Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative


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ABSTRACT

Objectives
To develop evidence-based recommendations for the use of methotrexate (MTX) in daily clinical practice in rheumatic disorders.

Methods
A total of 751 rheumatologists from 17 countries participated in the 3E (Evidence Expertise Exchange) Initiative of 2007-2008 consisting of 3 separate rounds of discussions and Delphi votes. Ten clinical questions concerning the use of MTX in rheumatic disorders were formulated. A systematic literature search in Medline, Embase, Cochrane Library and 2005-2007 ACR/EULAR meeting abstracts was conducted. Selected articles were systematically reviewed and the evidence was appraised according to the Oxford Levels of Evidence. Each country elaborated a set of national recommendations. Finally, multinational recommendations were formulated and agreement among the participants and the potential impact on their clinical practice was assessed.

Results
A total of 16979 references were identified, of which 304 articles were included in the systematic reviews. Ten multinational key recommendations on the use of MTX were formulated. Nine recommendations were specific for rheumatoid arthritis, including the work-up before initiating MTX, optimal dosage and route, use of folic acid, monitoring, management of hepatotoxicity, long-term safety, mono versus combination therapy and management in the peri-operative period and before/during pregnancy. One recommendation concerned MTX as a steroid-sparing agent in other rheumatic diseases.

Conclusions
Ten recommendations for the use of MTX in daily clinical practice focussed on RA were developed, which are evidence-based and supported by a large panel of rheumatologists, enhancing their validity and practical use.
INTRODUCTION
Methotrexate (MTX) is the disease modifying anti-rheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA) and is used in other systemic rheumatic disorders as well.[1,2] Despite its widespread use and more than two decades of experience, considerable variation exists among rheumatologists in prescribing MTX, including the dosage, folic acid supplementation and safety monitoring.[3,4] In addition, little is known about the optimal management of MTX in specific clinical situations such as the peri-operative period and before/during pregnancy. Existing guidelines often lack this level of detail.[5]

The 3E Initiative (Evidence, Expertise, Exchange) in rheumatology is a multinational effort, aimed at promoting evidence-based medicine, by formulating detailed recommendations addressing clinical problems.[6] In contrast to guidelines developed by a limited panel of experts, the 3E Initiative involves a broad international panel of practising rheumatologists. Furthermore, the initiative promotes epidemiology, by teaching and conducting systematic literature research following a strict methodology.[7]

Therefore, the objective of the 3E Initiative of 2007-2008 was to develop practical recommendations for the use of MTX in rheumatic disorders, by integrating systematically generated evidence and expert opinion of a broad panel of international rheumatologists.

METHODS
A total of 751 rheumatologists from 17 countries participated in the 3E Initiative of 2007-2008. Each country was represented by a scientific committee, consisting of one principal investigator and 5-16 members. The bibliographic team consisted of six international fellows (WK, EL, JM, CS, JT, KV), three mentors (CB, LC, DvdH) and the scientific organizer (MD). During the first international meeting (n=87 participants), 10 clinically relevant questions on the use of MTX in rheumatic disorders were formulated and selected via a Delphi vote. The areas addressed were: for RA, pre-administration work-up, optimal dosage and route, use of folic acid, safety monitoring, hepatotoxicity (also for psoriatic arthritis (PsA)), long-term safety (>2 years), mono versus combination therapy, management in the peri-operative period and before/during pregnancy, and MTX as a steroid-sparing agent in other rheumatic disorders.

