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Recommendations

# EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2025 update

Josef S. Smolen[1,*], Christopher J. Edwards[2], Victoria Konzett[1], Faidra Laskou[3], Daniel Aletaha[1], Roberto Caporali[4,5], Thomas Dörner[6], Kimme L. Hyrich[7,8], Elsa Mateus[9], Janet E. Pope[10], Jette Primdahl[11], Savia de Souza[12], Tanja Stamm[13,14], Tsutomu Takeuchi[15], Désirée van der Heijde[16], Patrick Verschueren[17], Kevin L. Winthrop[18], Jose Maria Alvaro-Gracia[19], Johan Askling[20], Joan Bathon[21], Maya H. Buch[7,8], Gerd R. Burmester[22], Catalin Codreanu[23], Philip G. Conaghan[24,25], Maurizio Cutolo[26], Bruno Fautrel[27,28], Joao Fonseca[29,30], Laure Gossec[31,32], Espen Haavardsholm[33,34], Merete Lund Hetland[35,36], Annamaria Iagnocco[37], Pierre-Antonie Juge[38,39], Zhanguo Li[40,41], Rikke Helene Moe[42], Peter Nash[43], Gyula Poór[44], Andrea Rubbert-Roth[45], Raquel dos Santos Sobrin[46], Hendrik Schulze-Koops[47], Russka Shumnalieva[48], Ladislav Senolt[49], Lucia Silva-Fernandez[50], Anja Strangfeld[51,52], Peter Taylor[53], Carl Turesson[54], Elsa van Duuren[55], Maarten de Wit[56], Ricardo Xavier[57], Andreas Kerschbaumer[1,58], Robert B. M. Landewé[59]

[1] *Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria*
[2] *NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK*
[3] *MRC Lifecourse Epidemiology Centre, Southampton, UK*
[4] *Department of Clinical Science and Community Health, University of Milan, Milan, Italy*
[5] *Department of Rheumatology and Medical Sciences, ASST Pini-CTO, Milan, Italy*
[6] *Department of Medicine/Rheumatology and Clinical Immunology, Charite Universitätsmedizin Berlin & Deutsches Rheumaforschungszentrum (DRFZ), Berlin, Germany*
[7] *Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, UK*
[8] *National Institute for Health and Care Research Manchester Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester, UK*
[9] *Portuguese League Against Rheumatic Diseases (LPCDR), Lisbon, Portugal*
[10] *Schulich School of Medicine, University of Western Ontario, London, ON, Canada*
[11] *Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, Sønderborg, Denmark*
[12] *Clinical Research Facility, King's College Hospital, London, UK*
[13] *Institute of Outcomes Research, Centre for Medical Data Science, Medical University of Vienna, Vienna, Austria*
[14] *Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Vienna, Austria*

*Correspondence to Prof Josef S. Smolen, Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria.
*E-mail address:* josef.smolen@meduniwien.ac.at (J.S. Smolen).
Josef S. Smolen and Christopher J. Edwards contributed equally as convenors of the task force.
Andreas Kerschbaumer and Robert B. M. Landewé contributed equally as methodologists.
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[15] *Department of Rheumatology and Applied Immunology/Clinical Immunology, Saitama Medical University, Saitama, Japan*
[16] *Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands*
[17] *Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium*
[18] *School of Public Health, Oregon Health & Science University, Portland, OR, USA*
[19] *Rheumatology Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Universidad Computense, Madrid, Spain*
[20] *Departement of Medicine Solna, Karolinska Institutet, Stockholm, Sweden*
[21] *Division of Rheumatology, Columbia University Irving Medical Center, New York, NY, USA*
[22] *Department Medicine/Rheumatology and Clinical Immunology, Charite Universitätsmedizin Berlin, Berlin, Germany*
[23] *Center for Rheumatic Diseases University of Medicine and Pharmacy, Bucharest, Romania*
[24] *Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, Leeds, UK*
[25] *NIHR Leeds Biomedical Research Centre, University of Leeds, Leeds, UK*
[26] *Laboratory of Experimental Rheumatology, Division of Rheumatology, Department of Internal Medicine – DiMI, University of Genova, Genova, Italy*
[27] *Sorbonne Université–APHP, Service de Rhumatologie, FCRIN CRI-IMIDIATE Clinical Research Network, Hôpital de la Pitié-Salpêtrière, Paris, France*
[28] *INSERM UMRS 1136, Paris, France*
[29] *Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisbon, Portugal*
[30] *ULS Santa Maria, Centro Académico de Medicina de Lisboa, Lisbon, Portugal*
[31] *Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Team Pepites, Paris, France*
[32] *AP-HP, Pitié-Salpêtrière hospital, Rheumatology Department, Paris, France*
[33] *Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway*
[34] *Faculty of Medicine, University of Oslo, Oslo, Norway*
[35] *Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet, Glostrup, Denmark*
[36] *Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*
[37] *Academic Rheumatology Center, University of Turin, AO Mauriziano, Turin, Italy*
[38] *Service de Rhumatologie, Hôpital Bichat-Claude Bernard, AP-HP, Paris, France*
[39] *Université de Paris, INSERM U-1153, Centre de recherche en épidémiologie et statistiques, Paris, France*
[40] *Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, People's Republic of China*
[41] *Beijing Key Laboratory for Rheumatism Mechanism and Immune Diagnosis (BZ0135), Peking University People's Hospital, Beijing, People's Republic of China*
[42] *Health Services and Innovation Unit & Center for Treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway*
[43] *School of Medicine, Griffith University, Brisbane, QLD, Australia*
[44] *Department of Rheumatology and Immunology Semmelweis University, Budapest, Hungary*
[45] *Cantonal Hospital St Gallen, HOCH Health Ostschweiz, St Gallen, Switzerland*
[46] *Clinical University Hospital in Santiago de Compostela and Health Research Institute in Santiago de Compostela, A Coruña, Spain*
[47] *Division of Rheumatology and Clinical Immunology, Department of Medicine IV. LMU University Hospital, Munich, Germany*
[48] *Department of Rheumatology, Clinic of Rheumatology, University Hospital "St. Anna" Sofia, Medical University-Sofia, Sofia, Bulgaria*
[49] *Institute of Rheumatology, and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic*
[50] *Servicio de Reumatología, Complexo Hospitalario Universitario de Pontevedra, Pontevedra, Spain*
[51] *Programme Area Epidemiology and Health Services Research, German Rheumatology Research Center, Berlin, Germany*
[52] *Department of Rheumatology and Clinical Immunology, Charité University Medicine Berlin, Berlin, Germany*
[53] *Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK*
[54] *Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden*
[55] *The Sefako Makgatho Health Science University, Pretoria, South Africa*
[56] *EULAR Patient Research Partner, Amsterdam, Netherlands*
[57] *Department of Internal Medicine, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil*
[58] *Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA*
[59] *Amsterdam University Medical Center, Amsterdam and Zuyderland MC, Heerlen, The Netherlands*

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ABSTRACT

*Objectives:* This study aims to provide an update of the European Alliance of Associations for Rheumatology (EULAR) rheumatoid arthritis (RA) management recommendations addressing the most recent insights.

*Methods:* An International Task Force was formed with a wide expertise and solicited 2 systemic literature research activities on the safety and efficacy of disease-modifying antirheumatic drugs (DMARDs). New evidence was discussed, considering the update from 2022. A voting process was applied to each item. Levels of evidence and strengths of recommendation were assigned, and participants voted on the levels of agreement.

*Results:* The task force agreed on 5 overarching principles and reduced the number of recommendations to 9 concerning use of conventional synthetic DMARDs (methotrexate [MTX], leflunomide, sulfasalazine); glucocorticoids (GCs); biological (b)DMARDs (tumour necrosis factor inhibitors [adalimumab, certolizumab pegol, etanercept, golimumab, infliximab], abatacept, rituximab, tocilizumab, sarilumab, including biosimilars) and targeted synthetic [ts]DMARDs (namely the Janus kinase inhibitors [JAKi] tofacitinib, baricitinib, filgotinib, upadacitinib). Guidance on monotherapy, combination therapy, treatment strategies (treat-to-target), and tapering following clinical remission is provided. Safety aspects, including risk of major cardiovascular events (MACEs) and malignancies, costs and sequencing of b/tsDMARDs were considered. Initially, MTX ideally in combination with short-term GCs is recommended; upon insufficient response after 3 to 6 months, a bDMARD should be added; after careful consideration of risks, including MACEs, malignancies and/or thrombo-embolic events, JAKi may also be considered. If the first bDMARD (or JAKi) fails, any other bDMARD (from another or the same class) or JAKi (considering risks) is recommended. With sustained remission, DMARDs may be tapered, but caution is required as stopping often leads to a flare. Levels of evidence and levels of agreement were high for most recommendations.

