention and aggressive management, this particular score is too blunt to pick out problems in what is now a very different population. It is also is heavily weighted to female patients. Therefore research may be more productive with an alternative score sensitive to early mild disability.	Thank you for your comment. The addition of a measure of functional ability at baseline assessment is to provide a reference for the assessment that is undertaken at the annual review. HAQ is given as an example of a functional ability measure that may be used as the committee recognise that there are other options.
76	[office use only]	Royal College of Physicians and Surgeons	Full	6	5	Monthly monitoring of disease activity was acknowledged as achievable in those hospitals which had early arthritis clinics. The College is concerned that the provision of these clinics is patchy is	Thank you for your comment. The evidence for frequency of monitoring was reviewed within the guideline, however no evidence

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		of Glasgow				often dependent on alocated time of a Specialist Nurse. This provision is highly variable throughout the UK.. To therefore deliver this more consistently this resource may need to be increased or quantified in areas without a specialist nurse service. Throughout the document there needs to be a clear distinction between disease activity monitoring and drug safety monitoring where there are agreed national guidelines (BSR). The intervals are defined and in the initial stages less than one month. Also Page 26 line 12. CRP or ESR can be used for measuring DAS score.	was identified to change the 2009 recommendation that this should be on a monthly basis. This is therefore not a change from the previous recommendation. The guideline distinguishes between disease activity monitoring and drug safety monitoring by separating recommendations for a treat to target approach with monthly monitoring (recommendations 1.2.1 – 1.2.3) from those for ongoing monitoring in recommendation 1.9.1, where ongoing drug monitoring Is recommended.
77	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	6	22	The commencement of a single cDMARD rather than the former combination recommendation is welcome. The evidence that combination DMARDS are superior is limited and side effects are greater. A small proportion of patients do better on combination therapy.	Thank you for your comment and support of this recommendation.
78	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	8	18	Potential side effects of NSAIDS have been over estimated by individuals. Cardiovascular side effects are in the region of 1-3 Adverse events per 1000 patients years which is low risk. Yet patients without risk factors are often denied these drugs. A discussion of absolute rather than relative risk would be helpful. Also Page 25 line 11	Thank you for your comment. We have recommended taking different factors into account when prescribing, but do not think further detail is required within these sections relating to this point.
79	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	11	16	Patients are increasingly having difficulty obtaining access to specialist care in a flare. Some estimation of the time interval that is the maximum expected should be included.	Thank you for your comment. The committee hope that reiteration of the recommendation in this updated guideline may improve access. The evidence review was unable to inform a time interval. Stating a specific maximum time

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							may put additional pressure on departments and therefore would have to be informed by robust evidence.
80	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	12	12	The recommendation that Ultrasound should not be used routinely in monitoring is welcome. It can however be helpful in difficult situations. However routine US has not been shown to been superior to clinical assessment	Thank you for your comment. An evidence review was undertaken for the added value of ultrasound in monitoring of people with rheumatoid arthritis. This did not demonstrate any added value from the use of ultrasound for routine monitoring. The committee's experience suggested that there may be circumstances in which monitoring with ultrasound may be useful, for example when clinical examination was uncertain or inconsistent with other signs of disease activity. As the current evidence base was unable to inform a recommendation in this group, a research recommendation was prioritised by the committee in this area to inform future updates of the guideline. This is also discussed in the rational and impact section on page 26.
81	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	12	17	Although in the grey area, an important complication has been omitted. Acute cervical cord compression or myelopathy from Rheumatoid cervical involvement is a reason for emergency referral. While with more effective treatment this is less common, it is still an important complication which needs acute referral.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
82	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	13	19	Oral cortico steroids have significant side effects and should be used sparingly. It is more difficult to wean them off once started whereas it easier to tide patients over with parenteral steroids for the necessary 2-3 months. We agree this an area for research (Page 15 line 9).Also page 23 line 15.	Thank you for your comment. The section you refer to is to provide a definition to explain the terms used within the guideline. Thank you for the support for the research recommendation, we agree this is an

