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2016 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Anti-rheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

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ABSTRACT

Objective: This collaboration between the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS) developed an evidence-based guideline for the perioperative management of anti-rheumatic drug therapy for adults with rheumatoid arthritis (RA), spondyloarthritis (SpA), including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE) undergoing elective total hip (THA) or total knee arthroplasty (TKA).

Methods: A panel of rheumatologists, orthopaedic surgeons specializing in hip and knee arthroplasty, and methodologists was convened to construct the key clinical questions to be answered in the guideline. A multi-step systematic literature review was then conducted, from which evidence was synthesized for continuing vs. withholding anti-rheumatic drug therapy and for optimal glucocorticoid management in the perioperative period. A patient panel was convened to determine patient values and preferences, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to rate the quality of evidence and the strength of recommendations using a group consensus process through a convened voting panel of rheumatologists and orthopaedic surgeons. The strength of the recommendation reflects the degree of certainty that benefits outweigh harms of the intervention, or vice versa, considering the quality of available evidence and the variability in patient values and preferences.

Results: The guideline addresses the perioperative use of anti-rheumatic drug therapy including traditional disease-modifying anti-rheumatic drugs (DMARDs), biologic agents, tofacitinib, and glucocorticoids in adults who are undergoing elective THA or TKA with RA, SpA, JIA or SLE. It provides recommendations regarding when to continue, when to withhold, and when to re-start these

medications, and the optimal perioperative dosing of glucocorticoids. The guideline includes seven recommendations, all of which are conditional and based on low or moderate quality evidence.

Conclusion: This guideline should help decision-making by clinicians and patients regarding perioperative anti-rheumatic medication management at the time of elective THA or TKA. These conditional recommendations reflect the paucity of high quality direct randomized controlled trial data.

SIGNIFICANCE AND INNOVATIONS

- This guideline is the first collaboration of rheumatologists and orthopaedic surgeons to formulate recommendations for the perioperative management of anti-rheumatic therapy.
- Patients with rheumatic diseases undergoing THA and TKA are at increased risk for periprosthetic joint infection.
- Appropriate management of anti-rheumatic medication in the perioperative period may provide an important opportunity to mitigate risk.
- Non-biologic DMARDs may be continued throughout the perioperative period in patients with rheumatic diseases who are undergoing elective THA and TKA.
- Biologic medications should be withheld as close to one dosing cycle as scheduling permits prior to elective THA and TKA and restarted after evidence of wound healing, typically 14 days, for all patients with rheumatic diseases.

INTRODUCTION

Although the wide utilization of disease modifying anti-rheumatic drugs (DMARDs) and biologics have improved the quality of life for patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), juvenile inflammatory arthritis (JIA), or systemic lupus erythematosus (SLE), rates of total hip (THA) and total knee arthroplasty (TKA) remain high (1-6). Patients with rheumatic conditions report significant improvement in pain and function after THA or TKA, yet critical outcomes such as infection, dislocation, and readmission are reported to be higher for patients with RA, SpA, or SLE (7-10) compared to patients with osteoarthritis (OA). At the time of arthroplasty in a high-volume orthopaedic hospital, 46% of RA patients were on biologics, 67% were on non-biologic DMARDs, and 25% were on corticosteroids, while 75% of patients with SLE were on immunosuppressive medications and 15% were on corticosteroids.

The optimal strategy to manage these medications is not known (11-14). Inherent risk factors for infection, such as overall disability and disease activity/severity may not be modifiable, but the optimal perioperative management of immunosuppressant therapy around the time of arthroplasty may present an opportunity to mitigate risk (15-19).

In this setting, clinicians require guidance regarding perioperative management of anti-rheumatic drug therapy. . Direct evidence, however, that addresses perioperative management is sparse (20,21). To our knowledge, there are no randomized controlled trials (RCTs) evaluating the cessation and reintroduction of biologics at the time of THA or TKA. The relevant outcomes considered for these guidelines are the potential increase in infection risk added by the medications vs. the risk of disease flare when the medications are withheld.

This guideline pertains only to adult patients with RA, SpA including Ankylosing Spondylitis (AS) and psoriatic arthritis (PSA), JIA, or SLE, who are undergoing elective THA or TKA, and incorporates patient preferences.

Scope and target audience. This guideline addresses anti-rheumatic medication management in those adult patients with diagnoses of RA, SpA, JIA, or SLE, but is not limited to those who meet classification criteria. This guideline is to be used for those who have elected and have been deemed appropriate candidates for THA or TKA. We would caution against extrapolation of these guidelines to other orthopaedic procedures until further data are available.

It is intended for use by clinicians, including orthopaedists, rheumatologists, and other physicians performing perioperative risk assessment and evaluation, as well as patients. The guideline addresses common clinical situations, but may not apply in all exceptional or unusual situations. It is imperative that open and informed communication between the patient, orthopaedic surgeon and rheumatologist

takes place. In addition, while cost is a relevant factor in healthcare decisions, it was not considered in this project.

Table 1 contains the populations included in this guideline (22-24). **Table 2** contains the drugs included in our evaluation, and their dosing intervals, as the panel determined that the dosing interval and route are more relevant for this guideline as they reflect the duration of effect.

This guideline does not address indications for THA or TKA, medical decisions unrelated to anti-rheumatic drug therapy, choice of implant, surgical approach, or perioperative evaluation and management of concurrent disease, such as that affecting the rheumatoid cervical spine. Although patients with RA, SpA, JIA, or SLE should be assessed for risk of venous thromboembolism (VTE) and major acute coronary event (MACE) (8,25), this guideline does not address cardiac risk assessment or perioperative VTE prophylaxis; both are covered in existing guidelines (26-29).

METHODS

Methodology Overview

This guideline followed the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop the recommendations (30). Conflicts of interest and disclosures were managed according to ACR policy (insert link here to full participant disclosure list just before publication). Supplementary Appendix 1 presents the full methods.

Using GRADE, a recommendation can be either in favor or against the proposed intervention and either strong or conditional (32). Much of the evidence was indirect, coming from non-surgical studies, and all evidence was low to moderate quality (33,34). A strong recommendation indicates that most or almost

all informed patients would choose the recommended action. Conditional recommendations are those in which the majority of the informed patients would choose to follow the recommended course of action, but a minority might not (35,36).

Teams Involved

This project was a collaboration between the ACR and AAHKS; all participating teams included representation from both organizations. This included a Core Leadership Team for project oversight (5 members), the Literature Review Team who reviewed the literature and compiled the literature report, the Expert Panel, who helped frame the scope of the project, and the Voting Panel, who determined the final recommendations, consisting of orthopaedic surgeons, rheumatologists, an infectious disease expert, an SLE expert, patient representatives, rheumatology methodologists and a GRADE expert (see Supplementary Appendix 2 for team rosters). Additionally, a Patient Panel consisting of 11 adults with RA and JIA, all of whom had undergone THA or TKA, reviewed the evidence and provided input on their values and preferences.

PICO Question Development and Importance of Outcomes

The Core Leadership Team initially drafted the project scope, key principles and relevant clinical Patient/Intervention/Comparator/Outcomes (PICO) questions, which were then presented to the Expert Panel, the Voting Panel, and the Literature Review Team for their review at a face-to-face meeting where the project plan was defined. The relevant topics addressed included: 1. Should anti-rheumatic medications be withheld prior to elective THA/TKA?; 2. If they are withheld, when should they be stopped?; 3. If withheld, when should they be restarted after surgery?; 4. In patients using glucocorticoids, what dose should be administered at the time of surgery (see list of PICO questions in Supplementary Appendix 3). Direct high quality RCT data available comparing the risk of THA or TKA in those taking versus not taking the medications of interest, or comparing the background risk of THA and

TKA in the populations of interest, were sparse. To address this gap, two questions were included to inform the recommendations. The first asked, "What is the background risk for serious adverse events including infections, or hospitalization, associated with use of each of the candidate drugs in patients not undergoing surgery?"; the second asked, "What is the background risk for adverse events associated with THA or TKA, independent of use of candidate medications in the populations of interest?"

The group determined that both superficial and deep surgical site infection (reported within the first year after surgery) non-surgical site infection, (within 90 days of surgery) and disease flare were the most critical outcomes; other outcomes such as hospital readmission, death, and long-term arthroplasty outcome were also deemed relevant.

Systematic Synthesis of the Literature and Evidence Processing

Systematic literature searches were performed in Embase (1974+), the Cochrane Library and PubMed (mid-1960s+) from January 1, 1980, through March 6, 2016. The search strategies were developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for PubMed and Cochrane Library; and Emtree terms for Embase (Supplementary Appendix 4). Text words were used in PubMed and Embase, and keyword/title/abstract words in the Cochrane Library. Searches resulted in 2,230 total references (see Supplementary Appendix 5). A final search update was performed for the time period of January 1 to September 8, 2016, using the inclusive search terms of the disease states, coupled separately with "arthroplasty;" no randomized trials were identified that were relevant to the guideline. DistillerSR software (available at: http://systematic-review.net/) was used to screen the literature search results grouped by their match with the pertinent PICO questions.

The Literature Review Team analyzed and synthesized data from eligible studies. Due to the lack of RCTs, we were unable to prepare GRADE Summary of Findings (SoF) tables for most PICO questions. Microsoft Excel was used for abstracting data from observational studies. When available, the evidence

summaries included the benefits and harms for outcomes of interest across studies, the relative effect (95% CI), the number of participants, and the absolute effects. We rated the quality of evidence for each critical and important outcome as high, moderate, low, or very low quality, taking into account limitations of study design (including the risk of bias), inconsistency, indirectness, imprecision, and other considerations (including publication bias).

Moving from Evidence to Recommendations

The Patient Panel attached far greater importance to infection at the time of surgery than to flares. They were unable to precisely quantify the difference in value, noting that it was greater than 10:1.

The Voting Panel met to decide the final recommendations. The panel discussed the evidence in the context of both their clinical experience and the input from the patient panel. The panel voted anonymously and an 80% agreement defined the threshold for a recommendation; if 80% agreement was not achieved during an initial vote, the panel members held additional discussions before re-voting.

Considerations that led to rating down of quality of evidence included indirectness (much of the evidence came from RCTs outside of the surgical context, or from foot or spine procedures in which infection risks may vary markedly from THA or TKA); heterogeneity in baseline medication dose and duration, particularly relevant in studies addressing glucocorticoid “stress-dose” therapy; and imprecision associated with small sample size.

All recommendations were supported by over 80% of the panel, and all but one were supported unanimously. In some instances, the panel combined PICO questions into one final recommendation. For recommendations to withhold a medication, a recommendation for the suggested timing of surgery in relation to the last drug-dose was included.