*Conclusions:* These updated EULAR recommendations provide consensus on RA management based on currently available evidence regarding efficacy, safety, and cost.

## INTRODUCTION

The pivotal therapeutic approach in the management of rheumatoid arthritis (RA) is the use of disease-modifying antirheumatic drugs (DMARDs). Among the DMARDs available, methotrexate (MTX), if used at an optimal dose and with folate supplementation, was the first highly and consistently effective drug [1,2]. Another therapeutic revolution in immune-mediated inflammatory diseases in general, and rheumatology in particular, was spearheaded by successful clinical trials of targeted therapies against tumour necrosis factor (TNF) in people with RA more than 30 years ago [3,4], leading to their regulatory approval at the end of the last millennium. Since then, numerous new agents directed at the same or different molecular or cellular targets have been developed and approved. The most recent class of DMARDs licensed for treating RA are targeted synthetic (ts) small molecule agents that inhibit intracellular signalling pathways, the Janus kinase inhibitors (JAKi) [5]. Also, transient use of glucocorticoids (GCs) has consistently shown significant beneficial effects [6,7], despite a number of caveats [8].

In parallel with these therapeutic advancements, strategic approaches and generally useful and effective outcome measures have been developed that enable the determination of response in clinical trials and the monitoring of patients from the start of a treatment cycle to a successful endpoint [9–11]. In this respect, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) have recently provided an updated definition of remission [12], the most important therapeutic goal in the approach to managing patients with RA [13].

Interestingly, irrespective of the molecule they bind to, the efficacy of licensed targeted DMARDs at a group level appears to be quite similar [14], and a major unmet need remains being able to predict who will respond best to which drug or mechanism of action. No refined predictors within individuals to guide which treatment to use and in what order are available. Moreover, cure of RA is extremely rare, as even in those patients achieving sustained remission, stopping DMARDs is followed by flares in the vast majority of patients [15–18]. On the other hand, while today's therapies are highly efficacious in a notable proportion of patients, there are individuals who do not respond to several successive advanced therapies, and, therefore, the term 'difficult to treat RA' (or 'treatment refractory' RA) has been defined [19].

Currently licensed DMARDs are indicated for the treatment of people with a diagnosis of RA. At the other end of the RA spectrum, persons at risk of developing RA have recently become a major focus of attention [20]. Therapeutic interventions to prevent the evolution of the disease, however, have so far only been successful in delaying but not in precluding the onset of classifiable RA [21–24].

The multiple treatment options, as well as the therapeutic objectives, have necessitated attempts to bring some direction into approaching optimal management of patients with RA, taking into account the efficacy and safety of the different agents while also considering the economic realities of health care systems in most parts of the world. The first results of such attempts in the modern era were provided by both the ACR and EULAR for the first time more than a decade ago [25,26]. Since then, both organisations have updated their recommendations in line with new therapeutic insights, the ACR most recently in 2021 [27] and EULAR every 3 years and most recently in 2022 [28]. In this last update, GC use in RA was re-evaluated [29], and the

cardiovascular and malignancy risks related to JAKi therapy based on a clinical trial of tofacitinib were addressed [30]. We now provide the next update of the EULAR recommendations for the management of RA as developed by the 2025 EULAR task force based on the newest insights.

## METHODS

The task force adhered to an approach similar to that followed in previous processes for this activity, and the methodological details have been published previously [28]. Therefore, we will provide only a brief summary here.

### *Steering committee and task force*

In line with the EULAR standard operating procedures for developing recommendations and the AGREE II document [31,32] and after approval by the EULAR council, the convenors (JSS and CJE) and the methodologists (RBML and AK) invited 15 experts to form the steering committee. This group consisted of rheumatologists from Europe, Asia, Latin America, and North America, an infectious disease specialist, as well as representatives of patients (SdS and EM) and health professionals (JP). The steering committee met for the first time in November 2024 in Washington, DC, to discuss the scope of the activity and, especially, to determine the research questions for the 2 systematic literature reviews (SLRs). Two fellows (VK and FL) were invited to perform SLRs on the efficacy and safety of DMARDs, respectively, focusing on data published since the last SLRs that had been performed in early 2022 [29,33,34]. The SLRs included specific questions on topics raised during the steering committee meeting, such as evidence on the efficacy of therapies for RA-interstitial lung disease (RA-ILD), studies investigating therapeutic interventions in patients at risk for development of RA as well as aspects of safety monitoring during DMARD treatment. Both SLRs included available literature published until the end of January 2025.

The full task force comprised 31 additional experts from all over the world. To ensure the incorporation of a global perspective, the EULAR council agreed to allow the invitation of many non-European participants who were from Africa (EvD), Asia (ZL and TT) Australia (PN), Latin America (RX), and North America (JB, JEP, and KLW). The Emerging EULAR Network (EMEUNET) was represented by 2 individuals (P-AJ and RdSS), EULAR's patient research partners were represented by 3 people (EM, SdS, and MdW) and the nonmedical health professionals also by 3 (RHM, JEP, and TS). Five of the task force members, as well as those from EMEUNET, were elected after a competitive application process announced by EULAR across its member organisations; the other participants were invited by the convenors and methodologists based on specific expertise and publication history. Thus, the full EULAR constituency was represented within the task force and supplemented by international experts. The total task force comprised 50 individuals, the largest group ever assembled for this purpose.

### *Procedures*

Once the SLRs had been completed, the steering group met at the end of March 2025 in Amsterdam to discuss the results in detail and develop a proposal for an update of the recommendations. This encounter was followed by a full task force meeting on the subsequent day.

At the beginning of the task force meeting, an abbreviated version of the SLR results was presented, and participants could address questions to the SLR researchers and the methodologists. The SLRs will be published separately [35,36]. Also, the suggestions by the steering group to leave, delete or amend previous recommendations were presented and discussed in detail. The task force was split into 3 groups to address the previous and potentially new overarching principles as well as the individual recommendations in light of the new efficacy and safety data and the steering group's proposals. A representative of each breakout group reported the results of the respective deliberations back to the whole task force. Thereafter, each item underwent further discussion and voting. Based on recommendations by the Oxford Centre of Evidence-Based Medicine (OCEBM) to determine levels of evidence (LoEs) and grades of recommendation (GoR) [37], the previous assignments of LoEs were evaluated and amended as needed, and new proposals also underwent this assessment. The reasons for the preference of using the OCEBM approach above other ones have been detailed previously [28].

The consensus-building developed in the course of deliberations on each item and the respective ballots, which were carried out as live voting by raising hands. To change a previous recommendation, a >75% majority was needed, given that previous task forces had good reasons to develop certain items based on the SLRs of those times. If this was the case, the suggested new wording, just like a proposed new recommendation, required a >75% majority for immediate approval. If a >75% majority was not achieved, discussions on the wording were restarted, and the next voting round required a >67% majority. If this was not attained, a further version was discussed, and the new wording required a >50% majority. If this majority was not achieved, the proposed recommendation or change was not accepted.

After the meeting, each item was scrutinised again for the LoE and GoR and subsequently sent to all task force members for anonymous voting on the level of agreement (LoA) on a scale of 0 (no agreement at all) to 10 (complete agreement). The means and SDs of these results are presented for each item.

The draft of the manuscript was sent to all task force members for their review and thereafter submitted to the EULAR council for further suggestions and approval. Once this approval was provided, the paper was submitted.

It should be noted that the task force members change with every new update; about one-third of the task force members are usually new to the group. Consequently, many questions arose which may (or may not) have been discussed previously. In this respect, those participants who were present at previous task force meetings provide 'memory' regarding previous decisions which were based on previous SLRs; these SLRs were not presented again to the current task force, but were generally available as publications, such as those informing the 2022 task force [29,33,34].

### *Target audience*

These recommendations are directed at all health care professionals who deal with DMARD therapy of people with RA, as well as at researchers who investigate new therapies or treatment responses. They are also relevant for people with RA, as they are an important source of information on the most recent therapeutic approaches and can be used in discussions with their care providers. Regulators, hospital managers, health care insurers and representatives of the pharmaceutical industry are also targets of these recommendations, since they have to weigh them against the current approaches used and may consider them for future developments. Furthermore, national societies are provided with a template to develop their own local recommendations that account for the availability and accessibility of

drugs in their country. The research agenda is meant to provide the thinking of the task force on gaps in knowledge and future research needs.

## RESULTS

Although no new drug has been approved since the 2022 update, several strategic trials have since been conducted, and clarification is now available on points that were previously based solely on expert opinion. These will be detailed when discussing the different items. Also, the definition of individual terms, such as 'low dose GCs', 'remission', and many others, has been addressed in glossaries presented in previous updates of these EULAR recommendations [28,38] and will not be repeated here.

