SUPPLEMENTARY APPENDIX 1: Methods

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

Methodology Overview

This guideline was developed following the American College of Rheumatology (ACR) guideline development process (https://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) (1-3).

Teams Involved

A Core Leadership Team (6 members) supervised the project and was responsible for defining the scope, drafting the clinical (Patient/Intervention/Comparator/Outcomes – PICO) questions, 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 2).

The Literature Review Team (15 members) conducted a systematic search, screened papers for relevance, assessed study quality, extracted data, computed pooled estimates of outcomes, graded the quality of evidence, generated the SoF tables, and compiled an evidence report.

The Voting Panel included 15 pediatric rheumatologists and 2 patients who were diagnosed with JIA in childhood. The role of the Voting Panel was to participate in the development of the scope and PICO questions, including making judgments regarding the relative importance of the outcomes, and vote on the final recommendations, keeping the evidence report, their expertise and experience, and patient values and preferences in mind.

A Patient and Parent Panel was convened virtually to discuss patient values and preferences related to treatment options, outcomes and evidence. The two patients on the Voting Panel also participated in the Patient and Parent Panel discussions. The Voting Panel used the input from the patient meeting to help guide their votes in balancing tradeoffs between the harms and benefits of the alternative management strategies.

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

Patient and Parent Panel

The Patient and Parent Panel, consisting of 9 adults with juvenile idiopathic arthritis (JIA) and 6 parents of children with JIA, was convened by webinar on September 16, 2020. Ten of the 11 patients/parents were female. Dr. Karen Onel, Principal Investigator (PI) of the guideline project, and 2 ACR staff members facilitated the 5-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 beneficial and adverse events of drugs and drug classes, including but not limited to efficacy, route of administration, and side effects, with particular attention paid to how values and preferences might differ in a pediatric population. The Patient and Parent 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 accordingly. The two patients on the Voting Panel, who had been at the patient meeting, presented the values and preferences of the patient panel and the voting results to the Voting Panel during the two-day Voting Panel meeting held by webinar October 1-2, 2020.

Disclosures and Management of Conflicts of Interest

Per ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all relationships (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Juvenile-Idiopathic-Arthritis). Disclosures were compared against a previously drafted list of "affected companies" (i.e., companies or organizations that were considered reasonably likely to be positively or negatively affected by care delivered in accordance with the guideline) to determine which relationships were considered potential conflicts of interest for purposes of this project. Individuals were also asked to explicitly highlight relationships with any companies *not* on the affected companies list that related to the topic of the guideline. 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 principal investigator (PI), the literature review leader, and the majority of the guideline development team members had no relevant conflicts of interest for the full 12 months before this project began, through the duration of the project. However, approximately one-third of team members did have some conflicts (the ACR allows up to 49%). A participant who had any relationship with an affected company was counted as conflicted (i.e., toward the allowed threshold) regardless of the type or subject of the relationship.

Intellectual conflicts, such as a prior publication or scientific presentation on JIA therapy, 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 included in the project plan that was posted online for public comment (see description below). In addition, disclosures of all participants were shared, in writing, with each project participant, including just before the Voting Panel meeting. Updated participant disclosures are included online with this manuscript. Finally, author disclosures are also included in this paper.

Scope and Target Audience

The scope of this project included both pharmacologic and non-pharmacologic treatment of patients with JIA, covering topics that were not covered in the ACR-Arthritis Foundation 2019 JIA and uveitis guidelines, including recommendations for the use of glucocorticoids, non-biologic, and biologic disease-modifying antirheumatic drugs (DMARDs) for the treatment of individuals with oligoarticular JIA arthritis, TMJ arthritis, and systemic JIA; screening recommendations for the use of conventional and biologic DMARDs for individuals with JIA; and guidance for the use of immunizations and imaging for individuals with JIA. The target audience for this guideline includes health care providers and patients with JIA (and/or their parents). The ACR plans to develop derivative products to facilitate implementation of this guideline.

Establishing Key Principles and PICO Development

The Core Leadership Team collaborated with the Voting Panel members to develop the initial set of PICO-formatted clinical questions for the guideline. The critical outcomes varied, depending on what the focus of the PICO question was. For PICOs relating to treatment, physical function, radiographic progression, quality of life, other patient-reported outcome

measures, and adverse events were defined as important outcomes. Toxicity of medications, inconvenience and company input were evaluated to make guidance regarding medication monitoring. Immunizations were evaluated while considering safety, risk of flare and ability to respond. (See Supplemental Appendix 3 for a summary list of outcomes evaluated.)