RESULTS/RECOMMENDATIONS

How to Interpret the Recommendations

1. All recommendations in this guideline are conditional due to the quality of the evidence (see highlighted and bolded statements in **Table 3)**. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. No strong recommendations are made in this guideline.
2. For each recommendation, a summary of the supporting evidence or conditions is provided.
3. Therapies that were approved after the original systematic literature review are not included in these recommendations.
4. PICO questions were combined in the final recommendations for clarity.

Recommendations

1. RA, SpA including AS and PsA, JIA, and SLE, Non-biologic DMARDs: Continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine for patients undergoing elective THA or TKA, (See Table 3).

This conditional recommendation was based on low-to-moderate quality evidence. A systematic review of literature, that included RCTs of continuing vs. discontinuing DMARDs at the time of surgery, revealed that the risk of infections was in fact decreased with continuing DMARDs having a relative risk (RR) of 0.39 (95%CI 0.17-0.91)(39,40). The evidence base is rated down from high to moderate for reduction in infection risk after orthopaedic surgery when these drugs are continued, because of risk of bias. There is indirect evidence describing a low infection risk with these specific DMARDs in settings other than THA and TKA (41). This recommendation was based on infection risk, although flares are also less frequent after surgery in those who continue DMARDs, and the relative risk for flares continuing vs. stopping DMARDs [RR 0.06 (95% CI 0.0 -1.10)] was from low-quality evidence (42,43).

2. RA, SpA including AS and PsA, JIA, or SLE: Withhold all current biologics prior to surgery in patients undergoing elective THA or TKA, and plan the surgery at the end of the dosing cycle for that specific medication (See Table 3).

This recommendation was based on evidence that was rated down in quality for indirectness, as no RCTs were performed in patients undergoing THA or TKA. We abstracted data from a systematic review of literature that included systematic reviews and meta-analyses of biologics vs. placebo (and occasionally vs. control treatment including non-biologic DMARD) in non-surgical patients, that revealed the risk of serious infections was increased with biologics with most odds/hazards/risk ratios ~ 1.5 (range, 0.61 to 8.87) and a higher risk of serious adverse events with most odds/hazards/risk ratios ~ 1.5 (range, 0.33 to 2.54) (44-90). Our systematic review did not provide ample evidence that would support a differential risk for serious infection among available biologics (44-90). As avoiding infection was significantly more important to patients than flares in the post-operative period, the panel did not support separating biologics regarding infection risk in the perioperative period until further studies clarify and establish differences in risk (44-90). The literature review also revealed that the risk of postoperative infection

complications after total joint arthroplasty (TJA) was increased in patients with RA close to 2-fold and deep infection complications increased by 1.5-fold (2,59); in SLE overall post-operative complications were increased 1.3-fold, and septicemia by 2-fold (8), although medication use at the time of surgery was not always reported. In addition, a systematic review, meta-analysis and network meta-analysis revealed that infection risk for biologics is strongly associated with high-dose therapy (higher dose than the standard) and may not be associated with low-dose biologics (91), so serum half-life may not correspond to the duration of the immune-suppressant effect. The dosing cycle was therefore chosen as more relevant in determining the withholding interval (92-95) and timing the surgery at the end of the dosing interval at the nadir of the drug effect.

In regard to patients with SLE, a systematic review of literature that included systematic reviews and meta-analyses of rituximab vs. placebo (and occasionally vs. control treatment including non-biologic DMARD) in non-surgical patients with rheumatoid arthritis and SLE revealed the risk of serious infections with rituximab with a range of RR from 0.66 to 0.73 (103,104), and a risk for all serious adverse events with a range from 0.85 (95% CI 0.62–1.17) (98,105) to RR = 0.89 (95% CI 0.7-1.14). However, most data were indirect and the panel considered these medications to be similar to TNF inhibitors, similar to those used for the treatment of RA, which usually have a risk of infection. Moreover, Rituximab is not approved by the U.S. Food and Drug Administration (FDA) for treatment of SLE, and belimumab, although FDA approved for use in SLE has not been studied in manifestations of severe SLE (e.g. lupus nephritis), so the panel recommended withholding these medications prior to surgery and planning the surgery for the end of the dosing cycle, due to the risk of infection and the paucity of data supporting perioperative benefit in SLE (100-102).

Observational studies reveal that patients with severe or active SLE are at a higher risk for adverse events after surgery, but there is no approved role for these biologics for patients with severe SLE

including perioperative risk mitigation. SLE manifestations of rash and synovitis, are the common clinical indications for belimumab (102,106), and are not thought to increase perioperative risk. There is no direct evidence, however, linking perioperative infection risk to the use of these biologics, and little is known about the association of surgical risk with biologics for patients with SLE. Since the duration of the immunologic effects of these drugs differs from the serum level, the panel based the recommendation on the dosing interval (92-95). The patient panel did not include patients with SLE, and they were reluctant to vote on SLE medication management strategies as they were unclear about the value patients with SLE would place on flares, which might be organ threatening, compared to infection risk.

For example, using this guideline, patients treated with adalimumab, routinely dosed at 2-week intervals, would plan their surgery during week three, while patients treated with infliximab, when dosed every 8 weeks, would schedule their surgery in the week after the first withheld dose during week 9. Patients treated with rituximab every 6 months would schedule their surgery when possible in the week after the first withheld dose during month 7. Patients with SLE receiving belimumab, which is given every 4 weeks, would schedule their surgery during week 5.

3. RA, SpA including AS and PsA, or JIA: Withhold tofacitinib for at least 7 days prior to surgery in patients with undergoing THA or TKA (See Table 3).

This recommendation was based on indirect evidence from systematic reviews and meta-analyses of tofacitinib vs. placebo (and occasionally vs. control treatment including non-biologic DMARDs) in non-surgical patients showing that the risk of serious infections was increased with tofacitinib with incidence rate (IR) 2.91 (95% CI 2.27-3.74) (96) and higher risk of all infections with RR of 5.7 (95% CI 1.8-18.1) (97). Although this drug has an extremely short serum half-life, little is known about the duration of immunosuppression after the drug is withheld except for indirect translational data suggests that host

defense returns to normal at 7 days. Therefore, the panel recognized that the recommendation for the duration of withholding may change in the future, as physician and patient experience with this drug grows (44,50,51,54,80,82,96,99).

4. Severe SLE* (as defined in Table 1): Continue the current dose of methotrexate, mycophenolate mofetil, azathioprine , cyclosporine, or tacrolimus through surgery in all patients undergoing THA or TKA (See Table 3).

There is much uncertainty and little published experience regarding risks associated with perioperative medication management in patients with severe SLE. There is, however, indirect evidence with organ transplant patients who continue anti-rejection therapy through surgery (107,108); the caveat to this analogy is that the time course of organ rejection after withholding immunosuppressant medication may be different from the time to SLE flare after withholding medications. These considerations led to the recommendation to continue the current dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through surgery in all patients with severe SLE. Nevertheless, the panel felt that decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist.

5. Not-severe SLE (as defined in Table 1)*: Withhold the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus, one week prior to surgery in all patients undergoing THA or TKA (See Table 3).

For patients with not-severe SLE, the time course to flares after withholding medications is not known, while there is a known infection risk associated with these medications. The panel felt that careful monitoring of the patient after surgery would permit re-starting the medications prior to clinical flares in patients with not-severe SLE, for whom the morbidity of infection might outweigh the risk of a flare. These medications can be withheld one week prior to surgery, permitting some return of normal

immune function, and restarted at 3-5 days after surgery in the absence of wound healing complications or infection at the surgical site or elsewhere. There are multiple mechanisms postulated for immune suppression with these medications, including leukopenia, interference with t-cell co-stimulatory signaling, and blocking the de novo pathway of purine synthesis, with different time courses for onset and reversal (109,110).

6. RA, SpA including AS and PsA, JIA or SLE: Restart biologic therapy in patients for whom biologic therapy was withheld prior to undergoing THA or TKA once the wound shows evidence of healing (normally about 14 days), all sutures/staples are out, there is no significant swelling, erythema or drainage, and there is no clinical evidence of non-surgical site infections (See Table 3).

The decision to restart anti-rheumatic therapy can be based on evaluation of the patient's wound status and clinical judgment for absence of surgical and non-surgical site infections; wound closure is typically reached by 14 days. Therefore, biologic therapy can be re-started once the wound shows evidence of healing (normally about 14 days), all sutures/staples are out, there is no significant swelling, erythema or drainage, and there is no clinical evidence of non-surgical site infections. There is no direct evidence regarding the optimal time to restart medication after surgery, but standard precautions for biologics warn of use with an active infection or in high-risk settings, such as with an open wound.

7. RA, SpA including AS and PsA, or SLE: Continue the current daily dose of glucocorticoids in adult patients with, who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called "stress dosing") (See Table 3).

Hemodynamic instability/hypotension and infection risk were two specific areas of concern in regard to perioperative glucocorticoid dosing.

Regarding hemodynamic instability, the recommendation to continue the current daily dose of glucocorticoids in adult patients who are receiving glucocorticoids, rather than administering perioperative supra-physiologic glucocorticoid doses ("stress dosing"), specifically refers to adults with RA, AS, PsA, or SLE, who are receiving glucocorticoids (≤16 mg/day prednisone or equivalent) for their rheumatic condition; it does not refer to patients receiving glucocorticoids for JIA who may have received glucocorticoids in childhood during development, or to those patients receiving glucocorticoids for treating primary adrenal insufficiency or primary hypothalamic disease. Low-quality RCT evidence (rated down for indirectness due to varying glucocorticoid doses, heterogeneity of surgical procedures, and imprecision due to small numbers) and evidence from observational trials summarized in a systematic review suggested that there was no significant hemodynamic difference between those patients given their current daily glucocorticoid dose compared to those receiving "stress-dose steroids" (111).

Regarding the infection risk, the panel noted that the cut-off for immunosuppression per the Centers for Disease Control (CDC) was 20 mg of prednisone/day for at least 2 weeks, in the context of risk associated with the administration of live vaccines. In addition, observational studies demonstrate an increase in infection risk following TJA for users of chronic glucocorticoids above 15 mg/day. Therefore, optimizing the patient for elective THA and TKA should include, when possible, minimizing the daily glucocorticoid dose prior to surgery to under 20 mg/day prednisone or equivalent, and administering the usual daily dose rather than "stress dose" in light of the effect on infection risk (110, 111).

DISCUSSION

The 2016 ACR/AAHKS guideline for the perioperative management of anti-rheumatic drug therapy for adults undergoing elective THA and TKA was designed for use by clinicians and patients in the perioperative period. Included recommendations address the use of anti-rheumatic drug therapy

including DMARDs, tofacitinib, biologics, and glucocorticoids for the adult patient with RA, SpA, including AS and PsA, JIA ,or SLE, recognizing that anti-rheumatic medication use is frequent at the time of THA or TKA and rates of infection and adverse events, including readmission, are increased in this population. The optimal management of anti-rheumatic medications to treat these diseases may mitigate risks. We have used GRADE methodology to synthesize the best available evidence and have been transparent regarding both the strength of the recommendation and the limited quality of the evidence for each recommendation.