The updated overarching principles and individual recommendations are shown in Table 1 and are described in the subsequent sections. It should be borne in mind that the text presented in the table is only an abbreviated form of the discussion content and that the additional information provided below for each item is an integral part of the recommendations. The results of the final ballot for each of the items will be presented to reveal the extent of agreement or disagreement over the course of the person-to-person meeting. It should be noted that 1 task force member had participated in both steering group meetings but could not attend the full task force meeting, and, therefore, the on-site ballots are based on 49 participants. The results are provided as per cent voting for and against a change, and per cent abstaining.

### *Overarching principles*

Overarching principles (OAPs) are general statements regarding patient-centred care and do not require a specific SLR or assessment of LoEs—they simply reflect and remind us of important aspects of good clinical practice in daily life. The task force was fully aligned that the 5 OAPs presented in the 2022 update were of continued importance and that no new ones were needed. Some wording was amended minimally for clarity.

Table 1
**EULAR RA management recommendations - 2025 update**

| No. | **Overarching principles** | LoE | SoR | LoA |
|---|---|---|---|---|
| A. | Treatment of patients with RA is aimed at the best care and must be based on shared decision making between the patient and the rheumatologist. | NA | NA | 9.98 ± 0.14 |
| B. | Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage. | NA | NA | 9.88 ± 0.44 |
| C. | Rheumatologists are the specialists who should primarily care for patients with RA. | NA | NA | 9.72 ± 0.57 |
| D. | Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life. | NA | NA | 9.94 ± 0.24 |
| E. | RA incurs high individual, medical, and societal costs, all of which should be considered in its management by the treating rheumatologist. | NA | NA | 9.58 ± 0.73 |
| No. | **Recommendations** | | | |
| 1. | Therapy with DMARDs should be started as soon as the diagnosis of RA is made. | 1a | A | 9.92 ± 0.34 |
| 2. | Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. | 1a | A | 9.82 ± 0.44 |
| 3. | Disease activity monitoring$^{+}$ should be frequent in active disease (every 1-3 mo); if there is no improvement by at most 3 mo after the start of treatment or the target has not been reached by 6 mo, therapy should be adjusted; when the target is sustained, monitoring can be less frequent$^{++}$. | $^{+}$2b; $^{++}$5 | $^{+}$B; $^{++}$D | 9.62 ± 0.6 |
| 4. | MTX should be part of the first treatment strategy; in patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered. | 1a | A | 9.38 ± 0.95 |
| 5. | Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible. | 1a | A | 9.46 ± 0.84 |
| 6. | If the treatment target is not achieved with the csDMARD strategy, a bDMARD should be added; JAK inhibitors may be considered, but pertinent risk factors* must be taken into account. | Efficacy: 1a<br>Safety: 2a | Efficacy: A<br>Safety: B | 9.28 ± 1.03 |
| 7. | bDMARDs/tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and JAK inhibitors may have some advantages compared with other bDMARDs. | Efficacy: 1a | Efficacy: A | 9.48 ± 0.71 |
| 8. | If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD$^{+}$ should be considered; if 1 TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/IL-6R-inhibitor$^{++}$. | Efficacy: 1a/$^{+}$5/$^{++}$3;<br>Safety: 1b | Efficacy: A/$^{+}$D;<br>Safety: B; $^{++}$IL-6R-inhibition: C | 9.48 ± 0.74 |
| 9. | After glucocorticoids have been discontinued and a patient is in sustained remission, continuation of DMARDs (bDMARDs/tsDMARDs and/or csDMARDs) is recommended, but dose reduction may be considered. | 1b | A | 9.56 ± 0.79 |

bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug (such as MTX); DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; LoA, level of agreement; LoE, level of evidence; MTX, methotrexate; NA, not applicable; R, receptor; SoR, strength of recommendation; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug (JAK inhibitor).
Mean ± SD.

*A. Treatment of patients with RA is aimed at the best care and must be based on shared decision making between the patient and the rheumatologist.*

Two minor changes were made compared with last time. First, the term 'Should aim at best care' is now replaced by '*is aimed* at the best care' to make it clearer that this is not an aspirational goal but a reality to be adhered to by all caregivers. Second, 'must be based on a shared decision' was amended to read 'must be based on shared decision-*making*', because it was felt that rheumatologists and patients must 'make' a shared decision in an ongoing and mutual process. There was also a discussion regarding advice for lifestyle behaviour, but this was found to be beyond the scope of this task force, and EULAR has already developed recommendations on lifestyle behaviours recently [39]. Some participants suggested that the term 'diagnosis of RA' could be better defined. However, since diagnostic criteria do not exist and classification criteria are meant for research and not for diagnostic purposes [40], it is up to the individual rheumatologist to arrive at a diagnosis of RA based on clinical and laboratory data. All but 1 person voted for this change (98%), and 1 person abstained.

*B. Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.*

In the context of the discussion, the question arose whether 'structural damage' should be better defined. However, there has been ample discussion on the definition of structural damage over the past decades [41] and, therefore, no further qualification was felt necessary. Consequently, only 31% of the task force members showed a preference for changing this OAP, far from the 75% needed. Ultimately, there was a unanimous vote for the above wording.

*C. Rheumatologists are the specialists who should primarily care for patients with RA.*

This item had already elicited discussions in the past, and it did so again this time. Some participants felt that the principle should be changed to: 'Rheumatologists are the primary specialists who should manage RA'. Further suggestions read: 'Rheumatologists should primarily oversee patients with RA' and 'The care of RA patients should be managed by rheumatologists' or 'Rheumatologists are the primary health care provider (or professional) for patients with RA'. However, *managing* RA and similar suggestions may imply managing all potential comorbidities, such as cardiovascular disease or diabetes, which often goes beyond usual rheumatology practice. Also, in many countries, nonphysician health professionals care for specific aspects of the disease. Then a discussion ensued around whether the term 'patients with RA' should be replaced just by 'RA' as a disease, but this would be counter to the fact that we care for people with a disease and do not just manage a disease. In the end, 61% voted for some change, and because the 75% majority was not reached, the recommendation remained in place as decided by many of the previous task forces.

*D. Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life.*

This OAP is the same as in 2022, and 100% of the task force members voted to keep it unchanged.

*E. RA incurs high individual, medical, and societal costs, all of which should be considered in its management by the treating rheumatologist.*

This OAP also remained unchanged with 100% agreement.

### *Individual recommendations*

As no new drugs have been approved since 2022 in the European Union, and also no new randomised controlled trials on the cardiovascular or malignancy risks of JAKi have been published over the last 3 years, the focus of the task force was on the evaluation of the previous recommendations and incorporation of recent insights from strategic trials and safety data. Consequently, several of the previous recommendations remained unchanged from 2022. Nevertheless, all these items were discussed at length, since every new task force looks at each recommendation from a new perspective, especially that of new members, in line with new evidence. Therefore, some recommendations were amended or some aspects deleted, others even combined. Ultimately, the task force arrived at 9 recommendations, 2 fewer than in 2022. The LoEs, GoRs, and LoAs are shown in Table 1.

*1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made.*

As before (see OAP A), the term 'diagnosis' was discussed, and in the course of these deliberations, it was reiterated that classification criteria should not be used as diagnostic criteria [40], although they may support the diagnostic decision process. A change to 'clinical diagnosis' rather than just 'diagnosis' was also suggested; however, a diagnosis is always clinical and, therefore, the addition would be redundant. The use of sonography for diagnostic purposes was also discussed, but refuted given that abnormal sonographic findings can also be seen in healthy individuals [42–44], and this is also true for magnetic resonance imaging (MRI) [45]. Moreover, ultrasound evidence of synovitis is not specifically diagnostic of RA, as it may be present in many rheumatic diseases. The most important diagnostic characteristic of RA is *clinical* joint swelling. People should only receive a diagnosis of RA when clinical joint swelling as a result of current inflammation (synovitis) is present.

Since DMARD treatment should be immediately initiated upon diagnosis of RA, the question also arose whether we should not address pre-RA in these recommendations. However, the recommendations are meant for management of patients with a 'diagnosis of RA'; while a diagnosis of RA also includes 'early RA', it does not include 'pre-RA' or more precisely, people who do not exhibit clinical joint swelling. People at risk of developing RA (pre-RA), who do not present with unequivocal clinical joint swelling but with certain other characteristics, such as signs of inflammation by sonography or MRI, have been treated in several trials, as reviewed by the efficacy SLR. Most of these trials did not reveal that RA could be prevented, since once the RA-specific treatment was stopped, symptoms and signs of arthritis (re)appeared, and the classification as RA was apparently simply delayed by having received therapy [21,22]. This was also seen in more recent trials that had suggested a cure in a small proportion of patients 1 year after stopping abatacept treatment, but this effect was not sustained in the longer term [23,24], as was expected from the earlier studies of other agents. The only trial that apparently led to long-lasting remission after stopping the drug, namely anti-TNF + MTX, was performed in

people with very early inflammatory arthritis [46], but not followed by a larger confirmatory study.