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							important area.
83	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	15	2	We agree this is an important area. The evidence that analgesics such as Paracetamol, Tramadol and codeine derivates are effective is limited. NSAIDS should be reconsidered with absolute risks ascertained. Many studies use relative risk which is unhelpful	Thank you for your comment and support of this research recommendation.
84	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	15	15	The document does not state the time intervals for escalation. As stated here the response rate may be two to three months yet current protocols suggest escalation at monthly intervals. Clarification through research is important.	Thank you for your comment. A specific time interval for dose escalation has not been specified as this will be determined on an individual basis according to the treat to target strategy. Further research on the use of glucocorticoids for bridging therapy may be able to inform the length that they should be used for at this stage.
85	[office use only]	Royal College of Physicians and Surgeons of Glasgow	Full	15	29	Fully agreed. While the place of Ultrasound in diagnosis is helpful, the place in monitoring is far less clear and work needs to be done in this area	Thank you for your comment and support of this recommendation.
86	[office	Sanofi UK,	Full	General	General	Sanofi are pleased to see this clinical guideline being reviewed, and	Thank you for your comment.

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	use only]					largely welcome the amendments being suggested. We are also very supportive of a 'treat to target' approach and a specified monitoring process to encourage effective management of patients with RA. There are some specific comments on the guideline, which follow. A general comment is that it would be helpful to clarify where the transition points are between different NICE guidelines or guidance documents. For example, this document could make clearer the circumstances under which biologic DMARDs could be introduced and reference the relevant guidance, rather than just saying that the guidance is available. This would help place these guidelines within NICE's overall RA treatment pathway. We would also welcome further initiatives which support the practical implementation of these guidelines. We look forward to seeing them delivered in clinical practice. Sanofi does not foresee any particular challenges or significant cost implications to the NHS arising from the revision of these guidelines. We feel there are a number of positive elements within the guideline wording that may clarify the advice being given and support communication with patients.	A link will be included to the relevant NICE technology appraisals in the NICE pathway that will accompany the guidance on the NICE website.
87	[office use only]	Sanofi UK,	Full	5	12	Whilst HAQ is a useful tool here, we would suggest it not be recommended in isolation. DAS28 would also provide a good marker of baseline disease severity (as well as during monitoring). For some patients HAQ measurements may be affected by comorbidities unrelated to RA therefore suggesting DAS as well as HAQ may give a more appropriate detail of a patients baseline health status with regard to their RA.	Thank you for your comment. HAQ was given as an example of a tool that is used to measure functional ability as agreed by the committee to be widely used. Disease activity monitoring is also recommended as part of the treat to target strategy, where DAS28 is given as an example (recommendation 1.2.3).
88	[office use only]	Sanofi UK,	Full	5	21	Sanofi UK are very supportive of a 'treat to target' approach and a specified monitoring process to encourage effective management of patients with RA.	Thank you for your comment.

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89	[office use only]	Sanofi UK,	Full	5	23	Whilst we support a treat-to-target approach, Sanofi UK feel that the treatment aim in RA should be the achievement of remission in all patients. As currently worded, it would suggest that treatment to a low disease activity would be acceptable, which implies a lower quality of patient outcome. This statement should also acknowledge that for patients failing to achieve remission, there is the possibility of further treatment (outside of cDMARDs) which could support that treatment aim. We also feel it would be helpful to clarify the criteria which define "remission", for example identifying markers of full clinical remission, rather than it being individually identified by blood samples, radiographic imaging etc.	Thank you for your comment. We agree that the aim should be remission; however, the committee recognised that for some people this is not achievable, and therefore low disease activity was included as an option for these people. The link to options for further pharmacological management is provided in section 1.5 of the guideline. In the committee's discussion of the evidence in Evidence reviews C and D (section headed 'Benefits and harms') there is further clarification provided regarding possible definitions of remission, noting that various composite scoring measures can be used, and therefore a definition is not given within the recommendation.
90	[office use only]	Sanofi UK,	Full	6	22	It is unclear in the document what options should be considered if methotrexate (or other cDMARD) is contraindicated before and/or during treatment. Whilst there is reference to offering subcutaneous therapy if a patient cannot tolerate oral, we feel the next steps where there is general intolerance towards methotrexate could be clarified.	Thank you for your comment. The evidence for subcutaneous methotrexate was reviewed, but no relevant evidence was identified to support a recommendation. A research recommendation was therefore prioritised by the committee to inform future updates of the guideline. In the discussion of the evidence in the review the committee noted that for people who have experienced adverse events on monotherapy or are at an increased risk of adverse events, switching to an alternative monotherapy (leflunomide, sulfasalazine, or for some people hydroxychloroquine) may be preferable to adding a second drug.
91	[office use only]	Sanofi UK,	Full	7	1	It would be beneficial to highlight that if a patient is intolerant of oral methotrexate, they could be offered subcutaneous methotrexate, which should be considered by the treating clinician.	Thank you for your comment. The evidence for subcutaneous methotrexate was reviewed, but no relevant evidence was identified to