This project brought together major stakeholders – orthopaedic arthroplasty surgeons, rheumatologists, methodologists and patients – to create a patient-centric, expert-led group to determine optimal management of these high-risk patients through a group consensus process. To date, there has been little to no consensus among orthopaedic surgeons or rheumatologists on the optimal way to manage anti-rheumatic medications in the TJA perioperative period, which often leads to uncertainty in decision making for physicians and patients alike.

A major limitation in this guideline is the paucity of high-quality, direct evidence regarding medications and perioperative risk of infection and flare. The indirect nature of the evidence was the primary reason the quality of evidence was considered low, which led to a conditional designation for all the recommendations. Nonetheless, as patients with rheumatic diseases frequently undergo THA and TKA while on DMARDs and biologics, we sought to fulfill the need for guidance based on the best available evidence and agreement among stakeholders. The patient panel thought infection risk was much more important than flare risk, and this drove the direction of the recommendations (uniformly in favor of withholding any medications in which evidence from non-operative populations suggested increase in infection).

Topics such as cardiac risk, deep venous thrombosis risk, risk of 90-day re-admissions, and management and care of the cervical spine are related to the perioperative care of patients with rheumatic disease who are undergoing THA or TKA. The guideline was limited, however, to risks attributable to perioperative management of anti-rheumatic drug therapy.

Anti-rheumatic medications and disease states were initially evaluated individually. Due to a lack of evidence, however, on each individual medication and disease state, the medications were combined by category and diseases, with the exception of SLE.

In regard to patients with SLE, the panel recognized that recommendations for perioperative medication management for a complex disease such as SLE would be challenging, as SLE is frequently complicated by multiple organ involvement, as well as complex or unusual medication regimens. Moreover, SLE flares may be organ threatening, and SLE patients may be more averse to risk of flare then infection, so our lack of SLE patients on the patient panel was a limitation. Nonetheless, the orthopaedic and rheumatology stakeholders felt strongly that perioperative medication management guidance was needed for SLE patients.

The recommendation to restart biologics was based on the patient's wound healing (generally requiring a minimum of 14 days) and clinical judgment for the absence of both surgical site and non-surgical site infection. While there are differences in practice patterns and many patients do not return to their surgeon within 2 weeks of discharge, screening mechanisms to assess the wound include utilizing visiting nurse services, as well as taking photographs of the wound available for review by e-mail, smartphone or other mobile health technologies; this would help to identify those who should be evaluated in person prior to restarting biologics.

The Voting Panel felt it worthwhile to suggest a research roadmap for future studies that could be conducted as part of a collaboration between the two organizations. The team discussed the following topics and recommended they be targeted for future research:

1. **Perioperative glucocorticoid management**. While the RCT data supports continuing the current glucocorticoid dose rather than "stress dosing," limited numbers of patients and heterogeneity of dose, diagnosis, and surgical procedure leaves us with only low-quality evidence.

2. **Perioperative management of biologics**. The Voting Panel suggested investigation of existing biologics through registries and administrative databases, as well as planning multicenter randomized controlled trials to define the optimal medication management strategy.

3. **Perioperative management of DMARDs**: Currently, data from RCTs for patients undergoing surgery reflects older, lower, dosing regimens for methotrexate, and studies for leflunomide include small numbers of patients. Multicenter RCTs should be performed to determine the optimal perioperative management regimens and include assessment of co-morbidities and glucocorticoid use in the study design.

The recommendations that form this guideline are not treatment mandates, but can be used to provide guidance and discussion regarding medication management prior to surgery. The authors recognize that not all potential perioperative clinical scenarios are covered by this guideline, but the most common clinical scenarios are addressed. This guideline does not replace perioperative clinical assessment and optimization, and does not preclude a discussion of risks and benefits to surgery as patients and their physicians prepare for THA and TKA.

In summary, this guideline provides clinicians and patients with a working document on how to manage anti-rheumatic drugs in the time leading up to elective THA and TKA. The recommendations provide

important guidance that was informed by the available literature, clinical expertise and experience, and patient values and preferences. The acknowledgement of low quality evidence in this area should lay the foundation for future research.

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Table 1. Populations included in this guideline.
Populations Adults ≥ age 18 diagnosed with RA, SpA, including AS and PsA , JIA, or SLE*, who are deemed to be appropriate surgical candidates, undergoing elective THA or TKA, and who are treated with anti-rheumatic drug therapy at the time of surgery.†
*SLE includes patients with severe or not severe SLE, defined as follows, and who have been medically optimized for surgery: *Severe SLE:* Currently treated (induction or maintenance) for severe organ manifestations: lupus nephritis, CNS lupus, severe hemolytic anemia (Hgb<9.9), PLT<50,000, vasculitis (other than mild cutaneous vasculitis), including pulmonary hemorrhage, myocarditis, lupus pneumonitis, severe myositis (with muscle weakness, not just high enzymes), lupus enteritis (vasculitis), lupus pancreatitis, cholecystitis, lupus hepatitis, protein losing enteropathy, malabsorption, orbital inflammation/myositis, severe keratitis, posterior severe uveitis/retinal vasculitis, severe scleritis, optic neuritis, anterior ischemic optic neuropathy (derived from the SELENA-SLEDAI Flare Index and BILAG 2004) (22-24). *Not severe SLE:* Not currently treated for above manifestations. †All patients carrying the diagnoses listed, without restriction to those meeting classification criteria.

Table 2. Medications included in this guideline.*		
DMARDs: CONTINUE these medications through surgery.	**Dosing Interval**	**Continue/Withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGICS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection or systemic infection.	**Dosing Interval**	**Schedule Surgery (relative to last biologic dose administered) during**
Adalimumab (Humira)	Weekly or every 2 weeks	Week 2 or 3
Etanercept (Enbrel)	Weekly or twice weekly	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab (Cimzia)	Every 2 o 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra)	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra (Kineret)	Daily	Day 2
Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Belimumab (Benlysta)	Every 4 weeks	Week 5
Tofacitinib (Xeljanz): STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate mofetil	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue

NOT-SEVERE SLE: DISCONTINUE these medications 1 week prior to surgery	**Dosing Interval**	**Continue/Withhold**
Mycophenolate mofetil	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Withhold

Dosing intervals obtained from prescribing information provided online by pharmaceutical companies.

*2016 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Anti-rheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

Table 3. Recommendations for perioperative management of anti-rheumatic drug therapy in patients with rheumatic diseases undergoing elective THA* or TKA†.	
RECOMMENDATION/STRENGTH OF RECOMMENDATION (CONDITIONAL)	**Level of Evidence**
RA‡, SpA§ including AS¶ and PsA#, JIA, or SLE††: Continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine (non-biologic DMARDs‡‡) for patients undergoing elective THA or TKA.** • RCTs§§ of continuing vs. discontinuing DMARDs at the time of surgery revealed that the risk of infections was not increased, but in fact decreased, when DMARDs were continued, with an RR¶¶ of 0.39 (95% CI 0.17-0.91) (39,40). Evidence indicates a low infection risk with these DMARDs in settings other than THA and TKA (41). • Disease flares after surgery occur frequently, and continuing DMARDs decreases the risk [RR 0.06 (95% CI 0.0-1.10)] (42,43), yet flares were significantly less important than infection for the patient panel.	Low to Moderate
RA, SpA including AS and PsA, JIA, or SLE: Withhold all current biologics (see Table 2) prior to surgery in patients undergoing elective THA or TKA, and plan the surgery at the end of the dosing cycle for that specific medication. • RCTs (non-surgical) demonstrated an increase in infection risk associated with use of all biologics (44-90). • Avoiding infection was significantly more important to patients than flares for patients with RA and JIA. • Meta-analysis and network meta-analysis revealed that infection risk for biologics is strongly associated with high-dose therapy and may not be associated with low-dose biologics (91). • Serum half-life may not correspond to the duration of the immune-suppressant effect, so the dosing cycle was chosen as more relevant in determining the withholding interval (92-95). • Until further studies have clarified and established differences in risk between biologics, there was insufficient evidence to support separating biologics management in the perioperative period (44-90). • For SLE, there was paucity of data supporting perioperative benefit in SLE (100-102). • A systematic review of rituximab vs. placebo (and occasionally vs. control treatment including non-biologic DMARD) in non-surgical patients with RA and SLE revealed the risk of all serious adverse events with a range from 0.85 (95% CI 0.62-1.17) (98,105) to RR= 0.89 (95% CI 0.7-1.14). • Observational studies reveal that patients with SLE, particularly those with active or severe SLE, are at a higher risk for adverse events after surgery. • Belimumab is indicated for use in non-severe SLE, which is not thought to increase perioperative risk (102,106). • For example, using this guideline, patients treated with rituximab every 6 months would schedule their surgery when possible in the week after the first withheld dose during month 7. Patients receiving belimumab, which is given every 4 weeks, would schedule their surgery during week 5. • Patients treated with adalimumab, dosed at 2 week intervals, would plan their surgery during week three, while patients treated with infliximab, when dosed every 8 weeks, would schedule their surgery in the week after the first withheld dose during week 9.	Low
RA, SpA including AS and PsA, or JIA: Withhold tofacitinib for at least 7 days prior to surgery in patients with undergoing THA or TKA.	Low

