SUPPLEMENTARY APPENDIX 1: Methods

2022 American College of Rheumatology (ACR) Guideline for Exercise, Rehabilitation, Diet, and Additional Integrative Interventions for Rheumatoid Arthritis

Methodology Overview

This guideline was developed following the American College of Rheumatology (ACR) guideline development process (www.rheumatology.org/Portals/0/Files/ACR%20Guideline%20Manual_Appendices_updated%202015.pdf). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) (1-4).

Teams Involved

A Core Leadership Team (7 members) met weekly to supervise the project and was responsible for confirming the scope and clinical (Patient/Intervention/Comparator/Outcomes – PICO) questions (see Supplementary Appendix 2), coordinating with the Literature Review Team, overseeing the voting process, and drafting the manuscript. The Core Team, together with the Literature Review Team, was comprised of individuals with content and methodological expertise, and included a GRADE methodologist who advised on the process of developing and presenting the evidence and provided input on the quality assessment of evidence and summary of findings (SoF) tables (provided in Supplementary Appendix 3).

The Literature Review Team (18 members) conducted a systematic search with the assistance of an experienced medical librarian, screened papers for relevance, assessed study quality, extracted data, computed pooled estimates of outcomes, graded the quality of evidence, generated an evidence summary for each PICO, and compiled an evidence report.

A Patient Panel was convened to discuss patient values and preferences related to outcomes, evidence, and drafted recommendation statements. The ACR solicited volunteers for the Patient Panel,

collecting details regarding RA disease experience, experience with therapies under consideration, and potential conflicts of interest. The Core Team reviewed the applications to select members for the Patient Panel including three patients to participate on the Voting Panel. The Voting Panel used the input from the Patient Panel meeting to help guide their votes in balancing tradeoffs between the harms and benefits of the alternative management strategies.

The Voting Panel consisted of 20 people, including rheumatologists, integrative medicine experts, physical therapists, occupational therapists, researchers, a nurse, a nutritionist, and three patient representatives. The role of the Voting Panel was to vote on the drafted recommendation statements derived from the PICO questions, keeping the evidence report, their expertise and experience, and patient values and preferences in mind.

The ACR provided training for everyone involved in the development of this guideline, which included explanations of the ACR guideline process and GRADE methodology. See Supplementary Appendix 4 for team/panel rosters.

Patient Panel

The Patient Panel, consisting of one adult man and 11 adult women with RA, was convened on June 21, 2022. Dr. Jennifer Barton, a member of the Core Team, Dr. Louise Thoma, a member of the Literature Review Team, and one ACR staff person facilitated the five-hour webinar discussion. The participants were first presented with the background and scope of the guideline project. They were then specifically queried on the relative importance of exercise, rehabilitation, diet, and additional integrative interventions for the treatment of RA, with particular attention paid to how values and preferences might differ. The Patient Panel reviewed the evidence synthesized by the Literature Review Team as several PICO questions were discussed. The participants were encouraged to consider their personal experiences relevant to the questions and judge the importance of the outcomes and vote on the drafted recommendation statements accordingly. Three patients on the Voting Panel, who

had been at the Patient Panel meeting, presented the values and preferences of the Patient Panel and their voting results to the Voting Panel during the two-day Voting Panel meeting held July 6-7, 2022.

Disclosures and Management of Conflicts of Interest

Per ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) was required to disclose all relationships (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Integrative-RA-Treatment). Disclosures were evaluated to determine if any relationships were considered potential conflicts of interest for purposes of this project. Individuals whose primary employment (≥ 51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project's co-principal investigators (PI) and the Literature Review Team leader had no relevant conflicts of interest for the full 12 months before this project began, and a majority of guideline development team members had no relevant conflicts of interest for the duration of the project. Intellectual conflicts, such as a prior publication or scientific presentation on exercise, rehabilitation, diet, and additional integrative interventions for RA, were recognized as important and were required to be disclosed, but because they were ubiquitous, intellectual conflicts were not counted as conflicted toward the allowed threshold.

Participant disclosures were initially shared in the project plan, which was posted online for public comment as the project began. Disclosures were updated and shared again with each project participant via email prior to the Voting Panel meeting. Updated participant disclosures are included online with this manuscript.

Scope and Target Audience

The scope of this project included the development of evidence-based recommendations for exercise, rehabilitation, diet, and additional integrative interventions for the management of rheumatoid arthritis.

The target audience for this guideline includes adults with rheumatoid arthritis and their health care providers. Derivative products may be developed in the future to facilitate implementation of this guideline to these audiences.