In the current recommendations, treating people with pre-RA (or suspected but not diagnosed RA) is purposely not addressed, as it is already complex enough to arrive at a therapeutic algorithm for clinically overt RA. However, given that diagnosis and classification are different, it is up to the rheumatologist to decide whether a person should be diagnosed as RA and undergo corresponding treatment. Since patients with early RA usually respond very well to the therapeutic approaches presented here, it might still be prudent to simply wait and follow patients with suspected RA regularly to start appropriate DMARD therapy as early as possible, once they can be diagnosed as RA by virtue of characteristic clinical joint swelling.

After these discussions, 100% of the task force members voted for keeping the first recommendation as it was, but addressing the deliberations in the manuscript text.

*2. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.*

Several aspects regarding this item were discussed.

First, some task force members asked if this recommendation should include safety aspects and comorbidities. Of course, these must be taken into account when planning to start a specific DMARD, but this recommendation pertains to a situation when the decision to initiate a particular drug has already been made after addressing comorbidities and potential safety risks of that drug. This has been stated in OAP B.

Second, it was suggested that remission should be defined more clearly than just by mentioning the term. To this end, since this is an EULAR task force that deals with EULAR recommendations, it is important to note that EULAR (together with ACR) has provided a clear definition of remission based on Boolean criteria and index (Clinical Disease Activity Index, Simplified Disease Activity Index) criteria [12,47]. Also, the use of DAS28-based remission definitions was clearly discouraged, since the DAS28 is heavily weighted on tender joints and on erythrocyte sedimentation rate or C-reactive protein (CRP). Acute phase reactants are blunted even in the absence of clinical improvement by drugs that target interleukin-6 (IL-6), including JAKi's, which interfere with IL-6 signalling, leading to exaggerated remission frequencies when using the DAS28, with a significant proportion of patients still having active disease [48]. This is also true for other instruments applied to define remission that include acute phase reactants [49]. Thus, when this document addresses remission, the ACR-EULAR definitions of remission are implied.

Third, the question arose whether remission or low disease activity should be the primary treatment target. As stated before, remission should be the main target in all patients, but especially in patients with early disease, in whom it can also be quite frequently attained, as seen in clinical trials [50] and practice. Remission results in better outcomes clinically, functionally and structurally than low disease activity [51]. However, as indicated in previous versions of this document and in the treat-to-target (T2T) recommendations, low disease activity can be an alternative goal, especially in patients with long-standing disease who already have failed 1 or more previous DMARD therapies. That said, any state other than low disease activity should be regarded as unacceptable, unless comorbidities or strong patient preferences preclude advancement of DMARD therapy. Importantly, T2T means achievement of at least 50% reduction of disease activity within 3 months and target attainment within 6 months [13], with amendment of therapy if these goals are not reached. With so many DMARDs available in 2025, there are ample alternatives for patients who continue to have moderate or high disease activity despite appropriate treatment. One suggestion was to add 'alternatively' before dealing with low disease activity, but this did not achieve majority support and so was not added.

Fourth, the question of imaging remission was addressed; however, several studies have clearly shown that sonographic remission is not superior to clinical remission in terms of clinical, functional, or structural outcomes, while being associated with more adverse events and higher costs [52,53]. Similar data pertain to aiming for remission by MRI [54].

Next, the issue of the limitations of the use of disease activity indices in the presence of some comorbidities like fibromyalgia, osteoarthritis or depression that are accompanied by (residual) pain was addressed. This challenge can result in patients having measurements of significant disease activity despite being in fact in clinical remission. Of note, only few patients in clinical trials have reported residual pain in the absence of objective inflammation [55]. Nevertheless, patients enrolled in clinical trials form a relatively healthy selection of all patients with RA compared with patients who may be encountered in clinical practice, where many more may report fibromyalgia-like symptoms of residual pain and fatigue. This could lead to inappropriate treatment decisions. However, currently, no clear data on overtreatment in patients with RA in clinical remission exist. Further, such potential overtreatment will usually only occur when previously existing or evolving pain syndromes are misinterpreted as residual inflammation. Such patients may not need treatment with DMARDs, let alone have their treatment changed to another DMARD, but would need other interventions. Indeed, as already stated in the T2T recommendations more than a decade ago, patients with specific comorbidities, when assessed with the usual instruments for determining RA disease activity, should be assessed differently, depending on the comorbidity [13]. In these situations, proper clinical judgement to interpret the scores is needed. Further, looking at alternative ways to assess disease activity in special situations does not change the importance of using composite outcome instruments, which have repeatedly been shown to be more reliable within and between patients, especially for clinical trials, but also when following patients in practice [56−58]. Also, ACR and EULAR revised the Boolean remission criteria in 2022, and this revision allows a patient global assessment of up to 2 cm rather than 1 cm [12].

Ultimately, a patient representative in the task force suggested that we keep the recommendation as it was, since it provided a clear approach, had been reviewed already in the course of developing the previous versions of these recommendations by the patient representatives and found to be necessary and sufficient by previous task forces.

At the end of all these deliberations, the item was kept as worded in 2022 by a 100% vote, with the many facets of the discussion reflected in this accompanying text.

*3. Disease activity monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted; when the target is sustained, monitoring can be less frequent.*

This recommendation previously may not have been as clear as originally desired, since 'monitoring should be

frequent in active disease' could be interpreted as assessment of either disease activity or safety. This has now been clarified by starting with 'Disease activity'. At the end of this recommendation, it is more explicitly stated that once the target is maintained, activity monitoring can be less frequent, such as every 6 months or even less, provided the patient is sufficiently informed about signs and symptoms of potential flares. Disease activity monitoring includes clinical assessment of a patient (especially joint counts) as well as laboratory tests for markers of inflammation, such as CRP, and patient-reported information. The extent of improvement to be expected during activity monitoring has been addressed in the discussion of recommendation 2.

Of course, safety monitoring is equally important, but this relates to every drug and every disease and is not specific to RA. Previous task forces have always stipulated that safety monitoring should be performed in line with the label after starting a new therapy, but it may be that the drug label recommendations, derived from the practices in registration trials, are too conservative. Evidence on this topic is scarce, in line with the fact that no articles were deemed eligible for inclusion from a separate SLR on DMARD monitoring conducted for this task force (included in the safety SLR). However, an increasing number of observational studies suggest that laboratory abnormalities occurring beyond 3 to 6 months after the initiation of a new DMARD are very infrequent and are usually of minor impact. Indeed, adverse events occur most frequently within the first 3 to 6 months, unless some organ function, such as kidney or hepatic function, changes unexpectedly; this has been seen for conventional synthetic (cs) DMARDs [59] and has recently been expanded to biological (b) DMARDs [60]. Thus, the task force was of the opinion that the currently available evidence does give confidence for a more lenient approach in terms of a reduction of laboratory examinations to semiannually or even less, once the patient has tolerated a new drug for about 3 to 6 months. Future updates may revise the current practice of lab monitoring and investigate a more personalised approach, as safety monitoring also depends on individual patient comorbidities, which may require more frequent laboratory assessments. Of note, certain adverse events, such as infections, cannot be 'monitored' and need special attention once they occur, although some, such as opportunistic infections, can be prevented by appropriate measures [61].

Subsequently, another question arose: would it be wrong to monitor patients every 3 to 6 months even if they were in sustained remission? It was discussed that there was nothing 'wrong' with more frequent assessments, but these are only considered necessary early on and under the circumstances already addressed [62]. On the other hand, special situations may require more frequent assessments at the discretion of the rheumatologist and the patient.

A final point of discussion related to the consequences of reduced monitoring frequencies on health care systems, but this will depend on the individual countries. It should be borne in mind that 'overmonitoring' elicits burdens for patients, providers, and health care resources.

As mentioned above, patient information, education, and guidance are key in all these considerations, and the frequency of clinical visits and laboratory testing should be part of the shared decision-making process between the patient and health care provider.

In the final ballot, 90% of participants voted in favour of the amended text, with 10% against it and no abstentions.

*4. MTX should be part of the first treatment strategy; in patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered.*

In 2022, csDMARDs were addressed in 2 separate recommendations: one (no. 4) related to MTX and another one (no. 5) addressing leflunomide and sulfasalazine. The current task force considered that this was not necessary and that the 2 could be combined to read as stated above. The wording remained essentially the same except for deleting 'as part of the (first) treatment strategy' after mentioning leflunomide and sulfasalazine, since this was already included when dealing with MTX.