• Indirect evidence from systematic reviews and meta-analyses of tofacitinib vs. placebo (and occasionally vs. control treatment including non-biologic DMARDs) in non-surgical patients shows that the risk of serious infections was increased with tofacitinib with odds/hazards/risk ratios 2.91 (95% CI 2.27-3.74) (96) and higher risk of all infections with an RR of 5.7 (95% CI 1.8-18.1) (97). • Although this drug has an extremely short serum half-life, little is known about the duration of immunosuppression after the drug is withheld. Therefore, the panel recognized that the recommendation for the duration of withholding may change in the future, as physician and patient experience with this drug grows (44,50,51,54,80,82,96,99).	
Severe SLE: Continue the current dose of mycophenolate, mofetil, azathioprine, cyclosporine, or tacrolimus through surgery in all patients with (see Table 2) undergoing THA or TKA. • The panel recognized that there is much uncertainty and little published experience regarding risks associated with perioperative medication management in patients with severe SLE. • Indirect evidence with organ transplant patients supports continuing anti-rejection therapy through surgery (107,108). • Decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist.	Low
SLE (not severe): Withhold the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus prior to surgery in all patients undergoing THA or TKA. • The time course to flares in not-severe SLE is not known. • The morbidity of prosthetic joint infection may be more severe than a flare in SLE that is not severe. • These medications can be withheld one week prior to surgery, permitting return of some immune function, and restarted at 3-5 days after surgery in the absence of wound healing complications or infection at the surgical site or elsewhere. • There are multiple mechanisms postulated for immune suppression with these medications, including leukopenia, interference with t-cell co-stimulatory signaling, and blocking the de novo pathway of purine synthesis, with different time courses for onset and reversal (109,110). • Suggest a conservative withhold of 7 days prior to surgery until additional research increases understanding of these medications.	Low
RA, SpA including AS and PsA, JIA or SLE: Restart biologic therapy in patients with for whom biologic therapy was withheld prior to undergoing THA and TKA once the wound shows evidence of healing (normally about 14 days), all sutures/staples are out, there is no significant swelling, erythema or drainage, and there is no clinical evidence of non-surgical site infections, rather than shorter or longer periods of withholding. • The decision to restart anti-rheumatic therapy should be based on careful assessment of the patient's wound status and clinical judgment for absence of surgical and non-surgical site infections. Normal wound closure typically requires 14 days.	Low
RA, SpA including AS and PsA, or SLE, Continue the current daily dose of glucocorticoids in patients who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called "stress dosing"). • This recommendation specifically refers to adults with RA, AS, PsA or SLE, who are receiving glucocorticoids for their	Low

rheumatic condition, and does not refer to patients receiving glucocorticoids for JIA who may have received glucocorticoids during development, or to those patients receiving glucocorticoids with primary adrenal insufficiency or primary hypothalamic disease. • The literature review found information on hemodynamic instability in a SLR for patients with rheumatic diseases whose mean prednisone (or equivalent) dose was ≤ 16 mg daily. • The CDC## considers the cut-off for immunosuppression at 20 mg of prednisone/day for at least 2 weeks, and observational studies demonstrate an increase in arthroplasty infection risk for chronic steroid users at 15 mg/day. • Optimization for THA and TKA should include carefully tapering the GC dose to below 20 mg/daily when possible prior to surgery (110,111).	

* Total hip arthroplasty
† Total knee arthroplasty
‡ Rheumatoid arthritis
§ Spondyloarthritis
¶ Ankylosing spondylitis
# Psoriatic arthritis
** Juvenile idiopathic arthritis
†† Systemic lupus erythematosus
‡‡ Disease-modifying anti-rheumatic drugs
§§ Randomized controlled trials
¶¶ Relative risk
Centers for Disease Control

SUPPLEMENTARY APPENDIX 1: Methods

Methodology Overview

This guideline followed the American College of Rheumatology (ACR) guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to facilitate the development of the recommendations (1).

Using the GRADE approach, the quality of evidence is rated as high, moderate, low, or very low. Randomized trials begin as high quality evidence, but may be rated down as a result of serious limitations with respect to risk of bias, imprecision, inconsistency, indirectness, or publication bias (2). Observational studies are typically rated as low or very low quality evidence, but may be rated up if the effect size is large in sufficiently large studies. (4,5)

GRADE methodology specifies that recommendations are made based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the estimated effects of an intervention), 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 in the outcomes. The Voting Panel, in keeping with the views of a patient advisory panel, estimated that typical patients place a much higher value on avoiding infection and a lower value on avoiding a disease flare.

Using GRADE, a recommendation can be either in favor or against the proposed intervention and either strong or conditional (3) and a clear distinction is made between the quality of the evidence and the strength of the recommendations. A strong recommendation indicates that all or almost all physicians would make the recommendation, and all or almost all informed patients would choose the

recommended action, and that additional research would be unlikely to change the recommendation. Conditional recommendations are those in which most informed patients would choose the recommended course of action, but a minority might not (6,7). All of the recommendations in this guideline are conditional due to the quality of the evidence, as there was little high quality evidence identified directly addressing questions about when to stop or re-start rheumatic medications, and much of the evidence used came from non-surgical studies. In addition, need for additional research was identified.

Teams Involved

This project was a collaboration between the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS); all participating teams included representation from both the organizations. A Core Leadership Team was comprised of ACR and AAHKS co-principal investigators (SG, BS) who co-led the project, the ACR and AAHKS Literature Review Team leaders (JS and AY), and a methodologist who had GRADE expertise (GG). Experts with content and methodology expertise helped define the scope of the project and drafted the Patient/Intervention/Comparator/Outcomes (PICO) questions (see list of PICO questions in Appendix 3), with participation of the Literature Review Team and the Voting Panel. The Expert Panel was comprised of 2 orthopaedists, 3 rheumatologists, 1 methodologist, 1 rheumatology methodologist, 2 infectious disease experts, 1 patient representative, and an SLE expert, with the support of the ACR staff.

The Literature Review Team was comprised of 8 orthopaedists and 6 rheumatologists, who had the support of ACR staff. The literature search was performed with the assistance of a medical research librarian.

A patient panel was convened to discuss patient values and preferences relative to outcomes and PICO findings; the results of the patient meeting were used as part of the weighing of risks and benefits by the

Voting Panel, which was comprised of 6 orthopaedists, 5 rheumatologists, an infectious disease expert, an SLE expert, 2 patient representatives, 2 rheumatology methodologists, as well as an expert in GRADE methodology, and was supported by ACR staff. The Voting Panel discussed the results of the literature review and reframed the PICO questions into recommendations after reviewing the evidence synthesis presented by the Literature Review Team leaders.

Patient Panel

A patient panel was convened the day prior to the Voting Panel meeting on July 10, 2016, consisting of 11 adults with RA and JIA, all of whom had undergone THA or TKA, with a range of 1 to 8 joints replaced per patient, with only one patient reporting a prosthetic joint infection. No patients with SLE or SPA were included in the panel. The mean age of the participants was 47 years (range of 23 to 71) and the mean duration of disease was 26 years (range of 8 to 42). Two members of the Core Leadership Team and one ACR staff person facilitated the day-long discussion. The participants, all of whom had completed research and guideline methodology webinars prior to meeting, were presented the background and scope of the guideline project determined at the first face-to-face meeting. The patients were specifically queried on the relevant importance of surgical-site or non-surgical site infection, rare post-operative events linked to continued immunosuppressant DMARD and biologic use, compared to the importance of flares of disease linked to withholding the medications, which are frequent after THA and TKA. The patient panel reviewed the evidence synthesized by the Literature Review Team as each PICO question was discussed. The participants were encouraged to consider their personal experiences relevant to the questions and judge the importance of the outcomes accordingly. The values and preferences of the patient panel and the voting results for each recommendation were presented to the Voting Panel by two core team members who facilitated the patient panel meeting during their discussions the following day.

Disclosures and Management of Conflicts of Interest

Per ACR policy, everyone who was considered for intellectual involvement in the project (i.e., considered for guideline authorship), disclosed all relationships (see XX link for full details on participant disclosures). The agreed upon next step was to compare disclosures 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 conflicts of interest for purposes of this project. However, because the focus of this guideline was to temporarily stop or restart medications that were already prescribed, in situations where surgery had already been scheduled, it was decided by the ACR and AAHKS that there were no affected companies for this guideline, and therefore, no conflict of interest for any individuals involved. Even so, in keeping with ACR policies, 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.

Intellectual conflicts, such as a prior publication or scientific presentation on perioperative management of DMARDs and biologics in patients with rheumatic diseases undergoing THA/TKA, were recognized as important and were required to be disclosed, but because they were ubiquitous, participants with intellectual conflicts were not counted as conflicted based on their intellectual conflict alone.

Participant disclosures were included in the project plan that was posted online for public comment. In addition, disclosures of all participants were shared, in writing, with each project participant. At the face-to-face Voting Panel meeting, verbal disclosures were provided before any content discussion. Updated participant disclosures, as well as ACR committee reviewer disclosures, are included online with this manuscript. In addition, author disclosures are also included in this paper.

PICO Question Development

The Core Leadership Team initially drafted the project scope, key principles and relevant clinical (PICO) questions, which were then presented to the Expert Panel, the Voting Panel, and the Literature Review Team for their review at a face-to-face meeting where the project plan was defined. The project plan, including these elements and other project details, was sent to ACR and AAHKS members via broadcast email and electronic newsletters, and was also posted on the ACR and AAHKS websites for public comment and revised accordingly. The group initially considered a wide range of outcomes, but eventually determined that infection (both deep surgical site, reported within the first year after surgery, or superficial surgical site and non-surgical site infections within 90 days of surgery) and disease flare were the most critical, although literature on other outcomes such as hospital readmission, non-surgical site or remote infection, death, and long-term arthroplasty outcome was also sought.

The outcome with the greatest weight for this guideline was deep surgical-site infection, an uncommon event on the order of 0.5 to 2.4% (8,9). The group acknowledged that there would likely not be direct high quality RCT data available comparing the risk of infection after THA or TKA in those taking versus not taking the medications of interest, or comparing the background risk of adverse events after THA and TKA in the populations of interest, due primarily to practical reasons (the inability to provide sufficient power for a study with a rare endpoint). To address this gap, two questions were included to inform the recommendations – the first sought indirect evidence of drug-related adverse effects from studies outside of the perioperative setting, and the second sought to establish the baseline risk of adverse events in patients with inflammatory arthritis undergoing THA or TKA who were not receiving the drugs of interest:

1. Indirect evidence: What is the risk for serious adverse events, infections, or hospitalizations, associated with use of each of the candidate drugs outside of the surgical setting, limiting

the search to systematic literature reviews (SLRs) and meta-analyses (MAS) for RA, SpA, and JIA, and including observational studies in SLE, as indicated?

2. What is the background risk for adverse events associated with THA or TKA in patients with RA, SpA, JIA, or SLE independent of the use of anti-rheumatic medications of interest?

Systematic Synthesis of the Literature

1. Literature Searches

Literature search strategies based on PICO questions were developed by the principal investigators, the systematic review leaders, and a research librarian, with input from the GRADE consultant. The search strategies were reviewed by another medical librarian using the Peer Review of Electronic Search Strategies (PRESS). Searches were performed in Embase (1974+), the Cochrane Library and PubMed (mid-1960s+) from January 1, 1980, through March 6, 2016.

The search strategies were developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for PubMed and Cochrane Library; and Emtree terms for Embase (Supplementary Appendix 1). Text words were used in PubMed and Embase, and keyword/title/abstract words in the Cochrane Library. Searches resulted in 2,230 total references. After title and abstract and full manuscript screening, 19 papers were included as relevant for PICO 1, 9 for PICO 2, 31 for PICO 3, 20 for PICO 4, and 69 for background questions 5 and 6 (Supplementary Appendix 2). A final search was performed for the time period of January 1 to September 8, 2016, using the inclusive search terms of the disease states (RA, SpA including AS and PsA, JIA, and SLE) coupled separately with “arthroplasty;” no randomized trials were identified that were relevant to the guideline.

2. Study Selection

DistillerSR software (available at: http://systematic-review.net/) was used to screen the literature search results grouped by their match with the pertinent PICO questions. Duplicate screening of each title and abstract was performed by two independent reviewers from among a pool (BJ, AY, MT, SS, LM, MG, SL, JG, LS, MM, PS, VD), with a third reviewer (AY or JS) resolving conflicts. The second screen was done with the full text of the papers available by two independent reviewers from the same pool. Selected manuscripts were then reviewed in their entirety.