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							support a recommendation. A research recommendation was therefore prioritised by the committee to inform future updates of the guideline.
92	[office use only]	Sanofi UK,	Full	7	4	Sanofi feel the document could benefit from a recommendation here to keep the patient informed of the wider issues in their treatment. This could support patients who encounter problems or adverse events when taking cDMARDs, potentially reassuring them as 'something that might happen', thereby promoting compliance. It would also be worthwhile including recommendations for wider reminders on contraindications and interactions eg. folate supplements, alcohol intake etc, which may support patients managing their lifestyle to get the most from their therapy. There can be longer term consequences for younger patients commencing DMARD therapy which should be borne in mind, for example, pulmonary fibrosis could be a possible adverse long-term consequence initiating DMARD treatment in a 30 year old patient. It may be worth recommending consideration of the patient-type being treated in making a treatment choice.	Thank you for your comment. All treatment decisions should be made in discussion and consultation with the patient. These principles are covered within the NICE guideline on patient experience in adult NHS services (CG138) and should apply across conditions. Involving patients in decision-making, medication review, supporting adherence and self-management plans are all also covered in the NICE medicines optimisation (NG5) and medicines adherence (CG76) guidelines

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93	[office use only]	Sanofi UK,	Full	7	8	Sanofi have reviewed the evidence used to support the recommendation to offer additional conventional disease-modifying anti-rheumatic drugs (cDMARD) in a step-up strategy when the treatment target has not been achieved: We are concerned that this recommendation may be based on evidence that is subject to a high risk of bias and/or imprecision which may prevent robust and reliable conclusions being drawn; This recommendation may encourage continuation and prolongation of cDMARD therapy potentially resulting in poorer long term outcomes for patients. In making these comments, Sanofi UK have observed that: Only 4 studies were included in this review and of the 21 separate outcomes evaluated across the studies, four were identified by the review team as being of "moderate quality", six were of "low quality", and 11 were of "very low quality". No individual study showed a consistent, favourable effect for step-up therapy in all efficacy outcomes evaluated. Moreover, only two single outcomes across all four studies (each in a separate study) showed a statistically significant relative effect in favour of step up therapy. Finally, we noticed that the recommendation and accompanying treatment algorithm is worded such that it can be interpreted that step-up treatment with cDMARDs **should** be continued despite multiple, repeated, treatment (target) failure. This is concerning due to the well-established toxicity of dual and triple cDMARD therapy, and the irreversible joint damage progression that occurs in patients whose disease is not adequately controlled.	Thank you for your comment. This evidence was reviewed by the committee and full details provided in the evidence report. Although there were some limitations to the evidence as you state, the benefits and harms section explains that there was evidence that after failing a DMARD, adding another DMARD ('step-up therapy') yielded better clinical results than replacing the DMARD ('sequential monotherapy') based on the differences in DAS, ACR50 response and low disease activity. The committee agreed improvement in various disease activity measures was most important, as seen with step-up therapy. While the difference between the treatment strategies was not as consistent for other outcomes, there were no clinical outcomes for which sequential monotherapy performed better than step-up therapy. In the event of inadequate response to monotherapy, the committee decided to recommend a step-up approach (adding another DMARD) rather than replacing the DMARD to which there had been insufficient response initially (sequential monotherapy). The committee do not agree that the recommendations or algorithm imply that the step-up strategy should be continued if it repeatedly fails. Section 1.5 within the guideline links to other treatment options and the algorithm includes a box stating 'Return to step-up strategy (see *) or see † for biological drugs for RA." if treatment target is not achieved.
94	[office use only]	Sanofi UK,	Full	7	8-14	The guideline may benefit from clarifying the time to 'stop' cDMARDs and move to the next stage in treatment, eg. biological DMARDs. While we welcome the mention of the biologics guidance, there is no continuity here to suggest when that should be looked at as a treatment option.	Thank you for your comment. This is informed by the treat to target strategy with monthly monitoring, and by the guidance in the relevant technology appraisals linked to in section 1.5. Unfortunately the evidence