The bibliographic team conducted a systematic literature review, following the updated guidelines of the Cochrane Collaboration.[7] Each question was rephrased according to the PICO-method with the population defined as adult RA, PsA or other rheumatic diseases, and specific interventions, comparisons and outcomes defined according to each question.[8] Comprehensive search strategies were developed in collaboration with experienced librarians, including terms for MTX, RA and specific key words, without language restriction. Subsequently, Medline, Embase, Cochrane Library and EULAR’05-'07 and ACR’05-'06 abstracts were systematically searched for articles published up to September 2007. Additional references were identified via a hand search. Articles were selected applying predefined inclusion and exclusion criteria and their methodological quality was graded according to the Levels of Evidence of the Oxford Centre for Evidence-Based Medicine [http://www.cebm.net/index.aspx?o=1025 (accessed March 2008)]. For each question, relevant data were extracted and appropriate statistics were
calculated, including effect sizes (ES), hazard ratios (HR), and standardized mortality ratios (SMR) with 95% confidence intervals (CI). If possible, meta-analyses were conducted using RevMan 4.2.10, calculating odds ratios (OR) with fixed effects and relative risks (RR) with random effects model.

In the second round, a national meeting was held in each country (total n=751 participants) to discuss the generated evidence and propose a set of recommendations. In a third joint meeting, the scientific committees (n=94 participants) merged all propositions to 10 final recommendations via discussion and Delphi vote. The grade of recommendation according to the Oxford Levels of Evidence was assessed and the level of agreement was measured on a 10-point visual analog scale (1=no agreement, 10=full agreement).[9] Finally, the potential impact among the participants was assessed using 3 statements: “this recommendation will change my practice”; “this recommendation will not change my practice as it is already my practice”; “this recommendation will not change my practice as I don’t want to change my practice for this aspect”.

RESULTS
A total of 16979 references were identified, of which 304 articles were systematically reviewed (table 1). The 10 multinational key recommendations are listed in table 2, with the corresponding Level of Evidence and grade of recommendation. The mean level of agreement among the rheumatologists was 8.1 (range 7.4 to 8.8). The percentage of rheumatologists who indicated they would change their clinical practice according to each recommendation is shown in table 3.

Recommendation 1: The work-up for patients starting MTX should include clinical assessment of risk factors for MTX toxicity (including alcohol intake), patient education, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, complete blood count (CBC), creatinine, chest X-Ray (obtained within the previous year); consider serology for human immunodeficiency virus (HIV), hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.

The evidence needed to decide whether to start a patient with RA on MTX or not might be extrapolated from data on risk factors for severe toxicity. These data suggest that estimated creatinine clearance <79 mL/min increases severe MTX (pulmonary) toxicity and that hypoalbuminemia is associated with MTX-induced thrombocytopenia, liver and pulmonary toxicity.[10-14] In addition, lung abnormalities on radiographs, but not pulmonary function tests, are predictive for the development of MTX-induced pneumonitis.[15-17] Additional subgroups at risk for exacerbation of hepatic disease with MTX are obese patients, diabetics and patients with viral or alcoholic hepatitis.[18-22] This observational evidence was combined with expert opinion, following from contraindications to MTX use frequently listed in randomised controlled trials (RCTs) in RA from the past 15 years: significant renal disease, hepatic disorders, leucopenia<3.0x10⁹/L, thrombocytopenia<100x10⁹/L, age >70 years, malignancy, pregnancy or inadequate contraception, history of alcohol/drug abuse, acute or chronic infection and pulmonary disease. Finally, four national recommendations from Austria, Germany, the Netherlands and Spain and the ‘96 ACR guidelines on monitoring RA
treatment, all suggest creatinine, CBC, AST/ALT with or without alkaline phosphatase, albumin, hepatitis B/C serology and a chest radiograph for the pre-administration work-up.[23]

Recommendation 2: Oral MTX should be started at 10-15 mg/wk, with escalation of 5 mg every 2-4 weeks up to 20-30 mg/wk, depending on clinical response and tolerability; parenteral administration should be considered in case of inadequate clinical response or intolerance.