3. Evidence Report Formulation

The Literature Review Team analyzed and synthesized data from included studies that addressed the PICO questions. An evidence summary was prepared as a PowerPoint presentation for each PICO question; due to the lack of RCTs, we were unable to prepare GRADE Summary of Findings (SoF) tables for most PICO questions as planned using GRADEprofiler (GRADEpro) software. Microsoft Excel was used for abstracting data from observational studies. When available, the evidence summaries contained the benefits and harms for outcomes of interest across studies, the relative effect (95% CI), the number of participants, and number needed to treat. We rated the quality of evidence for each critical and important outcome (i.e., high, moderate, low, or very low), taking into account limitations of study design, inconsistency, indirectness, imprecision, and other considerations. The Core Leadership Team reviewed the evidence summary and discussed possible evidence gaps prior to the presentation to the patient panel on July 10, 2016, and the Voting Panel the following day.

Moving from Evidence to Recommendations

The patient panel weighed the evidence first and analyzed it in the context of their experiences. The panel participants recognized that post-operative flares were very common and very difficult for them, and infection was rare. However, the importance they attached to infection at the time of surgery was far greater than the importance attached to flares. They were unable to precisely quantify the difference

in value, noting that it was greater than 10:1 or 20:1. They felt that flares represented a "known risk." The patients viewed endurance during the perioperative period as a "job" in which their task is to focus on the eventual positive outcomes of better mobility and less pain, while minimizing major risks as much as possible. From the perspective of the patients, there was no "average" infection – as all infections had potential to develop into significantly worse possible outcomes than flares (e.g., permanent loss of joint, amputation, death). While flares were perceived as difficult, infection could postpone recovery and/or introduce other health issues, which patients felt was unacceptable because it would delay achievement of the positive outcomes they sought.

Patients agreed that close coordination between the rheumatologist and the orthopaedist was essential, including timing surgery at the end of a patient's drug dosing cycle to minimize infection *and* flare risks. The presence of a coordinated approach was important to them and would influence their perspectives about which risks they were willing to take if they were confident that their individual needs were considered.

In regards to the recommendation for glucocorticoid dosing, patients agreed that there was little support for use of supra-physiologic "stress-dose steroids," but they wondered whether flares were prevented as an unexpected benefit related to the use of "stress-dose steroids." Finally, the patients noted that they were uncomfortable providing important input into the recommendations for management of patients with SLE, as there were no lupus patients in the group.

The next day, the Voting Panel met to decide the final guideline recommendations. PICO questions had been reformulated as drafted recommendation statements, for the panel's consideration. The panel, chaired by the co-PIs, discussed the evidence in the context of their clinical experience and expertise, as well as the input from the patient panel, which was summarized and presented during the Voting Panel meeting. The panel voted anonymously and an 80% consensus was used as the threshold for a

recommendation; if 80% consensus was not achieved during an initial vote, the panel members held additional discussions before re-voting. The Voting Panel meeting discussions were supported by the systematic review leaders, the GRADE expert, and selected members of the systematic review team, who attended the meeting to summarize the evidence and provide details, as requested.

Much of the evidence for this guideline was indirect, which lowered evidence quality ratings. Included studies were heterogeneous with regard to surgical procedures, including foot or spine procedures in which infection risks vary markedly from THA or TKA. Heterogeneity in baseline medication dose and duration was particularly relevant in studies addressing glucocorticoid "stress-dose" therapy. Most studies of drug-related infection risk are derived from RCTs and are not performed in patients undergoing surgery. Therefore, observational studies were used to determine baseline risk associated with THA or TKA in the patient populations addressed by this guideline, and additionally, imprecision led to rating the evidence down where studies reported on small numbers. The patient panelists, however, provided very clear guidance on their values and preferences, rating the importance of perioperative infection, a rare event, significantly higher than post-operative flares, which were frequent (10,11); this input helped inform the Voting Panel's final decisions even in the absence of high quality literature about risks.

All recommendations were supported by over 80% of the panel, and all but one were supported unanimously. In some instances, the panel combined PICO questions into one final recommendation. When we recommended that a medication be withheld, we included a recommendation for the suggested timing of surgery in relation to the drug-dosing interval.

Final Review and Approval of the Manuscript by the ACR and AAHKS

In addition to journal peer reviews, the manuscript was reviewed by the following committees and subcommittees of the ACR and AAHKS: ACR Guidelines Subcommittee; ACR Quality of Care Committee;

ACR Board of Directors; AAHKS Evidence Based Medicine Committee; and AAHKS Board of Directors. These ACR and AAHKS oversight groups did not make or mandate that specific recommendations be made within the guideline, but rather, served as peer reviewers.

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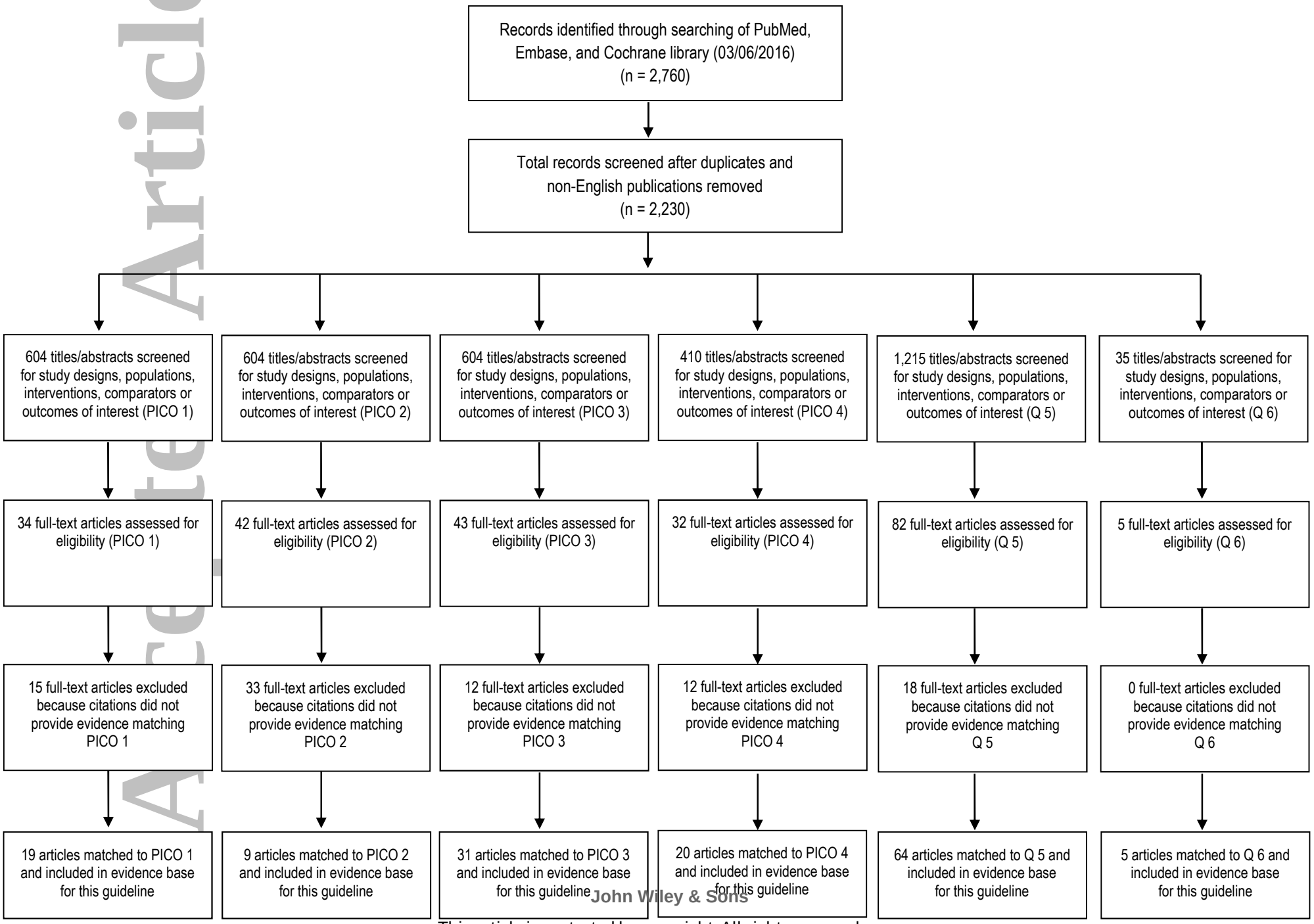
SUPPLEMENTARY APPENDIX 5: Flowchart of the study selection process*



*Full search dates (01/01-09/08/16)

SUPPLEMENTARY APPENDIX 4: ACR 2016 Perioperative Management Search Strategies

Pubmed, Embase

Perioperative Management - PubMed Search Strategy – March 6, 2016

Syntax Guide for PubMed	
[MH] = Medical Subject Heading, also known as MeSH	[TW] = Includes all words and numbers in the title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, Comment/Correction Notes, and Other Terms - typically non-MeSH subject terms (keywords)…assigned by an organization other than NLM
[SH] = a Medical Subject Heading subheading, e.g. drug therapy	[TIAB] = Includes words in the title and abstracts
[MH:NOEXP] = a command to retrieve the results of the Medical Subject Heading specified, but not narrower Medical Subject Heading terms	
Boolean Operators	
OR = retrieves results that include at least one of the search terms	AND = retrieves results that include all the search terms
NOT = excludes the retrieval of terms from the search	

Perioperative Management PubMed Search Strategy – March 6, 2016

Search	Query
#1	((((ARTHROPLASTY, REPLACEMENT, HIP[MH] OR HIP PROSTHES*[TW] OR HIP REPLACEMENT*[TIAB] OR HIP ARTHROPLAST*[TIAB] OR HIP TOTAL REPLACEMENT*[TIAB] OR FEMORAL HEAD PROSTHES*[TIAB]) OR (ARTHROPLASTY, REPLACEMENT, KNEE[MH] OR KNEE PROSTHES*[TW] OR KNEE REPLACEMENT*[TW] OR KNEE ARTHROPLAST*[TW] OR KNEE TOTAL REPLACEMENT*[TIAB]) OR (ARTHROPLAST*[TW] AND (HIP[TIAB] OR HIPS[TIAB] OR KNEE*[TIAB])) AND (("1980/01/01"[PDAT] : "2016/03/06"[PDAT]) AND ENGLISH[LANG])) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH])