Some participants raised the question whether leflunomide and sulfasalazine should only be used when MTX was contraindicated or not tolerated. Indeed, the EULAR recommendations have a preference for starting with MTX rather than leflunomide or sulfasalazine for reasons of efficacy and safety, but an individual rheumatologist may have reasons to prefer another csDMARD as the first treatment strategy in the context of shared decision making.

It was then suggested to change the word 'should' to 'could', but this was refuted in the discussion, since it would weaken the recommendation and suggest that bDMARDs are indirectly recommended as the first strategy, an approach which is not in line with the task force's current thinking. Indeed, such thought may have been a reason behind this suggestion, as some participants opted for the use of bDMARDs (or JAKi) in some patients as a first strategy, especially given that the prices of many biosimilars have significantly decreased in many cases. However, no trial has yet shown superiority of bDMARDs to MTX plus GCs in early RA, either clinically, functionally or radiographically [50,63] (see next recommendation). Therefore, the evidence is against using bDMARDs at this stage, also given safety aspects and that the costs of biosimilars are usually much higher than those of csDMARDs. The discussion also addressed parenteral MTX, whose costs may be similar to those of some biosimilars in certain countries, but a specific mention was not felt warranted, given parenteral MTX is not commonly needed, if oral MTX is handled appropriately, including sufficient folate supplementation [64,65], and pricing varies between countries. In the course of preparing this paper also, split-dose oral MTX was mentioned as yet another possibility of applying MTX [66].

There was also discussion regarding the use of triple therapy (MTX, sulfasalazine, and hydroxychloroquine). Indeed, already when the EULAR recommendations were developed for the first time in 2010, there was insufficient evidence that triple therapy plus GCs had better efficacy than MTX monotherapy plus GCs [26]. This has been further confirmed over subsequent years [67]. The new SLR on efficacy did not reveal any further insights regarding triple therapy [35]. Of note, after the cut-off date of the SLR, a comparison between triple therapy plus intraarticular GC vs MTX plus oral GC from the Nordic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) trial was published and, again, no significant advantage of triple therapy over MTX monotherapy at the time of the primary endpoint at 6 months was observed for remission frequencies, including swollen joint counts, as well as physical function or structural damage [68]. On the contrary, there were some numerical advantages for the MTX plus GC group, since only 5% of these patients, compared to 27% on triple therapy, showed progression of joint damage. Thus, the decision of the initial 2010 task force not to recommend the use of triple therapy has been reinforced over time.

In the ballot, 92% of participants voted to combine old recommendations 4 and 5 into a new no. 4 and to delete the last part of previous no. 5, as discussed above, with 4% each abstaining or voting for no change.

After this vote, there was more discussion of the advantages and disadvantages of having 2 separate recommendations for the csDMARDs, especially to increase the prominence of non-MTX csDMARDs with such separation. The convenors allowed for a ballot on returning to 2 separate recommendations or remaining with the combined one; only a minority of the members (29%) preferred 2 recommendations, which confirmed the previous ballot and wording of the new item 4.

> *5. Short-term GCs should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible.*

This point is identical to the previous recommendation 6. No new data have revealed any evidence against using GC as recommended here. It was mentioned, however, that stopping GC may be a successful target in clinical trials, but in clinical practice, discontinuation may not be realistically achieved. Consequently, the importance of tapering with the aim of stopping GC treatment was re-emphasised during the deliberations. Indeed, DMARD therapy can only be considered successful if remission or low disease activity can be sustained in the patient after discontinuing GCs. If GCs are needed to suppress disease activity, then a change of DMARDs should be considered. Regarding the route of administration, some rheumatologists prefer the application of parenteral GCs (such as intramuscular) to prescribing oral GCs.

Only 1 person abstained, and the rest (98%) voted for keeping this recommendation as it was. This was the largest majority ever achieved in favour of using GCs as a bridging therapy with csDMARDs.

> *6. If the treatment target is not achieved with the csDMARD strategy, a bDMARD should be added; JAK inhibitors may be considered, but pertinent risk factors must be taken into account.*

This item has undergone the biggest change when compared with all prior updates. It is a composite of previous recommendations 7 and 8, which suggested that we should stratify patients who did not respond to the initial therapy with MTX plus GCs according to prognostic factors. These prognostic factors had been defined as persistently moderate or high disease activity, including a high swollen joint count and high acute phase reactant levels; the presence of autoantibodies (rheumatoid factor and/or anticitrullinated peptide antibodies), especially at high levels; the presence of early erosions; and/or failure to respond to 2 or more csDMARDs. Those with any of these risk factors were recommended to have a bDMARD or JAKi added to MTX (no. 8 from 2022 and before) and in those without any of these factors, consideration of another csDMARD (plus GCs) was recommended (no. 7 from 2022 and before). However, there is now sufficient evidence to suggest that the addition of other csDMARDs compared with the addition of a bDMARD has a much lower persistence [69]. Also, it has been known for a long time that the efficacy of csDMARDs in patients who had an insufficient response to MTX is quite limited [70]. Most importantly, the recommendation to stratify patients with no risk factors to another round of csDMARDs, alone or in combination, was not based on substantial evidence but mainly on expert opinion. Given these aspects as well as the decreasing costs of biosimilar DMARDs and the fact that one of the JAKis has now become generic, the task force decided to abandon the stratification by prognostic risk. Thus, the suggestion for a new item 6 was based on the previous item 8, and it was proposed that the previous item 7 be deleted.

The proposal to delete stratification by prognostic factors achieved a 98% vote with 1 abstention.

Does this decision mean that rheumatologists should not look at prognostic factors or that the risks mentioned before are not valid anymore? Not at all—rather, the risk factors for a poor outcome remain the same, but insufficient response to MTX plus GCs in itself is already a bad prognostic sign [71].

Does this decision mean that rheumatologists should not use a second round of csDMARDs, alone or in combination? Not necessarily; as always, it is up to the rheumatologist, the patient, and also the economic situation in a specific country or for a specific situation to decide on therapeutic cycles. Indeed, the most important therapeutic aspect is adherence to a T2T-approach, in other words: regardless of the next step after failure of MTX + GC, one should aim at >50% reduction of disease activity within 3 months and attainment of the target set within 6 months.

Subsequently, the JAKi part of this recommendation was discussed. These deliberations ranged from suggestions not to mention risk factors for JAKi at all, to making the JAKi-part of this recommendation a separate bullet point specifying that JAKi should only be used after failure of bDMARDs. This discussion was reminiscent of the one in 2022, and participants were, and readers are, referred to the details addressed in the corresponding publication [28]. Since no new controlled trials were available to support a stronger or a weaker caveat regarding the use of JAKi, the task force ultimately decided to keep this part of the recommendation unchanged. The respective ballot revealed 81% of the task force members in favour of no change to this part of the recommendation, with 19% voting for a change and no abstentions. The risk factors for cardiovascular disease and malignancies when using JAKi have been detailed in the previous update and are also mentioned in a footnote to the Figure.

> *7. bDMARDs/tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and JAK inhibitors may have some advantages compared with other bDMARDs.*

Only a minor change was made when compared with item 9 from 2022, namely replacing the term ‘tsDMARDs’ with ‘JAK inhibitors’ to be more in line with the previous item, and given that for RA, the only currently available tsDMARDs are JAKi.

The new wording received an 88% majority with 4% against the change and 8% abstaining.

> *8. If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if 1 TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 receptor inhibitor.*

This recommendation is identical to the one from last time. While there are no data from randomised controlled trials on cycling between JAKi, positive observational data exist [72], and, therefore, it has to be assumed that this is a potentially effective approach, as also previously shown for anti-TNFs and other agents. Some participants wanted to change the word

tsDMARDs to JAK inhibitors, but this suggestion did not receive the necessary majority. Also, a drug of the same class should not be employed a third time.

The theme of therapeutic drug monitoring (TDM) was also covered in the efficacy SLR and discussed in the context of failure of bDMARD therapy. Previous task forces have not addressed TDM in the recommendations, since only a few anecdotal studies had suggested some merits in selected situations with selected drugs, while other studies did not show benefits. However, a recent trial revealed that TDM does not provide better outcomes compared to routine care [73]. Based on these data, the task force felt that TDM is not required in the management of patients with RA, especially in light of the costs of such assessments for no appreciable advantage.

Ultimately, keeping the recommendation unchanged attained a 100% vote.

At this point, it may be worth mentioning that the efficacy SLR included a search on therapeutic interventions specifically in patients with RA-ILD [35]. Subanalyses of a trial on nintedanib and early phase data on pirfenidone suggest a benefit in slowing the decline of lung function [74–76]. However, it is too early to make a definitive statement on these therapies for RA-ILD. Moreover, these drugs are not DMARDs for RA, which are the focus of this manuscript. Consultation with a pulmonologist may be necessary in these patients.