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							reviewed did not inform on timescales for each stage of the treatment. Following a treat-to-target strategy, these would be informed by the person's response to treatment on an individualised basis.
95	[office use only]	Sanofi UK,	Full	9	5 (out of scope?)	Whilst we recognise that this section is 'out of scope' for this consultation, we are also concerned that RA mostly affects an older population. As a result, RA patients can often have with many other complexities in their management. Therefore, close communication with carers and family regarding treatment compliance and satisfaction may be advisable and we would welcome this being reflected in this section.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
96	[office use only]	Sanofi UK,	Full	10	21-25	We feel the recommendation here could be strengthened from "offering help" to include more formal management to support patients living with their condition. For example, patients could be monitored by their GP for psychological wellbeing (eg. depression, which is mentioned) but the wording could be strengthened to include recommendation for follow up or suggested referral to mental health services.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
97	[office use only]	Sanofi UK,	Full	11	18	While outside the specific scope of this consultation, we feel that periodic monitoring assessments by the multidisciplinary team should also be sensitive to the potential side effects posed by cDMARDs, such as pulmonary fibrosis, liver fibrosis and renal toxicity, symptoms of which could be screened and acted upon early.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.
98	[office	Sanofi UK,	Full	11	18	As part of the ongoing monitoring for patients with RA, we feel the	Thank you for your comment. This topic was

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	use only]					patient should be consulted about their medication to ensure they remain compliant with their prescribed treatments. Patients who experience adverse events or are otherwise unhappy on their medication will often stop taking it. This would be supported by providing information on further or other treatment options which are also recommended by NICE as part of the wider treatment pathway for RA. A change to line 18 could be: "information about ongoing drug monitoring and potential treatments, including a possible move to biologic therapy".	not included in the scope for the update of this guideline.
99	[office use only]	Sanofi UK,	Full	12	12	Whilst we note that the use of ultrasound in routine monitoring of disease activity is not recommended, we do feel that this could be explored further as an area for further research in assessing (and assisting the physician's) treat-to-target thresholds and signs of subclinical inflammation.	Thank you for your comment. An evidence review was undertaken for the added value of ultrasound in monitoring of people with rheumatoid arthritis. This did not demonstrate any added value from the use of ultrasound for routine monitoring. The committee's experience suggested that there may be circumstances in which monitoring with ultrasound may be useful, for example when clinical examination was uncertain or inconsistent with other signs of disease activity. As the current evidence base was unable to inform a recommendation in this group, a research recommendation was prioritised by the committee in this area to inform future updates of the guideline. This is also discussed in the rational and impact section on page 26.
100	[office use only]	Sanofi UK,	Full	16	4-10	While the proposed guideline does not support the use of ultrasound in monitoring disease activity, we do feel that it can be a valuable tool in the diagnosis of RA, and would not wish to see any confusion here. Ultrasound has a number of advantages over other diagnostic measures, not least in that it is cheaper than other diagnostic methods and doesn't involve a radiation risk (eg. in pregnant patients).	Thank you for your comment. An evidence review was undertaken for the added value of ultrasound in diagnosis as well as monitoring of people with rheumatoid arthritis. For both of these areas the guideline committee agreed that a research recommendation should be drafted. In the case of monitoring, the evidence review did not demonstrate any added value from the use of ultrasound for routine monitoring; hence a recommendation was drafted stating 'do not use ultrasound for