Establishing Key Principles and PICO Development

The Core Leadership Team collaborated with Literature Review Team and Voting Panel members to develop the initial set of PICO-formatted clinical questions for the guideline, as well as identify pre-specified outcomes that were considered critical for each PICO question (see Supplementary Appendix 2).

The Core Leadership Team held weekly conference calls, convened an initial virtual meeting of the Core Leadership Team, Literature Review Team, and Voting Panel in which the scope of the guideline was determined, and then developed the PICO questions. The PICO questions were posted for 30 days on the ACR website for public comment and revised accordingly.

Systematic Synthesis of the Literature

Literature Searches

To identify relevant evidence for the PICO questions, a medical librarian, in collaboration with the Core Team, performed systematic searches of the published English language literature. Ovid MEDLINE, Ovid Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) original searches were performed from the beginning of each database to November 5, 2021, and updated searches were later performed from November 6, 2021 to May 1, 2022 (see Supplementary Appendix 5).

Study Selection

DistillerSR software (https://distillercer.com/products/distillersrsystematic-review-software/) was used to aid screening the literature search results. Teams of two independent reviewers performed duplicate screening of each title and abstract with articles identified as potentially eligible passing to

review of full text. Eligible articles underwent full-text screening by two independent reviewers. Articles with <80% of participants having RA were excluded. Selected manuscripts were matched to PICO questions. See Supplementary Appendix 6 for details related to the study selection process.

Data Extraction and Analysis

Comparative data (e.g., from RCTs and controlled non-randomized studies) for each PICO question were extracted into RevMan software (http://tech.cochrane.org/revman). Risk of bias of each primary study was assessed using the Cochrane risk of bias tool (http://handbook.cochrane.org/). The critical outcomes selected for this guideline were continuous, and they were reported as either mean differences or standardized mean differences (both with 95% confidence intervals). Random-effects meta-analyses were performed in RevMan. Data for which effect sizes were not computable (e.g., no standard deviations reported, or data reported as medians) were extracted into Word tables.

Evidence Report Formulation

RevMan files were exported into GRADEpro software (https://www.gradepro.org/) to formulate a GRADE Summary of Findings (SoF) table for each PICO question (2), when possible. The quality of evidence for each outcome was evaluated by one literature review team member, then verified by the literature review leader (JT) using GRADE quality assessment criteria (1) with discordance resolved by discussion. The resulting SoF tables were compiled in an evidence report (Supplementary Appendix 3). The Core Leadership Team reviewed the evidence report prior to presentation to the Voting Panel.

During the Voting Panel meeting, the panel expressed interest in additional analyses combining critical outcome data from all exercise-related PICOs (4, 5, 6, and 7). These analyses were conducted by the literature review team leader following the same process as above and then considered by the Voting Panel when voting on an exercise or no exercise recommendation.

Moving from Evidence to Recommendations

GRADE methodology specifies that voting panels make recommendations based on a consideration of the balance of benefits and harms/burdens of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the trade-off between desirable and undesirable outcomes; recommendations require estimating the relative value patients place on the outcomes.

A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision-making. Judgments made in this guideline were based on the experience of the clinician panel members in shared decision making with their patients, on the experience and perspectives of this guideline's Patient Panel members and, to a considerable extent, on the results of discussion with the Patient Panel.

Consensus Building

The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. Individual online voting took place first, to ascertain any existing consensus on drafted recommendation statements that were based on the PICOs. This process was followed by a 2-day virtual webinar meeting of the Voting Panel, where they reviewed the evidence, edited recommendation statement wording, and provided final votes on the direction and strength of each recommendation. The webinar voting process was conducted using Poll Everywhere software (www.polleverywhere.com). A 70% consensus was used as the threshold for a recommendation; if 70% consensus was not achieved during an initial vote, the panel members held additional discussions

before re-voting until at least 70% consensus was achieved. Following the meeting, additional clarifying questions were discussed by email and related voting took place via online survey.

Final Review and Approval of the Manuscript by the ACR

In addition to journal peer reviews, the manuscript was reviewed by the ACR Guideline Subcommittee, the ACR Quality of Care Committee, and the ACR Board of Directors. These ACR oversight groups did not make or mandate that specific recommendations be made within the guideline, but rather, served as peer reviewers.

Moving from Recommendations to Practice

These recommendations are designed to support health care providers who work with patients in selecting therapies. Health care providers and patients must take into consideration not only clinical phenotype and level of disease activity, but also comorbidities, response and tolerance of prior therapies, patient's values and preferences, and patient's functional status and functional goals in choosing the optimal therapy for an individual patient at the given point in treatment.

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