> *9. After GCs have been discontinued and a patient is in sustained remission, continuation of DMARDs (bDMARDs/tsDMARDs and/or csDMARDs) is recommended, but dose reduction may be considered.*

There is an increasing amount of data that stopping therapy leads to flares in the vast majority of patients [15–18]. Therefore, the task force felt that the previous version of the recommendation did not sufficiently take this risk into account and suggested a change of the wording to clarify that continuation of DMARD therapy is important. However, dose reduction (or dosing-interval increases, depending on the drug) is an option, especially after a patient has been in sustained remission for at least 6 months.

This change was approved by 96% of the participants, with 2% each voting no or abstaining.

### *Finalisation of the process*

As indicated before, each of the updated recommendations was supplemented by the research fellows and methodologists with the LoE and GoR (Table 1) and then underwent anonymous voting for the LoA by all 50 task force members, the results of which are also presented in Table 1. In line with previous updates, an algorithm is also provided, which is a graphical summary of the recommendations (Fig). This algorithm does not account for all aspects of the recommendations, and the readers are referred to Table 1 and the text accompanying each of the items in the Results section.

Finally, a research agenda was identified in order to focus future research activities on some of the unmet needs as perceived by members of this task force (Table 2). One of the research agenda items is the implementation strategy for these recommendations, which is also of clinical relevance and shown in Table 3.

For those interested in a direct textual comparison between the 2022 and the 2025 updates, the 2 sets of recommendations are provided next to each other in the Supplementary Table.

## DISCUSSION

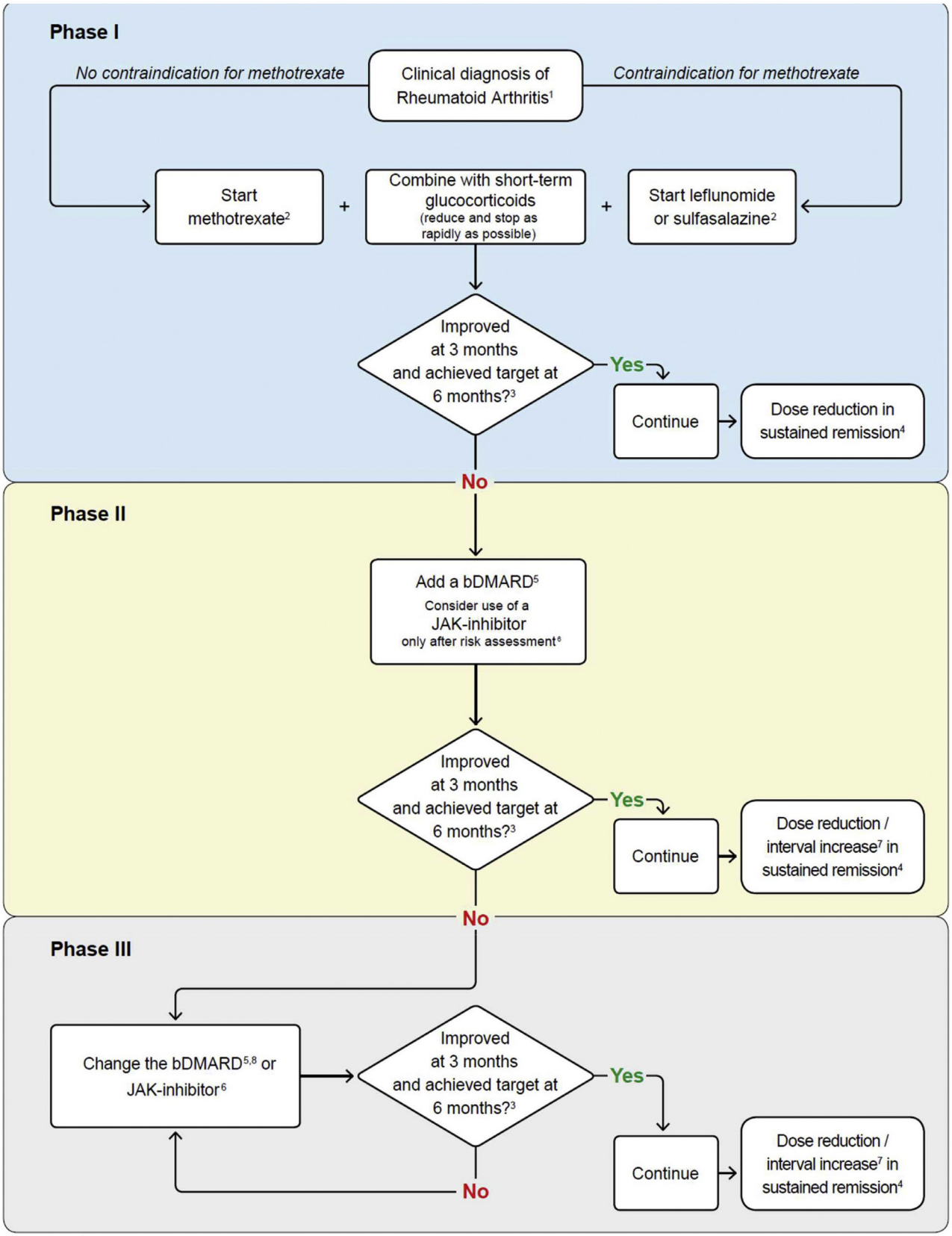
The task forces developing EULAR's RA management recommendations and their updates were composed of participants across the spectrum of EULAR's constituency (patients, health professionals and rheumatologists); across nations and continents, coming from more and less affluent health care systems; and included expertise beyond the field of rheumatology. This allowed the development of a broad international view on what might be an optimal therapeutic approach to treating patients with RA at the respective point in time. Over the decades, the updates have reflected the evolution of the field and provided readers with the newest evidence-based thinking and guidance derived from intensive discussions and a rigorous voting process. The recommendations are meant to inform those giving care to people with RA, as well as those living with the disease themselves, but also other stakeholders, as mentioned above. Basic and clinical scientists can also see the gaps and unmet needs that arise from the recommendations and the respective LoE as well as the research agenda proposed by the task force.

Initially, the availability of several bDMARDs targeting other molecules than just TNF necessitated the compilation of EULAR's first management recommendations to propose a logical sequence to the use of different drugs in light of their efficacy, safety, comparability, and costs [26]. This was followed by updates which covered newly developed drugs and newly emergent safety issues. The latest update concentrated primarily on therapeutic strategies and fine-tuning of the guidance, with a focus on the novel insights into safety aspects of the most recently introduced class of drugs, the JAKi [28]. Thus, while some safety aspects have been addressed in the context of the evolution of these recommendations, readers are also referred to the package inserts of the various drugs for more information on safety. For advice regarding the use of DMARDs in patients with some comorbidities, such as chronic viral infections, consultation with respective experts was recommended.

The new task force has further restructured the recommendations based on 2 SLRs that addressed the most recent insights into efficacy and safety of DMARD and GC therapies [35,36]. Each item, whether an OAP or individual recommendation, has been thoroughly evaluated and intensively discussed within the task force, and details of these discussions have been presented in the results section. They reflect the many facets within a large group of experts who ultimately arrived at a unified view with a high level of confidence, as revealed by the very high LoA. It is the first time in the history of these EULAR recommendations that all items were rated at an average score that was higher than 9 of 10, despite the large size of the task force and the broad international representation. This result suggests an increasing satisfaction of the task force with the rationality and validity of the entirety of the recommendations, the derivation of which has matured and gradually become part of clinical practice over the years

Apart from some minor wordsmithing, all OAPs and most individual recommendations remained unchanged from the 2022 update. Previous recommendations 4 and 5, which dealt with the use of MTX (no. 4) and other csDMARDs (no. 5) as initial treatment strategies once the diagnosis of RA has been made (no. 1), were now combined, as they deal with the same conceptual approach.

The importance of treatment to the target of remission (in early disease) or at least low disease activity (in long-established RA; no. 2) has been reiterated as a principle of utmost




1. 2010 ACR-EULAR classification criteria can support early diagnosis.
2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit may be expected. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. Leflunomide or sulfasalzine may also be considered as an interim step if MTX is insufficiently efficacious before adding a bDMARD or JAKi.
3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (reduction of disease activity by 50%) is seen after 3 months.
4. Sustained remission: ≥ 6 months ACR/EULAR index based (CDAI/SDAI) or Boolean remission.
5. Consider contraindications and risks. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), abatacept, IL-6R inhibitors, or rituximab (under certain conditions) and EMA/FDA approved bsDMARDs; in patients who cannot use csDMARDs as comedication IL6-inhibitors and JAKi have some advantages.
6. The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAKi: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC), risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or who are immobile)
7. Dose reduction or interval increase can be safely done with all bDMARDs and JAKi with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/JAKi. Glucocorticoids must have been discontinued before tapering DMARDs.
8. From a different or the same class.