The results of three RCTs directly comparing different dosages of oral MTX in RA showed dose-dependent efficacy and toxicity.[24-26] A starting dose of 25mg/wk versus 15mg/wk was more effective, but with a trend for more gastrointestinal toxicity.[25] Starting doses of 12.5-20mg/wk versus 5-10mg/wk resulted in higher clinical efficacy, without more toxicity.[24] Rapid dose escalation of 5mg/month to 25-30mg/wk was associated with higher efficacy, but also with more adverse events, in comparison with slow escalation of 5mg/3 months.[26] Regarding the optimal route of administration, retrospective studies suggest higher efficacy and less gastrointestinal toxicity with parenteral versus oral MTX,[27,28], which might be explained by higher bioavailability of the parenteral form [29,30]. Indeed, the single RCT that compared 15mg/wk subcutaneous with oral MTX, showed higher clinical efficacy, but also more withdrawal due to toxicity with subcutaneous MTX in early MTX-naïve RA.[31] In contrast, in RA patients who failed MTX 15-20mg/wk plus other DMARDs, neither a switch to 15mg/wk intramuscular, nor subsequent dose escalation, resulted in increased efficacy.[32] In conclusion, the experts preferred the oral route, dosed according to the recommendation, with a possible switch to parenteral in case of an insufficient response at the highest tolerable dose.

Recommendation 3: Prescription of at least 5 mg folic acid per week with MTX therapy is strongly recommended.

A meta-analysis of nine studies including 788 RA patients suggests that folic acid supplementation reduces gastrointestinal and liver toxicity of MTX, without reducing efficacy.[33] Four studies using folic acid 7-35mg/wk showed a significant reduction in the risk of gastrointestinal side effects (OR 0.42 [0.21-0.85])[34-37], in contrast with only one study using 5mg/wk folic acid, which did not reach significance[36]. After further stratification, however, the protective effect was only significant in the two studies that used MTX <10mg/wk (OR=0.21 [0.07-0.69])[35,36] and not in the two largest studies using MTX 14-18mg/wk (OR=0.61 [0.25-1.48])[34,37]. The two studies in which hepatotoxicity was analyzed, showed a significant protective effect with 1mg/day folic acid (OR=0.17 [0.09-0.32]), irrespective of the MTX dose,[34,35] Only folinic acid doses ≤5mg/wk significantly decreased gastrointestinal side effects and hepatotoxicity (OR=0.39 [0.2-0.76], OR=0.16 [0.09-0.29] respectively).[34,38-40] Furthermore, folinic acid >5mg/wk was associated with a significant increase in the number of tender and swollen joints (OR=6.27 [1.64-10.90], OR=5.3 [0.03-10.58] respectively), while folic acid or low dosages (≤5mg/wk) folinic acid were not.[38,41,42] In conclusion, the experts favoured folic acid and recommended at least 5mg/wk, taking into account the potential need for higher dosages, with the currently higher dosed MTX.
**Recommendation 4:** When starting MTX or increasing the dose, ALT with or without AST, creatinine, and CBC should be performed every 1 to 1.5 months until a stable dose is reached, and every 1 to 3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.

Both the mean AST and the percentage of elevated AST have been reported to correlate with histological grades of liver disease in RA.[14,43-46] The ’94 ACR guidelines for monitoring hepatotoxicity showed 80% sensitivity and 82% specificity for detecting fibrosis/cirrhosis of serial abnormal AST tests, with less costs and complications, compared with routine liver biopsy.[47,48] One study suggests that ALT alone might detect 90% of the elevated AST or paired tests.[49] In contrast, alkaline phosphatase seems over-sensitive for monitoring hepatotoxicity.[47] In addition to transaminases, renal function should be monitored, as it is associated with increased (pulmonary) toxicity and CBC is required to monitor haematological toxicity.[10,50] Less evidence is available on the frequency of monitoring, although two observational studies showed an optimal interval for identifying abnormal liver enzymes of 30-60 days and a decreasing incidence of abnormal liver enzymes in the first months of MTX therapy.[47,51] Accordingly, the four national recommendations and the ’96 ACR guidelines suggest monitoring every 1-3 months, with initially more frequent assessments.[23]

**Recommendation 5:** MTX should be stopped if there is a confirmed increase in ALT/AST >3 times the upper limit of normal (ULN), but may be reinstated at a lower dose following normalization. If the ALT/AST are persistently elevated up to 3 times the ULN, the dose of MTX should be adjusted; diagnostic procedures should be considered in case of persistent elevated ALT/AST more than 3 times the ULN after discontinuation.