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							routing monitoring'. In the case of the use of ultrasound for diagnosis, the evidence was limited and inconsistent and therefore no recommendation was made, but a research recommendation was drafted to inform who, if anyone, should have ultrasound to aid diagnosis.
101	[office use only]	Thermo Fisher Scientific	Full	4	15-17	**Comment 2.** In the guidelines draft, NICE advises testing for RF, but does not give advice on which isotypes to use. RF-IgM is referred to (together with anti-CCP) in the ACR/EULAR criteria 2010 [Aletaha et al., 2010], so obviously it becomes important to know what is being tested. In fact, nephelometry tests are available in the market that do not allow discrimination between RF-IgM and RF-IgA. The consequence of this is that the test result contains only partial information, and this can affect the clinicians' decision making. The scientific literature shows that an increase in both RF IgM and IgA is almost exclusively observed in patients with RA [Jónsson et al., 1998; Jónsson et al, 1998]. The three RF isotypes are already available in pre-symptomatic individuals years before disease onset, and they are the first appearing antibodies, RF-IgM displaying the highest frequency, followed closely by RF-IgA [Brink et al., 2016; Gan et al., 2015]. RF-IgA may have important implications for the understanding of the disease [Brink et al., 2016]. In fact, patients presenting with raised RF IgA are known to develop more severe, erosive disease: they developed a greater number of erosions, required much more pharmaceutical treatment [Teitsson et al., 1984; Eggelmeijer et al., 1992]. The presence of RF IgA could justify more aggressive treatment at an early stage [Teitsson et al., 1984], but may predict a poor response to TNF inhibitors [Bobbio-Pallavicini et al., 2007]. Concerning RF-IgM, Jaskowski et al. showed that specimens having only RF-IgM are associated with low probability of RA, as also shown previously on defined patient populations [Jaskowski et al., 2010]. Therefore, in the NICE guidelines draft **we suggest to specify the intended RF isotype(s).**	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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102	[office use only]	[UCB Pharma Ltd.]	Full draft guideline	9	5-10	We feel this recommendation should also include an opportunity for patients to discuss the impact of RA and treatments on their decisions to plan a family, safely carry a pregnancy to full term and breastfeeding, while on treatment for RA. As an example we propose the following minor amendment (in **bold text**): 1.7.1 Adults with RA should have ongoing access to a multidisciplinary team. This should provide the opportunity for periodic assessments (see 1.9.1, 1.9.2 and 1.9.3) of the effect of the disease on their lives (such as pain, fatigue, everyday activities, mobility, ability to work or take part in social or leisure activities, quality of life, mood, impact on sexual relationships, **as well as family planning and pregnancy related issues**) and help to manage the condition. [2009] This is supported by the EuLAR article "**The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation**" (Götestam Skorpen C et al. Ann Rheum Dis. 2016;75:795–810), wherein the EuLAR overarching principles are discussed and then summarised below (Skorpen et al.): Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy. Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the fetus/ child to no harm. The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child. The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

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						Our recommendation is further supported by the British Society of Rheumatology (BSR), who in their 2016 Guidelines provide evidence-based recommendations for clinicians when prescribing anti-rheumatic drugs before/during pregnancy and breastfeeding. "**BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease-modifying anti-rheumatic drugs and corticosteroids" (**Flint et al. *Rheumatology*, Volume 55, Issue 9, 1 September 2016, Pages 1693–1697.)	
103	[office use only]	[UCB Pharma Ltd.]	Full draft guideline	11-12	22-23 to 1-6	We feel the annual review, for those women with RA who have achieved the treatment target and who are of child bearing age (18-45 years old), should include discussions about: whether they are considering starting a family in the coming year whether they have any concerns about continuing treatment while pregnant the safety of breastfeeding while on treatment As an example, we would suggest the following amendment (in **bold text**): 1.9.3 Offer all adults with RA, including those who have achieved the treatment target, an annual review to: assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ]) check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes organise appropriate cross referral within the multidisciplinary team assess the need for referral for surgery (see section 1.10) assess the effect the disease is having on a person's life. **whether they are considering starting a family in the coming year** **whether they have any concerns about continuing treatment while pregnant** **the safety of breastfeeding while on treatment** [2009, amended 2018]	Thank you for your comment. This topic was not included in the scope for the update of this guideline. Considerations for pharmacological treatment of pregnant women were detailed within the relevant evidence reviews in the committee's discussion of the evidence. These include Evidence review F on DMARDS where it is noted that this should be done by means of an individualised and consultant-led service, with involvement of obstetric services and broader rheumatology MDT as indicated. This should include pre-conception advice and management of pharmacological therapies, assessment of potential impact of disease on the pregnancy, advice on disease course during pregnancy, and discussions regarding the disease and its treatment in the post-partum period. Particular attention should be paid to therapeutic management of rheumatoid arthritis, especially conventional DMARDs and biologic DMARDs, to ensure potentially teratogenic therapies are not continued in the pre-conception stage or into early pregnancy. Alternative management strategies should be considered, depending on each patient's level of disease control and symptoms, for the duration of the pregnancy.