The Core Leadership Team held weekly conference calls, convened an initial 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. Final PICO questions are included within the evidence report, in Supplemental Appendix 2 (at the top of each evidence summary that relates to a particular PICO).

Framework for the JIA Guideline Development

During initial scoping, it was agreed that the scope of the populations to be addressed would include individuals with JIA with the phenotypes of oligoarticular JIA arthritis, TMJ arthritis, and systemic JIA, with additional guidance for immunizations and imaging use for JIA patients.

After defining population groups, interventions and comparators were specified for each PICO question. The Core Leadership Team agreed that the guideline should include both pharmacologic and non-pharmacologic treatment approaches and elected to include the following interventions: NSAIDS; glucocorticoids (oral and intra-articular injections); non-biologic disease modifying anti-rheumatic drugs (nbDMARDs), including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and calcineurin inhibitors; biologic disease modifying anti-rheumatic drugs (bDMARDs), including TNF inhibitors (adalimumab, etanercept, infliximab, golimumab, and certilizumab pegol), IL-1 inhibitors (anakinra,

canakinumab and rilonacept), tocilizumab, and abatacept; as well as immunizations, physical therapy, occupational therapy, diet and supplement use.

Systematic Synthesis of the Literature

Literature Searches

To identify relevant evidence for the PICO questions, a medical librarian, in collaboration with the Literature Review Team, performed systematic searches of the published English language literature. OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects (DARE); Cochrane Central Register of Controlled Trials (CENTRAL); and Health Technology Assessments (HTA)) were searched. Medline (PubMed) and Cochrane searches were originally run from the beginning of each database through August 3, 2019 and were updated on July 8, 2020. Embase searches were originally run from database inception through August 5, 2019 and were updated on July 8, 2020. See Supplementary Appendix 7 for detailed search strategies.

Study Selection

DistillerSR software (https://distillercer.com/products/distillers-systematic-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. Selected manuscripts were then matched to PICO questions. RCTs were preferred, when available, but in clinical scenarios not addressed by RCT data, data from observational cohort studies was used to estimate relative effects. See Supplementary Appendix 6 for details related to the study selection process.

Data Extraction and Analysis

Data from RCTs for each PICO question was 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/). Certain critical/important outcomes selected for this guideline were binary, and if meta-analysis was appropriate, they were analyzed using the Mantel-Haenszel method in a random effects model and reported as relative risks or odds ratios with 95% confidence intervals. Critical/important continuous outcomes and binary outcomes not combinable in a meta-analysis were tabled as reported in the individual studies.

Evidence Report Formulation

RevMan files were exported into GRADEpro software to formulate a GRADE Summary of Findings (SoF) table for each PICO question (4). The quality of evidence for each outcome was evaluated in duplicate by two independent reviewers using GRADE quality assessment criteria (1) with discordance resolved by discussion. The resulting SoF tables were compiled in an evidence report (Supplementary Appendix 2). The Core Team reviewed the evidence report and addressed possible evidence gaps prior to presentation to the Voting Panel.

Moving from Evidence to Recommendations

GRADE methodology specifies that panels make recommendations based on a consideration of the balance of benefits and harms 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 are based on the experience of the clinician panel members in shared decision making with their patients, on the experience and perspectives of the two patient members of the Voting Panel, 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. During a two-day, virtual meeting held October 1-2, 2020, the Voting Panel, for each PICO question, reviewed the evidence and feedback from the Patient Panel, and provided votes on the direction and strength of the recommendations. The virtual voting process was conducted using Poll Everywhere software (http://www.polleverywhere.com/). A 70% consensus was used as the threshold for a recommendation; if 70% consensus was not achieved during an initial vote, panel members held additional discussions before re-voting until at least 70% consensus was achieved.

Consistent with GRADE guidance, in some instances, the Voting Panel chose to provide a strong recommendation despite a low or very low quality rating of evidence (3). In such cases, a written explanation is provided describing the reasons behind this decision with reference to GRADE guidance on the matter (3).

Final Review and Approval of the Manuscript by the ACR

In addition to journal peer reviews, the manuscript was reviewed by the following committees and subcommittees of the ACR: ACR Guideline Subcommittee; ACR Quality of Care Committee; and ACR Board of Directors. These ACR oversight groups did not mandate that certain 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 and parents in selecting therapies. Health care providers, patients and parents must take into consideration not only clinical phenotype and level of disease activity, but also comorbidities, response and tolerance of prior therapies, a patient's values and preferences, and a 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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