Pooled data of 2062 RA patients after a mean of 3.3 years on MTX showed that the cumulative incidence of abnormal ALT/AST was 48.9% above the ULN and 16.8% above 2-3 times the ULN.[52] MTX was frequently continued without a dose change, but the frequency of (spontaneous) normalisation was insufficiently reported. In addition, pooled percentages of mild and severe fibrosis and cirrhosis in 1113 RA patients after a mean of 4.1 years on MTX, were 15.3%, 1.3% and 0.5%, respectively. However, results of pre-MTX biopsies already showed a prevalence of 9.1% mild fibrosis, and 0.3% cirrhosis.[52] For PsA, a somewhat higher incidence of elevated LE and fibrosis/cirrhosis compared with RA was found, but the evidence is very limited.[20,53-56] For RA, the evidence suggests that liver enzyme elevation is frequent, but often transient, that multiple rather than single findings associate with an abnormal biopsy (as noted earlier), and that MTX-induced fibrosis/cirrhosis is rare. The experts emphasized considering other causal factors including non-steroidal anti-inflammatory drugs (NSAIDs), obesity and alcohol and other diagnostic procedures than liver biopsy in case of persistently elevated liver enzymes after discontinuation of MTX.[21,43,57]
**Recommendation 6: Based on its acceptable safety profile, MTX is appropriate for long term use.**

RA patients have an increased mortality rate compared with the general population (SMR=1.9 [1.3-2.8]). However, RA patients on MTX compared to patients without MTX, had a lower mortality incidence rate (23/1000 versus 26.7/1000 patient-years) and reduced cardiovascular mortality (HR=0.3 [0.2-0.7]) in a large six-year prospective study.[59] In addition, in two case-control studies, MTX was not a risk factor and even reduced the risk of cardiovascular disease, respectively (OR=0.11 [0.02-0.56]).[60,61] In a meta-analysis and several cohorts with 5-12 years follow-up, MTX was less often discontinued due to toxicity than other DMARDs, except for hydroxychloroquine.[62,63] Gastrointestinal events and elevated liver enzymes are the most frequently encountered toxicities.[63] However, as discussed earlier, the risk of severe fibrosis and cirrhosis seems low. Long-term MTX use was not associated with an increased risk for serious infections (HR=0.91 [0.57-1.45]), including herpes zoster (HR=1.0 [0.8-1.3]).[64,65] Although RA patients have an increased risk of lymphoma compared with the general population, evidence on the risk of MTX use independent of RA is inconclusive, because studies did not address RA as the reference population and the risk was not adjusted for disease severity.[66,67] Five case-reports suggest that MTX might be associated with EBV-related lymphoproliferative disease and regression after MTX withdrawal.[68-72]

**Recommendation 7: In DMARD naïve patients the balance of efficacy/toxicity favours MTX monotherapy over combination with other conventional DMARDs; MTX should be considered as the anchor for combination therapy when MTX monotherapy does not achieve disease control.**