Search	Query
	OR "INFANT"[MESH]) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) AND ("ADULT"[MESH])))) NOT ((("COMMENT"[PUBLICATION TYPE]) OR "EDITORIAL"[PUBLICATION TYPE]) OR "LETTER"[PUBLICATION TYPE])) NOT (("ANIMALS"[MESH]) NOT (("ANIMALS"[MESH]) AND ("HUMANS"[MESH]))))
#2	(("LUPUS ERYTHEMATOSUS, SYSTEMIC"[MESH] OR LUPUS ERYTHEMATOSUS DISSEMINATUS[TIAB] OR LIBMAN-SACKS DISEASE[TIAB] OR LIBMAN SACKS DISEASE[TIAB]) OR (SLE[TIAB]) OR (LUPUS[TIAB])) OR ((INFLAMMATORY ARTHRITIS*[TIAB]) OR (("ARTHRITIS, RHEUMATOID"[MESH:NOEXP] OR RHEUMATOID ARTHRITIS*[TIAB]) OR ("RHEUMATOID NODULE"[MESH] OR RHEUMATOID NODULE*[TIAB]) OR ("STILL'S DISEASE, ADULT-ONSET"[MESH]) OR ((STILL DISEASE[TIAB] OR STILL'S DISEASE[TIAB]) AND (ADULT ONSET[TIAB] OR ADULT-ONSET[TIAB])))) OR (("SPONDYLARTHRITIS"[MESH:NOEXP]) OR (SPONDYLARTHRITIS*[TIAB]) OR (SPONDYLOARTHRITIS*[TIAB]) OR ("SPONDYLARTHROPATHIES"[MESH] OR SPONDYLARTHROPATH*[TIAB]) OR (MARIE-STRUMPELL SPONDYLITIS[TIAB] OR MARIE STRUMPELL SPONDYLITIS[TIAB] OR BECHTEREW SYNDROME*[TIAB]) OR (ARTHRITIC PSORIASIS[TIAB] OR PSORIATIC ARTHRITIS[TIAB] OR PSORIASIS ARTHROPATHICA[TIAB] OR PSORIATIC ARTHROPATH*[TIAB]) OR (SPONDYLOARTHRITIS ANKYLOPOIETICA[TIAB] OR ANKYLOSING SPONDYLARTHRIT*[TIAB] OR ANKYLOSING SPONDYLITIS OR SPONDYLARTHRITIS ANKYLOPOIETICA[TIAB] OR BECHTEREW DISEASE[TIAB] OR BECHTEREW'S DISEASE[TIAB] OR BECHTEREWS DISEASE[TIAB] OR RHEUMATOID SPONDYLITIS[TIAB] OR SPONDYLITIS

Search	Query
	ANKYLOPOIETICA[TIAB]) OR (REACTIVE ARTHRITI*[TIAB] OR POST-INFECTIOUS ARTHRI*[TIAB] OR POST INFECTIOUS ARTHRI*[TIAB] OR REITER SYNDROME*[TIAB] OR REITER'S DISEASE*[TIAB] OR REITERS DISEASE[TIAB] OR REITER DISEASE[TIAB] OR POSTINFECTIOUS ARTHRI*[TIAB])) OR ((JUVENILE ARTHRITIS[TW] OR JUVENILE ENTHESITIS-RELATED ARTHRITIS[TW] OR JUVENILE CHRONIC ARTHRITIS[TW] OR JUVENILE IDIOPATHIC ARTHRITIS[TW] OR JUVENILE OLIGOARTHRITIS[TW] OR JUVENILE PSORIATIC ARTHRITIS[TW] OR JUVENILE SYSTEMIC ARTHRITIS[TW] OR JUVENILE-ONSET STILL DISEASE[TW] OR JUVENILE ONSET STILL DISEASE[TW] OR JUVENILE-ONSET STILL'S DISEASE[TW] OR JUVENILE-ONSET STILLS DISEASE[TW] OR JUVENILE ONSET STILLS DISEASE[TW] OR JUVENILE INFLAMMATORY ARTHRITIS[TW]) OR (INFLAMMATORY AUTOIMMUNE ARTHRITI*[TW]))
#3	("BIOLOGICAL THERAPY"[MESH] OR BIOLOGICAL THERAP*[TIAB] OR BIOLOGIC THERAP*[TIAB] OR BIOTHERAP*[TIAB]) OR (((CHLOROCHIN[TIAB] OR KHINGAMIN[TIAB] OR CHINGAMIN[TIAB] OR NIVAQUINE[TIAB] OR ARALEN[TIAB] OR ARECHINE[TIAB]) OR ((ACEDAPSONE[TIAB] OR AMARIIN[TIAB] OR AMODIAQUINE[TIAB] OR ARTEFLENE[TIAB] OR ARTEMETHER*[TIAB] OR ARTEMISININS[TIAB] OR ARTEMOTIL[TIAB] OR ARTESUNATE[TIAB] OR ATOVAQUONE[TIAB] OR BETULINIC ACID[TIAB] OR BREDININ[TIAB] OR BRL 6231[TIAB] AND CHLORPROGUANIL[TIAB] OR CINCHONINE[TIAB] OR CRYPTOLEPINE[TIAB] OR CURDLAN SULFATE[TIAB] OR CYCLOGUANIL[TIAB] OR DAPSONE[TIAB] OR DERMASEPTIN[TIAB] OR DIHYDROARTEMISININ[TIAB] OR E 64[TIAB] OR HALOFANTRINE[TIAB] OR LAPACHOL[TIAB] OR LUMEFANTRINE[TIAB] OR MALOPRIM[TIAB] OR MEFLOQUINE*[TIAB]

Search	Query
	OR MIRINCAMYCIN[TIAB] OR MONORDEN[TIAB] OR PARVAQUONE[TIAB] OR PEPSTATIN[TIAB] OR PIPERAQUINE[TIAB] OR PRIMAQUINE[TIAB] OR PROGUANIL[TIAB] OR PYRIMETHAMINE[TIAB] OR PYRONARIDINE[TIAB] OR QUINIDINE[TIAB] OR QUININE[TIAB] OR RV 538[TIAB] OR SILICON PHTHALOCYANINE[TIAB] OR SINEFUNGIN[TIAB] OR SPIROGERMANIUM[TIAB] OR SULFADOXINE[TIAB] OR SULFALENE[TIAB] OR TAFENOQUINE[TIAB] OR TETRANDRINE[TIAB] OR TRIMETHOPRIM[TIAB]) OR ((("BARICITINIB"[SUPPLEMENTARY CONCEPT] OR BARICITINIB[TIAB] OR LY3009104[TIAB] OR INCB028050[TIAB]) OR ("TOFACITINIB"[SUPPLEMENTARY CONCEPT] OR TASOCITINIB[TIAB] OR XELJANZ[TIAB] OR CP 690,550[TIAB] OR CP690550[TIAB] OR CP-690550[TIAB] OR CP 690550[TIAB] OR CP-690,550[TIAB]) OR (TOFACITINIB*[TW]) OR (((SULFASALAZINE) OR ("SULFASALAZINE"[MESH] OR SULFASALAZINE*[TW] OR SULPHASALAZINE*[TW] OR SALICYLAZOSULFAPYRIDINE[TIAB] OR SALAZOSULFAPYRIDINE[TIAB] OR COLO-PLEON[TIAB] OR COLO PLEON[TIAB] OR PLEON[TIAB] OR UCINE[TIAB] OR AZULFIDINE[TIAB] OR SALAZOPYRIN[TIAB] OR PYRALIN EN[TIAB]) OR ("ANTIRHEUMATIC AGENTS"[PHARMACOLOGICAL ACTION]) OR ("ANTIRHEUMATIC AGENTS"[MESH] OR ANTIRHEUMATIC*[TIAB] OR ANTI-RHEUMATIC[TIAB] OR ANTI RHEUMATIC[TIAB] OR DMARD*[TIAB]) OR ("LEFLUNOMIDE"[SUPPLEMENTARY CONCEPT] OR LEFLUNOMIDE*[TIAB] OR ARAVA[TIAB] OR HWA 486[TIAB] OR HWA-486[TIAB] OR SU101[TIAB])) OR (("MYCOPHENOLIC ACID"[MESH] OR MYCOPHENOLIC ACID*[TW]) OR ("MYCOPHENOLATE MOFETIL"[SUPPLEMENTARY CONCEPT] OR MYCOPHENOLATE MOFETIL[TW] OR RS

Search	Query
	61443[TW] OR RS-61443[TW] OR MYCOPHENOLATE SODIUM[TW] OR SODIUM MYCOPHENOLATE[TW] OR MYFORTIC[TW] OR CELLCEPT[TW]) OR (MMF[TIAB]) OR ("AZATHIOPRINE"[MESH] OR AZATHIOPRINE[TIAB] OR AZOTHIOPRINE[TIAB] OR IMUREL[TIAB] OR IMURAN[TIAB] OR IMMURAN[TIAB]) OR ("BREDININ"[SUPPLEMENTARY CONCEPT] OR MIZORIBINE*[TIAB]) OR ("CYCLOSPORINE"[MESH] OR CYCLOSPORINS[MH] OR CYCLOSPORINE*[TIAB] OR CYCLOSPORIN*[TW] OR NEORAL[TIAB] OR CYA-NOF[TIAB] OR CYA NOF[TIAB] OR SANDIMMUNE[TIAB] OR SANDIMMUN[TIAB] OR CSA-NEORAL[TIAB] OR CSA NEORAL[TIAB] OR OL 27-400[TIAB] OR OL 27 400[TIAB] OR OL 27400[TIAB]) OR ("TACROLIMUS"[MESH] OR PROGRAF[TIAB] OR PROGRAFT[TIAB] OR TACROLIMUS[TIAB] OR FR-900506[TIAB] OR FR 900506[TIAB] OR FR900506[TIAB] OR FK-506[TIAB] OR FK 506[TIAB] OR FK506[TIAB]) OR (CYCLOPHOSPHAMIDE*[TIAB] OR CYCLOPHOSPHANE[TIAB] OR ENDOXAN[TIAB] OR NEOSAR[TIAB] OR NSC-26271[TIAB] OR NSC 26271[TIAB] OR NSC26271[TIAB] OR PROCYTOX[TIAB] OR SENDOXAN[TIAB] OR B-518[TIAB] OR B 518[TIAB] OR B518[TIAB] OR CYTOXAN[TIAB]) OR ("CYCLOPHOSPHAMIDE"[MESH]) OR ("METHOTREXATE"[MESH] OR AMETHOPTERIN[TIAB] OR METHOTREXATE[TIAB] OR MEXATE[TIAB]) OR ("RITUXIMAB"[MESH] OR RITUXIMAB[TIAB] OR RITUXIMAB[TW] OR MABTHERA[TIAB] OR IDEC-C2B8[TIAB] OR IDEC C2B8[TIAB] OR GP2013[TIAB] OR RITUXAN[TIAB]) OR ("BELIMUMAB"[SUPPLEMENTARY CONCEPT] OR BELIMUMAB[TIAB]) OR ("HYDROXYCHLOROQUINE"[MESH] OR HYDROXYCHLOROQUINE*[TIAB] OR OXYCHLOROQUINE[TIAB] OR PLAQUENIL[TIAB]) OR