**Figure.** Algorithm of the 2025 EULAR RA management recommendations. ACR, American College of Rheumatology; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EMA,

importance. It initially requires frequent disease activity monitoring using appropriate, validated instruments (no. 3). Remission should be judged by the remission definitions developed by EULAR and ACR [12]. Once the desired state is sustained, the frequency of disease activity monitoring may be reduced (no. 3, 9). The use of composite indices that include joint counts is invaluable to assess disease activity and is more reliable than individual core set measures, as has been shown long ago [56,58]. While it is well established that some patients may continue to have pain despite lacking signs of inflammation, this situation is quite rare, at least in clinical trials [55] and needs further evaluation in clinical practice. Importantly, such patients often have a pain syndrome as a comorbid condition. Therefore, in these patients the results obtained when using the usual instruments developed to assess RA disease activity may be misleading, and, consequently, other means to distinguish RA activity from pain due to a comorbid condition should be used, such as the swollen joint count. Management of such residual pain situations has been previously addressed by other EULAR activities [77,78]. Importantly, similar considerations apply to other comorbidities that may erroneously lead to high RA disease activity scores, such as osteoarthritis (joint swelling, tenderness) or infection (acute phase reactants) [79], and, therefore, a mere focus on inflammatory aspects of disease activity instruments, like swollen joint counts or acute phase reactant levels, will likewise be misleading in some though other groups of patients. In line, when IL-6R blockers or JAKi are used, acute phase reactant levels may decrease or normalise independently of clinical improvement and, therefore, disease activity scores that are strongly weighting acute phase reactants such as CRP or erythrocyte sedimentation rate should be avoided when using these agents; it must also be borne in mind that when using such drugs CRP responses in the course of infections may be blunted [80,81].

Based on the available evidence, the task force also reiterated that the use of MTX in combination with short-term GC as a first treatment strategy is unsurpassed by any other therapy (nos. 4 and 5). Indeed, the agreement with this approach as the initial strategy received backing by 98% of the task force members, the largest proportion ever when dealing with GCs in the course of the evolution of these recommendations.

Compared with previous versions, the most important change in the current update is the omission of stratification according to risk factors for bad outcomes, once the initial treatment strategy has failed (old nos. 7 and 8). In previous versions, a switch of csDMARDs had been advocated in patients who lacked bad prognostic markers (old no. 7). Backed by some new data, the task force felt the vast majority of patients would not respond sufficiently to a second csDMARD after MTX-failure and, therefore, the failure itself of MTX (or another csDMARD) plus GC was considered an adverse prognostic sign. This decision by the task force led to the deletion of item 7 from 2022 and the rewording of old item 8. The new wording can be found in item 6 of the current work.

Given the availability and recent expansion of the types of biosimilar (bs) DMARDs [82,83] as well as of generic JAKi [84,85], economic aspects also become less of an issue in many countries when advancing into phase 2 of the EULAR algorithm. Nevertheless, while no longer a major recommendation by EULAR, switching to or adding another csDMARD (plus GC) in patients with an insufficient response to MTX may still be a viable option for patients in less affluent countries or in some specific situations.

The use of JAKi underwent renewed discussions, which spanned from suggestions that the safety caveats of the last update should be deleted, since most observational data have not consistently confirmed the safety concerns raised by the ORAL-Surveillance trial [80,86–88], to recommending the use of JAKi only when bDMARDs had failed. None of these proposals received sufficient support within the task force, and, therefore, the place of JAKi remains as decided in 2022. It is placed at the same level as bDMARDs, but only in patients in whom pertinent risk factors have been considered [28], as mentioned again in the footnote of the Figure showing the current algorithm. Of note, a recent post-hoc subanalysis of the ORAL-Surveillance data presented after the task force meeting suggests that the use of statins may mitigate the cardiovascular risk of tofacitinib observed in the original study [89].

Since a significant proportion of patients will not respond sufficiently to any given drug employed in phase 2 of the algorithm, EULAR continues to recommend use of another agent of the same or different class in accordance with the T2T strategy. Given the many DMARDs available today, sufficient therapeutic options exist to ensure most patients achieve a good outcome, provided comorbidities do not preclude such treatment options.

With respect to tapering DMARDs in sustained remission, the task force reiterated and even strengthened the position that DMARD dose or frequency of administration may be reduced (item 9), but that DMARDs should not be stopped, as most patients in whom DMARDs are withdrawn will eventually flare within a year [18,90].

It is noteworthy that over the last 6 years, no new drug class has been approved for the treatment of RA in Europe or the USA. Since approximately 20% to 30% of the patients in the affluent world (and many more in economically disadvantaged countries) do not achieve the treatment target, new therapies are still needed. This is part of the research agenda, which also details all items that have been mentioned and not yet been addressed since the last version of this document was published [28].

It is well established that clinical RA is the result of a process that may be ongoing for many years, not least by the presence of autoantibodies a decade or more before RA onset [91], and EULAR has already accounted for research in this area [20]. Consequently, the 2022 research agenda also included a point related to developing a strategy to prevent RA, in other words to interfere with pre-RA to stop the disease. This was considered as one of the questions for the efficacy SLR [35], though it was evident to the task force that the current recommendations are only meant for patients who already have a diagnosis of RA, ideally also including those who are in the very early stages of the disease. While averting RA has been attempted repeatedly in people at risk of developing the disease who do not yet have any joint swelling, such as with rituximab or abatacept, all these trials have only led to a temporary delay of the diagnosis of RA compared to placebo [22–24]; in other words, what one sees is a therapeutic response in those patients who are destined to be diagnosed with RA but not prevention of its occurrence. Thus, it seems likely that steps other than the usual therapies approved for treating RA, such as immunologic tolerisation approaches [92,93], will have to be taken to prevent the evolution of RA in

European Medicines Agency; EULAR, European Alliance of Associations for Rheumatology; FDA, US Food and Drug Administration; IL, interleukin; JAK, Janus kinase; JAKi, JAK inhibitors; MI, myocardial infarction; MTX, methotrexate; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

Table 2
**Research agenda 2025**

**Treatment strategy**
1. Can we identify new biomarkers to stratify patients and to predict therapeutic response and lack of response?
2. How good is patient adherence to a bDMARD or tsDMARD, and can nonadherence explain secondary loss of efficacy?
3. If secondary loss of efficacy is due to true loss of efficacy rather than nonadherence of a given drug, what is the reason for this loss of efficacy?
4. Is there a way to detect and prevent loss of response in advance of flares?
5. Can the identification of disease phenotypes inform tailored therapeutic use?

**DMARD therapy**
1. How safe and efficacious is the use of an IL-6 pathway inhibitor if a JAK inhibitor (JAKi) has failed?
2. How safe and efficacious is the use of a JAKi after another JAKi has failed?
3. Is monotherapy of JAKi or a combination of JAKi plus MTX more efficacious than MTX + GC?
4. To which extent do *in vitro* selectivity and *in vivo* selectivity differ among JAKi?
5. Do JAKi as a class increase the risk of malignancies, CV events and VTE compared to bDMARDs or do they not lower the risks as much as bDMARDs?
6. If JAKi increase the risk of CV events, malignancies and VTE, what are the mechanisms which cause these events? Is there a difference in the risks with different JAKi? Is there a difference in the risks with different bDMARD modes of action?
7. How safe and efficacious is the combination of a JAKi with a bDMARD, such as a TNF-inhibitor?
8. Can we accurately predict which patients might achieve DMARD-free remission?

**Glucocorticoids**
1. Is the risk of glucocorticoids (GCs) different if a specific cumulative dose has been reached within relatively short-term, such as within 3 to 6 mo when compared to the same cumulative dose used over years?
2. What are the barriers and facilitators of GC cessation after induction therapy, and how can a strategy for tapering and discontinuing be best implemented?
3. Does the concomitant use of GCs at very low doses (1-3 mg prednisone equivalent) increase therapeutic success without producing unacceptable side effects?
4. Can the chronic use of GCs be prevented by more intensive DMARD use?
5. How frequent is the chronic use of GCs among patients with RA followed in resource-poor countries, and how could such chronic use be mitigated or prevented?
6. Is there a superiority of one GC route of administration vs another one?
7. What are the effectiveness and safety profile of (repeated) intramuscular glucocorticoids, for example, methylprednisolone 120 mg or triamcinolone 80 mg 1 to 4 times annually?
8. To which extent are safety issues with chronic GC use related to pre-existing comorbidities and do patients with such comorbidities preferentially receive GCs rather than advancing b/ts DMARD therapies?
9. Is there an optimal route of administration for GCs to be effective and most efficiently tapered?
10. Is it useful to determine morning serum concentrations of endogenous cortisol to optimise dosages of GCs?