A meta-analysis of 20 RCTs evaluated MTX mono- versus combination therapy in RA, excluding combinations with corticosteroids or biologicals.[73] Analyses were stratified for DMARD-naïve patients and patients with an inadequate response to prior MTX or other DMARDs. MTX combination therapy was superior to MTX monotherapy mainly in patients with prior inadequate response to MTX, resulting in significantly more ACR20 (RR=2.51 [1.92-3.28]), ACR50 (RR=4.54 [2.51-8.2]) and ACR70 responses (RR=5.59 [2.08-15.01]).[74-77] In contrast, in patients who failed other DMARDs, only significantly more ACR20 responses (RR=1.85 [1.21-2.83]) were seen with combination therapy and a trend for more EULAR good response and remission.[78,79] In DMARD-naïve patients, combination therapy showed a trend for more EULAR moderate response and remission, but only ACR70 responses were significantly more often achieved (RR=2.41 (95% CI [1.07-5.44]).[80-84] Regarding toxicity, MTX combined with sulfasalazine and MTX combined with leflunomide each significantly increased the risk of gastrointestinal side effects and hepatotoxicity, with a trend for more withdrawal due to toxicity.[75,78,80,81,85,86] In contrast, MTX combined with sulfasalazine and hydroxychloroquine did not increase the risk of withdrawal due to toxicity.[87] Weighing efficacy and toxicity, the experts favored MTX monotherapy over the combination with conventional DMARDs in DMARD-naïve RA patients. As such, the recommendation does not contradict the well-established superiority of combination therapies including either prednisone or anti-TNF.[88-91]
Recommendation 8: **MTX, as a steroid-sparing agent, is recommended in giant-cell arteritis (GCA) and polymyalgia rheumatica (PMR) and can be considered in patients with systemic lupus erythematosus (SLE) or (juvenile) dermatomyositis (DM).**

An individual patient data meta-analysis evaluated the steroid-sparing effect of MTX 7.5-17.5mg/wk versus placebo in GCA patients on high dose prednisone.[92] The results showed a higher prednisone discontinuation rate (HR=2.84 [95%CI 1.52-5.28]), significantly lower cumulative steroid dose and less relapses with MTX therapy after 1 year. Two RCTs in PMR also showed significantly more prednisone discontinuation with MTX 10mg/wk versus placebo, significantly less relapses, and a trend towards lower prednisone duration and cumulative dose.[93,94] SLE patients in two RCTs evaluating MTX 7.5-20mg/wk versus placebo, had significantly more prednisone reduction, less skin and joint flares, but more adverse events with MTX therapy.[95,96] Finally, in a cohort study, juvenile DM patients discontinued prednisone significantly earlier and had significantly lower cumulative prednisone doses with concomitant MTX therapy, but without an additional beneficial effect on disease activity.[97] No studies were found comparing the steroid-sparing effect of MTX with other DMARDs.

Recommendation 9: **MTX can be safely continued in the peri-operative period in RA patients undergoing elective orthopaedic surgery.**

Four studies evaluated stopping or continuing MTX ≥1 week before elective orthopaedic surgery in RA. In one RCT, no differences in postoperative complications were observed between patients who continued or stopped MTX (mean dose 10mg/wk).[98] In a second RCT, patients who continued MTX (mean dose 10mg/wk) reported significantly less RA flares than patients who stopped MTX.[99] In contrast, in a prospective cohort study postoperative infections occurred in 30% of the patients who continued MTX versus none of the patients who stopped MTX, without postoperative flares of RA in either group.[100] However, a multivariate analysis in another cohort study showed that peri-operative use of MTX was not associated with wound morbidity (p=0.84) and significantly reduced RA flares.[101] Although these studies suggest that MTX can be safely continued in the peri-operative period of elective orthopaedic surgery, no studies were found regarding (non-) elective non-orthopaedic surgery.

Recommendation 10: **MTX should not be used for at least 3 months prior to planned pregnancy for males and females, and should not be used during pregnancy or breast feeding.**

Six studies assessed the outcome of continued MTX therapy before/during pregnancy in (mostly) RA patients via surveys and database searches.[102-107] A total of 101 pregnancies were exposed to MTX during pregnancy (n=92) or prior to conception (n=9). Eighteen induced abortions were reported, but the reasons were not stated. A total of 20 (24%) miscarriages, 5 (6%) congenital malformations and 62 (75%) live births were reported, with 1 (1%) patient lost to follow-up. In healthy women, corresponding percentages are 12-16% miscarriages and 3-5% congenital malformations.[108,109] In contrast, no studies were found that evaluated the effect of MTX for males on miscarriages/birth defects, male and female fertility or on newborns during lactation.
Nevertheless, expert opinion is to stop MTX at least 3 months before planned pregnancy in both males and females and not to use MTX during pregnancy nor breast feeding.

