SUPPLEMENTARY APPENDIX 1: Methods

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases

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 (10 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 (15 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.

The Voting Panel consisted of 15 people, including adult and pediatric rheumatologists, pediatricians, infectious disease experts, and 2 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.

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/Vaccinations). 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 principal investigator (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 Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases, 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. Finally, author disclosures are also included in this paper.

Scope and Target Audience

The scope of this project included the development of evidence-based recommendations for vaccination in adults and children with RMD or those on immunosuppressive or immunomodulating medications.

The target audience for this guideline includes adults and children with rheumatic and musculoskeletal diseases (RMDs) and their clinicians. 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. Once the PICO questions were finalized and the literature review completed, individual online voting took place to ascertain any existing consensus, followed by a virtual meeting of the Voting Panel, where voting on the PICO questions was finalized. Following the meeting, additional clarifying questions were discussed by email and related voting took place via online survey.

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 May 3, 2021, and updated searches were performed from May 3, 2021, to January 31, 2022 (see Supplementary Appendix 5).

In addition, because the ACR's 2021 rheumatoid arthritis guideline (5) initially included vaccinations in its scope and literature review but the final guideline did not include the vaccination topic, vaccine-related articles initially included for the 2021 RA guideline were reviewed to ensure that this project's searches captured all relevant articles from that previous project. As a result, 7 references were added to the pool of references to be screened for this guideline.

Systematic literature reviews that were retrieved by this project's formal searches were also reviewed for possible additional relevant papers. From this effort, 8 references were added to this guideline's pool of papers for screening.

Finally, the initial searches included COVID-19 vaccination, but the update searches did not. It was determined in early 2022 that COVID-19 vaccination would be removed from the scope of this guideline, given the large search yield, the continually changing nature of the evidence retrieved, and the certainty that this part of the guideline would almost certainly be outdated well before publication. The ACR has other COVID-19 vaccine guidance publications (6) that may be consulted, as needed (see the COVID-19 Guidance page on the ACR website at https://www.rheumatology.org/Practice-Quality/Clinical-Support/COVID-19-Guidance).

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.

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 some controlled observational studies) 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/). The critical outcomes selected for this guideline were mostly binary, and they were reported as relative risks with 95% confidence intervals. When possible, binary outcomes from different studies were meta-analyzed using the Mantel-Haenszel method in a random effects model. Continuous outcomes were reported as mean differences. Data not suitable for RevMan was extracted into Word tables.

In clinical scenarios not addressed by RCT or controlled observational data, data from observational uncontrolled studies was used to estimate effects. In situations in which evidence for a specific intervention in a patient population with rheumatic disease (RMD) was sparse or absent, evidence for the intervention in a non-RMD population was included. In these cases, the effect sizes in non-RMD patients were postulated to be generalizable but the quality of evidence was lowered by rating down for indirectness.

Evidence Report Formulation

RevMan files were exported into GRADEpro software to formulate a GRADE Summary of Findings (SoF) table for each PICO question (4), when possible. The quality of evidence for each outcome was evaluated by one literature review team member, then verified by the literature review leader (JR) 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.

Moving from Evidence to Recommendations

GRADE methodology specifies that voting 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 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 initial consensus, followed by a virtual webinar meeting of the Voting Panel, where they reviewed the evidence and provided votes on the direction and strength of each drafted 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.

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 ACR Guideline Subcommittee, 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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