Search	Query
	("ANTIMALARIALS"[PHARMACOLOGICAL ACTION]) OR ("QUINACRINE"[MESH] OR QUINACRINE[TIAB]) OR ("CHLOROQUINE"[MESH] OR CHLOROQUINE[TIAB])) OR ("DOXYCYCLINE"[MESH] OR DOXYCYCLINE*[TIAB] OR ALPHA-6-DEOXYOXYTETRACYCLINE*[TIAB] OR ALPHA 6 DEOXYOXYTETRACYCLINE*[TIAB] OR VIBRAVENOS*[TIAB] OR BU 3839T[TIAB] OR DORYX[TIAB] OR HYDRAMYCIN*[TIAB] OR ORACEA[TIAB] OR PERIOSTAT[TIAB] OR VIBRA-TABS[TIAB] OR VIBRA TABS[TIAB] OR VIBRAMYCIN[TIAB] OR ATRIDOX[TIAB] OR BMY 28689[TIAB])) OR ("APREMILAST"[SUPPLEMENTARY CONCEPT] OR APREMILAST[TIAB] OR OTEZLA[TIAB] OR CC 10004[TIAB] OR CC-10004[TIAB]) OR (ANTI-TNF BIOLOGIC[TI]) OR (ANTI-TNF*[TW] OR ANTI TNF*[TW] OR ANTI TUMOR NECROSIS FACTOR*[TW] OR ANTI-TUMOR NECROSIS FACTOR*[TW] OR ANTI-TUMOUR NECROSIS FACTOR*[TIAB] OR ANTI TUMOUR NECROSIS FACTOR*[TIAB] OR TNF INHIBITOR*[TIAB] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TIAB] OR TUMOR NECROSIS FACTOR INHIBITOR*[TIAB]) OR ("TUMOR NECROSIS FACTOR-ALPHA/ANTAGONISTS AND INHIBITORS"[MESH]) OR (TUMOR NECROSIS FACTOR ANTAGONIST*[TIAB] OR TUMOUR NECROSIS FACTOR ANTAGONIST*[TIAB]) OR (TUMOR NECROSIS FACTOR-ALPHA ANTAGONIST*[TIAB] OR TUMOUR NECROSIS FACTOR-ALPHA ANTAGONIST*[TIAB]) OR ("ADALIMUMAB"[MESH] OR ADALIMUMAB[TIAB] OR D2E7 ANTIBOD*[TIAB] OR HUMIRA[TIAB]) OR ("ETANERCEPT"[MESH] OR ETANERCEPT[TIAB] OR ENBREL[TIAB] OR TNF RECEPTOR TYPE II-IGG FUSION PROTEIN*[TIAB] OR TNF RECEPTOR TYPE II IGG FUSION PROTEIN*[TIAB] OR TNFR-FC FUSION PROTEIN*[TIAB] OR TNFR FC FUSION PROTEIN*[TIAB] OR TNR-001[TIAB] OR TNR

Search	Query
	001[TIAB] OR TNF RECEPTOR FUSION PROTEIN*[TIAB]) OR ("GOLIMUMAB"[SUPPLEMENTARY CONCEPT] OR GOLIMUMAB[TIAB] OR SIMPONI[TIAB]) OR ("CERTOLIZUMAB PEGOL"[MESH] OR CERTOLIZUMAB PEGOL*[TIAB] OR CIMZIA*[TIAB] OR CDP870[TIAB] OR CDP 870[TIAB]) OR ("INFLIXIMAB"[MESH] OR INFLIXIMAB[TIAB] OR MAB CA2[TIAB] OR MONOCLONAL ANTIBODY CA2[TIAB] OR REMICADE[TIAB]) OR ("ABATACEPT"[MESH] OR ABATACEPT[TIAB] OR BELATACEPT[TIAB] OR BMS-224818[TIAB] OR BMS 224818[TIAB] OR LEA29Y[TIAB] OR NULOJIX[TIAB] OR ORENCIA[TIAB] OR BMX 188667[TIAB] OR CTLA-4-LG[TIAB] OR CTLA4-IG[TIAB] OR CTLA4-FC[TIAB] OR CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN*[TIAB] OR CYTOTOXIC T LYMPHOCYTE ASSOCIATED ANTIGEN 4 IMMUNOGLOBULIN*[TIAB]) OR ("TOCILIZUMAB"[SUPPLEMENTARY CONCEPT] OR TOCILIZUMAB[TIAB] OR ATLIZUMAB[TIAB] OR ACTEMRA[TIAB]) OR ("INTERLEUKIN 1 RECEPTOR ANTAGONIST PROTEIN"[MESH] OR URINE-DERIVED IL1 INHIBITOR*[TIAB] OR URINE DERIVED IL1 INHIBITOR[TIAB] OR IL1 FEBRILE INHIBITOR*[TIAB] OR URINE IL-1 INHIBITOR*[TIAB] OR IL-1RA[TIAB] OR ANTRIL[TIAB] OR ANAKINRA[TIAB] OR KINERET[TIAB]) OR ("SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR SECUKINUMAB[TIAB] OR COSENTYX[TIAB] OR AIN 457[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB]) OR ("GLUCOCORTICOIDS"[MESH] OR GLUCOCORTICOID*[TIAB]) OR ("GLUCOCORTICOIDS"[PHARMACOLOGICAL ACTION]) OR (ALCLOMETASONE DIPROPIONATE[TIAB] OR AMCINONIDE[TIAB] OR BECLOMETHASONE[TIAB] OR BETAMETHASONE[TIAB] OR BUDESONIDE[TIAB] OR CICLESONIDE[TIAB] OR CLOBETASOL[TIAB] OR CLOBETASONE

Search	Query
	BUTYRATE*[TIAB] OR CLOCORTOLONE[TIAB] OR DESOXIMETASONE[TIAB] OR DEXAMETHASONE[TIAB] OR DICHLORISONE ACETATE[TIAB] OR DIFLORASONE[TIAB] OR DIFLUCORTOLONE[TIAB] OR DIFLUPREDNATE[TIAB] OR DROCINONIDE PHOSPHATE POTASSIUM[TIAB] OR FLUMETHASONE[TIAB] OR FLUOCINOLONE ACETONIDE*[TIAB] OR FLUOCINONIDE*[TIAB] OR FLUOCORTIN BUTYL ESTER[TIAB] OR FLUOCORTOLONE[TIAB] OR FLUOROMETHOLONE[TIAB] OR FLUPEROLONE ACETATE*[TIAB] OR FLUPREDNIDENE ACETATE*[TIAB] AND FLUPREDNISOLONE[TIAB] OR FLURANDRENOLONE[TIAB] OR FLUTICASONE[TIAB] OR MEDRYSONE[TIAB] OR MELENGESTROL ACETATE*[TIAB] OR METHYLPREDNISOLONE[TIAB] OR PARAMETHASONE[TIAB] OR PREDNICARBATE[TIAB] OR PREDNISOLONE[TIAB] OR PREDNISONE[TIAB] OR RIMEXOLONE[TIAB] OR TRIAMCINOLONE[TIAB]))))) OR ("USTEKINUMAB"[MESH] OR USTEKINUMAB*[TIAB] OR STELARA[TIAB] OR CNTO 1275[TIAB] OR CNTO1275[TIAB]))
#4	#1 AND #2 AND #3

Perioperative Management - Embase Search Strategy – March 6, 2016

Syntax Guide for Embase	
/ = at the end of a word or phrase means that it is searched as a subject heading	EXP = a command to retrieve all narrower emtree terms
* truncation symbol	ADJ = adjacency; terms are adjacent to each other, in either direction ; adj2 = terms are within 2 words of each other, in either direction
.TI,AB,DE= word or phrase is searched for in the title, abstract, and descriptor (index term)	LIM = command to limit results to age groups, years, language, publication types, etc.
Boolean Operators	
OR = retrieves results that include at least	AND = retrieves results that include all the

one of the search terms	search terms
NOT = excludes the retrieval of terms from the search	

Database: Embase
Search Strategy:

#1 'KNEE ARTHROPLASTY'/EXP OR 'HIP ARTHROPLASTY'/EXP

#2 'HIP REPLACEMENT':AB,TI OR 'HIP ARTHROPLASTY':AB,TI OR 'HIP PROSTHESIS':AB,TI OR 'HIP PROSTHESES':AB,TI OR 'FEMORAL HEAD PROSTHESIS':AB,TI OR 'FEMORAL HEAD PROSTHESES':AB,TI OR 'HIP TOTAL REPLACEMENT':AB,TI

#3 'KNEE REPLACEMENT':AB,TI OR 'KNEE ARTHROPLASTY':AB,TI OR 'KNEE TOTAL REPLACEMENT':AB,TI OR 'KNEE PROSTHESIS':AB,TI OR 'KNEE PROSTHESES':AB,TI

#4 KNEE*:DE,AB,TI OR HIP:DE,AB,TI OR HIPS:DE,AB,TI AND (ARTHROPLAST*:DE,AB,TI OR REPLACEMENT*:DE,AB,TI OR PROSTHES*:DE,AB,TI)

#5 #1 OR #2 OR #3 OR #4

#6 #5 AND [EMBASE]/LIM NOT [MEDLINE]/LIM AND (1980:PY OR 1981:PY OR 1982:PY OR 1983:PY OR 1984:PY OR 1985:PY OR 1986:PY OR 1987:PY OR 1988:PY OR 1989:PY OR 1990:PY OR 1991:PY OR 1992:PY OR 1993:PY OR 1994:PY OR 1995:PY OR 1996:PY OR 1997:PY OR 1998:PY OR 1999:PY OR 2000:PY OR 2001:PY OR 2002:PY OR 2003:PY OR 2004:PY OR 2005:PY OR 2006:PY OR 2007:PY OR 2008:PY OR 2009:PY OR 2010:PY OR 2011:PY OR 2012:PY OR 2013:PY OR 2014:PY OR 2015:PY OR 2016:PY) AND [ENGLISH]/LIM

#7 'JUVENILE'/EXP

#8 'ADULT'/EXP

#9 #7 NOT (#7 AND #8)

#10 #6 NOT #9

#11 'ANIMAL'/EXP NOT ('ANIMAL'/EXP AND 'HUMAN'/EXP)

#12 #10 NOT #11

#13 'CASE REPORT'/EXP

#14 'EDITORIAL'/EXP OR 'LETTER'/EXP OR 'ABSTRACT REPORT'/EXP

#15 #13 OR #14

#16 #12 NOT #15

#17 'GLUCOCORTICOID'/EXP OR GLUCOCORTICOID*:AB,TI

#18 'MYCOPHENOLIC ACID'/EXP OR 'MMF':AB,TI OR MYFORTIC:AB,TI OR MYCOPHENOLATE*:AB,TI OR MELBEX:AB,TI

#19 'ANTIRHEUMATIC AGENT'/EXP OR ANTIRHEUMATIC*:AB,TI OR 'ANTI RHEUMATIC':AB,TI OR 'ANTI RHEUMATICS':AB,TI OR 'ANTI-RHEUMATIC':AB,TI OR 'ANTI-RHEUMATICS':AB,TI