**DISCUSSION**
Ten multinational recommendations for the use of MTX in daily clinical practice were developed, which are practical, evidence-based and supported by a large panel of international rheumatologists in the 3E Initiative. The involvement of 751 rheumatologists from 17 countries was unique in the development of the current recommendations. It allowed a selection of relevant topics, reflecting frequently encountered questions on the use of MTX in daily practice. Furthermore, a broad participation increases external validity and enhances future dissemination and implementation into rheumatological practice worldwide. A second principal feature of the initiative was the systematic literature research. Following a strict methodology, we aimed to find all available evidence regarding each topic, which resulted in a large number of reviewed articles. Although for some areas little to no evidence was found, including (the frequency of) toxicity monitoring, the timing of folic acid, non-orthopaedic surgery and the effect of MTX on fertility and lactation, the majority of the recommendations are supported by evidence from RCTs and high quality cohort studies. The same evidence, however, might limit the recommendations, as many studies were old and included longstanding RA patients who received MTX in low dosages without folic acid. As this may not reflect current clinical practice, the results should be interpreted and extrapolated with caution. In addition, patient’s participation and preferences may influence the recommendations. Nevertheless, the recommendations are based on currently available evidence, and can be adjusted if future studies or clinical experience reveal new insights.

In summary, multinational recommendations for the use of MTX in daily clinical practice focussed on RA were developed, integrating systematic literature review and expert opinion, with the aim of promoting evidence-based medicine and ultimately improving patient care.

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Table 1. Results of the systematic literature search for each recommendation topic.