**Difficult to treat RA (D2T RA)**
1. What is the optimal treatment approach to refractory RA?
2. To which extent does lack of adherence or intermittent use of DMARDs (b/tsDMARDs) contribute to D2T RA?
3. Are there factors that can be identified earlier in a patient as additional risks for the development of refractory RA?
4. Could drug monitoring predict drug failure concerning bDMARDs or JAKi and allow checking for adherence?
5. For patients with active RA who have failed multiple drugs, are there combinations that may be more successful, such as a JAKi with a bDMARD?
6. What is the role of bispecific antibodies, including bispecific T-cell engagers, and cellular therapies in the treatment repertoire of RA?
7. Can early use of more aggressive therapy such as bDMARDs as a first-line therapy without a prior csDMARD lead to reduced D2T RA frequencies?

**Pain syndromes**
1. How frequent is pain without inflammation in RA patients treated with DMARDs?
2. Did these patients have a pain syndrome in the first place?

**RA-ILD**
1. Perform RCTs in patients with RA-ILD to determine the best use of DMARDs and anti-fibrotic therapies.

**People at risk to develop RA**
1. What is the optimal (therapeutic) approach to arthralgia suspicious for progression to RA?
2. Is TNF-inhibition preventive?
3. Can we define which characteristics are highly predictive for the development of RA based on available clinical trial data in people at risk for RA?

**Biomarkers**
1. Do high levels of CRP predict response to a particular therapy?
2. Do high RF or ACPA levels predict response to a particular therapy?

**Monitoring of therapies**
1. Is there a cost-effective and safe approach to lab monitoring of DMARD therapies in RA?
2. When and how often should safety monitoring be done?
3. Formal study to define frequency of efficacy and safety monitoring?

**Implementation**
1. How can implementation of the recommendations be ensured?
2. Can we demonstrate that the recommendations have produced improvements in patient outcomes?

ACPA, anticitrullinated peptide antibodies; bDMARD, biological disease-modifying antirheumatic drug; CRP, C-reactive protein; CV, cardiovascular; csDMARD, conventional synthetic disease-modifying antirheumatic drug; D2T, difficult to treat; IL, interleukin; JAK, Janus kinase; JAKi, JAK inhibitor; MTX, methotrexate; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-interstitial lung disease; RCT, randomised controlled trial; RF, rheumatoid factor; TNF, tumour necrosis factor; VTE, venous thromboembolic event.

Table 3
**Quality indicators for the assessment of adherence to the EULAR RA management recommendations**

| Recommendation | Quality indicator | Measure | When to measure | Source |
|---|---|---|---|---|
| **R1**. Therapy with DMARDs should be started as soon as the diagnosis of RA is made. | Time to start DMARD | % of individuals on DMARD | 3 mo after first rheumatology visit | Clinical records, local, regional or national audit |
| **R2**. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. | Achievement of remission or low disease activity | % of individuals achieving remission or low disease activity | 6 mo after starting DMARD | Clinical records, local, regional or national audit |
| **R4.** MTX should be part of the first treatment strategy; in patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered. | Time to start MTX | % of individuals on MTX | 3 mo after first rheumatology visit | Clinical records, local, regional or national audit |
| **R5**. Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible. | Stopping glucocorticoids | % of individuals not on corticosteroids | 1 y after first rheumatology visit | Clinical records, local, regional or national audit |
| **R7.** bDMARDs/ tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and JAK inhibitors may have some advantages compared with other bDMARDs. | Addition of a bDMARD or csDMARD after insufficient response to a csDMARD | % of individuals on combination therapy | Within 3 mo after determination of an insufficient response to a csDMARD | Clinical records, local, regional or national audit |

bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

those at risk for the disease. But it is also suggested that such patients are regularly followed for any signs of clinically active arthritis and that DMARD therapy is immediately started once the diagnosis of RA is established. Future updates of these recommendations may have to address people at risk of developing RA and consider elaborating a recommendation regarding the approach to this group of individuals who do not (yet) have a diagnosis of RA but may develop the disease (see research agenda).

The research agenda also includes studies on RA-ILD, another topic from this year's efficacy SLR, which did not reveal sufficiently strong evidence to warrant a specific item in this new version of the EULAR recommendations, especially regarding DMARD therapy.

Yet another point for future research is the identification of predictors of response to specific therapies. Currently, all b/tsDMARD exhibit similar efficacy at least at the group level, including using a second bDMARD of the same class when compared indirectly with bDMARDs of a different class. This, indeed, is the basis for EULAR's recommendation in phase 3 of the algorithm (recommendation 8). Hitherto, trials stratifying patients with a B-cell-rich synovial histology or signature to receive rituximab, an anti-B-cell agent, vs tocilizumab, an anti-IL-6 receptor drug, or vs a TNF-inhibitor, did not result in significant differences among the drug responses at the time of the primary endpoint [94,95]. There are data suggesting that very high CRP levels may predict a good response to anti-IL-6R therapy [96] and high serum rheumatoid factor levels may differentiate response rates to different agents [97,98], but these data come from post-hoc or observational analyses and need to be confirmed by properly controlled trials. Of note, the task force also arrived at the conclusion that TDM is not helpful regarding response prediction [73].

While quality indicators have not been discussed at the task force meeting, such indicators have been developed before and should be used to monitor the implementation of the EULAR recommendations [99]; a table outlining quality indicators for the current set of recommendations is also provided here.

In summary, this update of the EULAR recommendations for RA management with DMARDs comprises the smallest

number of recommendations in the history of this activity and thus further simplifies the approach to treating RA effectively. The main characteristics, such as starting the treatment algorithm with MTX plus short-term GC, switching to a b/tsDMARD when the first strategy fails, and targeting remission or low disease activity at all stages of the therapeutic cascade as well as attempting to achieve such a state within 6 months, remain fully in place, since over the last few decades evidence for the validity of these strategies has further accumulated. Some fine-tuning was made in the context of initiation of and switching between b/tsDMARDs, and when dealing with situations in which the target has been achieved and sustained. Thus, this update has addressed the newest evidence-based insights on efficacy and safety of the use of cs-, b-, and tsDMARDs. As always, these insights have been condensed into a graphic algorithm, and we will follow the developments in the field and will update these recommendations as needed within a few years.

## CRediT authorship contribution statement

**Josef S. Smolen:** Conceptualization. **Christopher J. Edwards:** Conceptualization. **Victoria Konzett:** Conceptualization. **Faidra Laskou:** Conceptualization. **Daniel Aletaha:** Conceptualization. **Roberto Caporali:** Conceptualization. **Thomas Dörner:** Conceptualization. **Kimme L. Hyrich:** Conceptualization. **Elsa Mateus:** Conceptualization. **Janet E. Pope:** Conceptualization. **Jette Primdahl:** Conceptualization. **Savia de Souza:** Conceptualization. **Tanja Stamm:** Conceptualization. **Tsutomu Takeuchi:** Conceptualization. **Désirée van der Heijde:** Conceptualization. **Patrick Verschueren:** Conceptualization. **Kevin L. Winthrop:** Conceptualization. **Jose Maria Alvaro-Gracia:** Conceptualization. **Johan Askling:** Conceptualization. **Joan Bathon:** Conceptualization. **Maya H. Buch:** Conceptualization. **Gerd R. Burmester:** Conceptualization. **Catalin Codreanu:** Conceptualization. **Philip G. Conaghan:** Conceptualization. **Maurizio Cutolo:** Conceptualization. **Bruno Fautrel:** Conceptualization. **Joao Fonseca:** Conceptualization. **Laure Gossec:** Conceptualization. **Espen Haavardsholm:** Conceptualization. **Merete Lund Hetland:** Conceptualization. **Annamaria Iagnocco:** Conceptualization. **Pierre-Antonie Juge:** Conceptualization. **Zhanguo Li:** Conceptualization. **Rikke Helene Moe:** Conceptualization. **Peter Nash:** Conceptualization. **Gyula Poór:** Conceptualization. **Andrea Rubbert-Roth:** Conceptualization. **Raquel dos Santos Sobrin:** Conceptualization. **Hendrik Schulze-Koops:** Conceptualization. **Russka Shumnalieva:** Conceptualization. **Ladislav Senolt:** Conceptualization. **Lucia Silva-Fernandez:** Conceptualization. **Anja Strangfeld:** Conceptualization. **Peter Taylor:** Conceptualization. **Carl Turesson:** Conceptualization. **Elsa van Duuren:** Conceptualization. **Maarten de Wit:** Conceptualization. **Ricardo Xavier:** Conceptualization. **Andreas Kerschbaumer:** Conceptualization. **Robert B. M. Landewé:** Conceptualization.

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## ORCID iDs

Espen Haavardsholm http://orcid.org/0000-0003-4229-6818

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