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						Again, this is further supported by the article by Skorpen et al. "**The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation**" (Götestam Skorpen C et al. Ann Rheum Dis. 2016;75:795–810), wherein the EuLAR overarching principles are discussed and then summarised (Skorpen et al.): Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy. Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the fetus/ child to no harm. The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child. The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate	Similar considerations are noted in reviews G and H for analgesics and corticosteroids respectively.
104	[office use only]	University Hospitals Birmingham	RA draft guidance (update)	4 5	13-19 1-8	The recommendations for investigations are prefaced by the statement 'These recommendations on investigations are for specialist care'. The reality of blood tests at least is that many are done by GPs to help with diagnosis and to help decide whether to refer or not. Our immunology laboratory does as many anti-CCP and Rheumatoid factor tests for GPs as it does for our hospital. In relation to rheumatoid factor and anti-CCP testing I feel the recommendations are somewhat illogical. In my experience our department is referred many patients with low level rheumatoid factor positive results. Often anti-CCP antibody testing is not done and most of these patients do not have rheumatoid arthritis. Given the higher specificity of anti-CCP and accepting that clinical judgment (rather than laboratory test result) should be the key determinant of a decision to refer it would make sense to do away with routine rheumatoid factor tests. My feeling is that GPs should be advised to forego rheumatoid factor testing in favour of anti-CCP testing.	Thank you for your comment. The committee are aware these may be done in primary care – as implied in recommendation 1.1.1 but had wanted to highlight that results of these tests should not delay referral for further investigation, diagnosis and rapid treatment as appropriate. The line 'these recommendations on investigations are for specialist care' has been edited to say 'If the following investigations are ordered in primary care, they should not delay referral for specialist opinion (see recommendation 1.1.1)' to clarify that they may be done in primary care.

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						Investigations for diagnosis should be framed for a more general medical audience rather than specialists. If that were done my preference would be to remove the recommendation that x-rays of hands and feet are done. Such x-rays are still requested by primary care physicians and generally have very little value. One might debate the true value of these tests in hospital practice and certainly the value of repeated x-rays to monitor disease should be challenged robustly.	
105		Department of Health and Social Care				Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding this consultation.	Thank you for your comment.
106		Royal College of Nursing	General	General	General	The Royal College of Nursing welcomes proposals to update this guidance. The Royal College of Nursing (RCN) invited members who care for people with rheumatoid arthritis to review the draft document on its behalf. The comments below reflect the views of our reviewers.	Thank you for your comment.
107		Royal College of Nursing	General	General	General	The guidance highlights the importance of multi-disciplinary team and specialist nursing support for people with rheumatoid arthritis (RA). However, the simplicity of the statements does not outline to commissioners the benefit and importance of having specialist team support to provide effective and well informed guidance on monitoring, treating to target and managing potential problems that may cause the patient to stop treatment. Equally educational initiatives that tailor information and support are greatly valued by patients and enable confident self-management approaches.	Thank you for your comment. This topic was not included in the scope for the update of this guideline.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
AbbVie Ltd.doc	AbbVie Ltd.	N/A	10	
Bristol-Myers Squibb Pharmaceuticals Ltd.doc	Bristol-Myers Squibb Pharmaceuticals Ltd.	None.	6	
British Society for Rheumatology.doc	British Society for Rheumatology	None	4	
Eli Lilly and Company Limited.doc	Eli Lilly and Company Limited	No links	2	
Gilead Sciences.doc	Gilead Sciences	N/A	11	
GreenVits.doc	GreenVits	N/A	6	
Keele University.doc	Keele University	[Nothing to declare]	9	
medac Pharma.DOC	medac Pharma (formerly medac GmbH)	None	5	
MSD.doc	MSD	None	0	
NHS England.doc	NHS England	[Insert disclosure here]	4	
Pfizer Ltd.doc	Pfizer Ltd	None	2	
Podiatry Rheumatic Care Association.doc	Podiatry Rheumatic Care Association		2	
Primary Care Rheumatology Society.doc	[Primary Care Rheumatology Society]	[None]	6	
Royal College of Anaesthetists.doc	Royal College of Anaesthetists	N/A	1	
Royal College of General Practitioners.doc	Royal College of General Practitioners	None known	4	

Royal College of Physicians and Surgeons of Glasgow.doc	Royal College of Physicians and Surgeons of Glasgow	None	13	
Sanofi UK.doc	Sanofi UK,	[Insert disclosure here]	15	
The Royal College of Ophthalmologists.doc	[The Royal College of Ophthalmologists]	[None]	0	
Thermo Fisher Scientific.doc	Thermo Fisher Scientific	N/A	1	
UCB Pharma Ltd.doc	[UCB Pharma Ltd.]	[None]	2	
University Hospitals Birmingham.doc	University Hospitals Birmingham	[None]	1	