<table>
<thead>
<tr>
<th>Recommendation (Number and topic)</th>
<th>Retrieved references by systematic literature search (n)</th>
<th>Articles included in the systematic reviews (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pre-MTX work-up</td>
<td>1214</td>
<td>52</td>
</tr>
<tr>
<td>2. Dosage and route</td>
<td>1748</td>
<td>50</td>
</tr>
<tr>
<td>3. Folic acid</td>
<td>334</td>
<td>9</td>
</tr>
<tr>
<td>4. Monitoring</td>
<td>857</td>
<td>23</td>
</tr>
<tr>
<td>5. Hepatotoxicity</td>
<td>426</td>
<td>46</td>
</tr>
<tr>
<td>6. Long-term safety</td>
<td>2449</td>
<td>88</td>
</tr>
<tr>
<td>7. Mono vs combination</td>
<td>6958</td>
<td>20</td>
</tr>
<tr>
<td>8. Steroid-sparing agent</td>
<td>527</td>
<td>6</td>
</tr>
<tr>
<td>9. Peri-operative period</td>
<td>303</td>
<td>4</td>
</tr>
<tr>
<td>10. Pregnancy</td>
<td>2163</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>16979</td>
<td>304</td>
</tr>
</tbody>
</table>
Table 2. Multinational recommendations for the use of methotrexate in RA (1-7, 9-10) and other rheumatic disorders (8).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Grade of recommendation</th>
<th>Agreement mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The work-up for patients starting MTX should include clinical assessment of risk factors for MTX toxicity (including alcohol intake), patient education, AST, ALT, albumin, CBC, creatinine, chest X-Ray (obtained within the previous year); consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.</td>
<td>4</td>
<td>C</td>
<td>8.2 (1.9)</td>
</tr>
<tr>
<td>2. Oral MTX should be started at 10-15 mg/wk, with escalation of 5 mg every 2-4 weeks up to 20-30 mg/wk, depending on clinical response and tolerability; parenteral administration should be considered in case of inadequate clinical response or intolerance.</td>
<td>2b</td>
<td>B</td>
<td>7.8 (2.6)</td>
</tr>
<tr>
<td>3. Prescription of at least 5 mg folic acid per week with MTX therapy is strongly recommended.</td>
<td>1a-</td>
<td>A</td>
<td>7.5 (2.7)</td>
</tr>
<tr>
<td>4. When starting MTX or increasing the dose, ALT with or without AST, creatinine, and CBC, should be performed every 1 to 1.5 months until a stable dose is reached, and every 1 to 3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.</td>
<td>4</td>
<td>C</td>
<td>8.1 (2.1)</td>
</tr>
<tr>
<td>5. MTX should be stopped if there is a confirmed increase in ALT/AST &gt; 3 times the ULN, but may be reinstituted at a lower dose following normalization. If the ALT/AST are persistently elevated up to 3 times the ULN, the dose of MTX should be adjusted; diagnostic procedures should be considered in case of persistent elevated ALT/AST more than 3 times the ULN after discontinuation.</td>
<td>2b</td>
<td>C</td>
<td>7.4 (2.3)</td>
</tr>
<tr>
<td>6. Based on its acceptable safety profile, MTX is appropriate for long term use.</td>
<td>2b</td>
<td>B</td>
<td>8.7 (1.9)</td>
</tr>
<tr>
<td>7. In DMARD naïve patients the balance of the efficacy/toxicity favours MTX monotherapy over combination with other conventional DMARDs; MTX should be considered as the anchor for combination therapy when MTX monotherapy does not achieve disease control.</td>
<td>1a-</td>
<td>A</td>
<td>8.3 (2.1)</td>
</tr>
<tr>
<td>8. MTX, as a steroid-sparing agent, is recommended in giant-cell arteritis and polymyalgia rheumatica and can be considered in patients with systemic lupus erythematosus or (juvenile) dermatomyositis.</td>
<td>1b</td>
<td>B</td>
<td>7.7 (2.1)</td>
</tr>
<tr>
<td>9. MTX can be safely continued in the peri-operative period in rheumatoid arthritis patients undergoing elective orthopaedic surgery.</td>
<td>1b</td>
<td>B</td>
<td>8.8 (1.9)</td>
</tr>
<tr>
<td>10. MTX should not be used for at least 3 months prior to planned pregnancy for males and females, and should not be used during pregnancy or breast feeding.</td>
<td>4</td>
<td>C</td>
<td>8.2 (2.7)</td>
</tr>
</tbody>
</table>

MTX=methotrexate, AST=aspartate aminotransferase, ALT=alanine aminotransferase, CBC=complete blood count, HIV=human immunodeficiency virus, ULN=upper limit of normal, DMARDs=disease modifying anti-rheumatic drugs, SD=standard deviation
Table 3. Percentage of rheumatologists in the 3E Initiative who indicated for each recommendation if it would change their clinical practice.

<table>
<thead>
<tr>
<th>Recommendation (Number and topic)</th>
<th>The recommendation will change my practice (%)</th>
<th>The recommendation is already my practice (%)</th>
<th>I don't want to change my practice for this aspect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pre-MTX work-up</td>
<td>29.8</td>
<td>61.2</td>
<td>9.0</td>
</tr>
<tr>
<td>2. Dosage and route</td>
<td>16.2</td>
<td>68.7</td>
<td>15.1</td>
</tr>
<tr>
<td>3. Folic acid</td>
<td>15.3</td>
<td>78.6</td>
<td>6.1</td>
</tr>
<tr>
<td>4. Monitoring</td>
<td>21.1</td>
<td>53.5</td>
<td>25.4</td>
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<td>5. Hepatotoxicity</td>
<td>16.5</td>
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<td>6. Long-term safety</td>
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<td>7. Mono vs combination</td>
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<td>8. Steroid-sparing agent</td>
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<td>9. Peri-operative period</td>
<td>41.3</td>
<td>46.7</td>
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<td>10. Pregnancy</td>
<td>19.5</td>
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<td>9.2</td>
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