#20 'AZATHIOPRINE'/EXP OR AZATHIOPRINE*:AB,TI OR MERCAPTOPURINE:AB,TI OR ARATHIOPRIN*:AB,TI OR AZAFALK:AB,TI OR AZAHEXAL:AB,TI OR AZAMEDAC:AB,TI OR AZAMUN*:AB,TI OR AZANIN:AB,TI OR AZAPIN:AB,TI OR AZAPRESS:AB,TI OR AZAPRINE:AB,TI OR AZAREX:AB,TI OR AZASAN:AB,TI OR AZATHIODURA:AB,TI OR AZATHIOPINE:AB,TI OR AZATHIOPRIM:AB,TI OR AZATHIOPRIN:AB,TI OR AZATHIOPURINE:AB,TI OR AZATHROPSIN:AB,TI OR AZATIOPRIN:AB,TI OR AZATOX:AB,TI OR AZATRILEM:AB,TI OR AZOPI:AB,TI OR AZORAN:AB,TI OR AZOTHIOPRIN:AB,TI OR AZOTHIOPRINE:AB,TI OR COLINSAN:AB,TI OR IMMURAN:AB,TI OR IMMUREL:AB,TI OR IMMUTHERA:AB,TI OR IMUNEN:AB,TI OR IMUPRIN:AB,TI OR IMURAN:AB,TI OR IMURANE:AB,TI OR IMUREK:AB,TI OR IMUREL:AB,TI OR IMUREN:AB,TI OR THIOAZEPRINE:AB,TI OR THIOPRINE:AB,TI OR TRANSIMUNE:AB,TI OR ZYTRIM:AB,TI

#21 'MIZORIBINE'/EXP OR MIZORIBINE:AB,TI OR BREDININ:AB,TI

#22 'CYCLOSPORIN'/EXP OR CYCLOSPORIN*:AB,TI OR DEXIMUNE:AB,TI OR IMPLANTA:AB,TI OR IMUSPORIN:AB,TI

#23 'TACROLIMUS'/EXP OR TACROLIMUS:AB,TI OR PROGRAF:AB,TI

#24 'CYCLOPHOSPHAMIDE'/EXP OR CYCLOPHOSPHAMIDE*:AB,TI

#25 'METHOTREXATE'/EXP OR METHOTREXATE*:AB,TI OR RHEUMATREX:AB,TI

#26 'RITUXIMAB'/EXP OR RITUXAN:AB,TI OR RITUXIMAB:AB,TI

#27 'BELIMUMAB'/EXP OR BENLYSTA:AB,TI OR 'LYMPHOSTAT B':AB,TI

#28 'HYDROXYCHLOROQUINE'/EXP OR PLAQUENIL:AB,TI OR HYDROXYCHLOROQUINE*:AB,TI

#29 'ANTIMALARIAL AGENT'/EXP OR ANTIMALARIAL*:AB,TI OR 'ANTI MALARIAL':AB,TI OR 'ANTI-MALARIAL':AB,TI OR 'ANTI MALARIALS':AB,TI OR 'ANTI-MALARIALS':AB,TI

#30 'MEPACRINE':AB,TI OR QUINACRINE:AB,TI OR CHROLOQUINE*:AB,TI

#31 'LEFLUNOMIDE'/EXP OR ARAVA:AB,TI OR LEFLUNOMIDE:AB,TI

#32 'DISEASE MODIFYING ANTIRHEUMATIC DRUG'/EXP OR DMARD:AB,TI OR DMARDS:AB,TI

#33 'SALAZOSULFAPYRIDINE'/EXP OR AZULFIDINE:AB,TI OR SALAZOSULFAPYRIDINE*:AB,TI OR SULFASALAZINE*:AB,TI OR SSZ:AB,TI OR SALICYLAZOSULFAPYRIDIN:AB,TI

#34 'DOXYCYCLINE'/EXP OR DORYX:AB,TI OR DOXYCYCLINE*:AB,TI OR MONODOX:AB,TI OR VIBRAMYCIN:AB,TI OR 'VIBRA-TABS':AB,TI

#35 'TOFACITINIB'/EXP OR TOFACITINIB:AB,TI OR TASOCITINIB*:AB,TI OR XELJANZ:AB,TI

#36 'BARICITINIB'/EXP OR BARICITINIB:AB,TI

#37 'APREMILAST'/EXP OR ACETAMIDE:AB,TI OR OTEZLA:AB,TI OR APREMILAST:AB,TI

#38 'ADALIMUMAB'/EXP OR HUMIRA:AB,TI OR TRUDEXA:AB,TI OR ADALIMUMAB:AB,TI

#39 'ETANERCEPT'/EXP OR ENBREL:AB,TI OR ETANERCEPT:AB,TI OR EMBREL:AB,TI

#40 'GOLIMUMAB'/EXP OR SIMPONI:AB,TI OR GOLIMUMAB:AB,TI

#41 'CERTOLIZUMAB PEGOL'/EXP OR CIMZIA:AB,TI OR 'CERTOLIZUMAB PEGOL':AB,TI

#42 'INFLIXIMAB'/EXP OR REMICADE:AB,TI OR INFLIXIMAB:AB,TI

#43 'TUMOR NECROSIS FACTOR INHIBITOR'/EXP OR 'ANTI TNF':AB,TI OR 'ANTI TUMOR NECROSIS FACTOR':AB,TI OR 'ANTI TUMOUR NECROSIS FACTOR':AB,TI OR 'TNF INHIBITOR':AB,TI OR 'TNF INHIBITORS':AB,TI OR 'TUMOUR NECROSIS FACTOR INHIBITOR':AB,TI OR 'TUMOUR NECROSIS FACTOR INHIBITORS':AB,TI OR 'TNF ANTAGONIST':AB,TI OR 'TNF ANTAGONISTS':AB,TI OR 'TUMOR NECROSIS FACTOR ANTAGONIST':AB,TI OR 'TUMOUR NECROSIS FACTOR ANTAGONIST':AB,TI

#44 'ABATACEPT'/EXP OR ORENCIA:AB,TI OR ABATACEPT:AB,TI

#45 'TOCILIZUMAB'/EXP OR ACTEMRA:AB,TI OR ATLIZUMAB:AB,TI OR ROACTEMRA:AB,TI OR TOCILIZUMAB:AB,TI

#46 'RECOMBINANT INTERLEUKIN 1 RECEPTOR BLOCKING AGENT'/EXP OR ANAKINRA:AB,TI OR KINERET:AB,TI

#47 'SECUKINUMAB'/EXP OR COSENTYX:AB,TI OR SECUKINUMAB:AB,TI

#48 'USTEKINUMAB'/EXP OR STELARA:AB,TI OR USTEKINUMAB:AB,TI

#49 'BIOLOGICAL THERAPY'/EXP

#50 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49

#51 'SYSTEMIC LUPUS ERYTHEMATOSUS'/DE OR 'SLE':AB,TI OR 'LUPUS':AB,TI OR 'LIBMAN-SACKS DISEASE':AB,TI OR 'LIBMAN SACKS DISEASE':AB,TI

#52 'ANKYLOSING SPONDYLITIS'/EXP OR 'ANKYLOSING SPONDYLITIS':AB,TI

#53 'SPONDYLARTHRITIS'/EXP OR SPONDYLARTHRIT*:AB,TI

#54 SPONDYLOARTHRIT*:AB,TI

#55 SPONDYLARTHROPATH*:DE,AB,TI

#56 'SPONDYLOARTHROPATHY'/EXP

#57 'MARIE STRUMPELL SPONDYLITIS':AB,TI

#58 BECHTEREW*:AB,TI

#59 'PSORIATIC ARTHRITIS'/EXP OR 'ARTHRITIC PSORIASIS':AB,TI OR 'PSORIATIC ARTHRITIS':AB,TI OR 'PSORIASIS ARTHROPATHICA':AB,TI OR 'PSORIATIC ARTHROPATHY':AB,TI OR 'PSORIATIC ARTHROPATHIES':AB,TI

#60 SPONDYLOARTHRITIS ANKYLOPOIETICA':AB,TI OR 'ANKYLOSING SPONDYLARTHRITIS':AB,TI OR 'SPONDYLARTHRITIS ANKYLOPOIETICA':AB,TI OR 'RHEUMATOID SPONDYLITIS':AB,TI OR 'SPONDYLITIS ANKYLOPOIETICA':AB,TI

#61 'REACTIVE ARTHRITIS'/EXP OR 'REACTIVE ARTHRITIS':AB,TI OR 'POST-INFECTIOUS ARTHRITIS':AB,TI OR 'POSTINFECTIOUS ARTHRITIS':AB,TI

#62 'REITER SYNDROME'/EXP OR REITER:DE,AB,TI

#63 'RHEUMATOID ARTHRITIS'/EXP OR 'RHEUMATOID ARTHRITIS':AB,TI OR 'INFLAMMATORY ARTHRITIS':AB,TI

#64 'RHEUMATOID NODULE':AB,TI OR 'RHEUMATOID NODULES':AB,TI

#65 'ADULT ONSET STILL DISEASE':AB,TI

#66 'STILLS DISEASE':AB,TI OR 'STILL DISEASE':AB,TI

#67 #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66

#68 ‘JUVENILE RHEUMATOID ARTHRITIS'/EXP OR 'JUVENILE ARTHRITIS':AB,TI

#69 #68 OR #67

#70 #69 AND #50 AND #16

SUPPLEMENTARY APPENDIX 3: Population, Intervention, Comparator, Outcome (PICO) Questions

PICO 1

In patients with RA, AS, PsA, JIA, severe or not severe SLE undergoing THA or TKA and who are receiving one or more of the candidate drugs, what is the effect of stopping the drug prior to surgery versus continuing?

PICO 2

In patients with RA, AS, PsA, JIA, severe or not severe SLE undergoing THA or TKA who are receiving one or more of the candidate drugs in whom one has decided to stop the drug, what is the effect of stopping the drug early prior to surgery versus stopping late?

PICO 3

In patients with RA, AS, PsA, JIA, severe or not severe SLE undergoing THA or TKA who are receiving one or more of the candidate drugs in whom one has decided to stop the drug, what is the effect of restarting the drug early after surgery versus restarting late?

PICO 4

In patients with RA, AS, PsA, JIA, severe or not severe SLE undergoing THA or TKA who are receiving chronic glucocorticoids, what is the effect of administering supra-physiologic doses of glucocorticoids perioperatively (stress-dose corticosteroids) vs. continuing the usual glucocorticoid dose?

QUESTION 5: Indirect evidence of drug-related adverse effects from non-surgical studies

What is the risk for serious adverse events, infections, or hospitalizations, associated with use of each of the candidate drugs outside of the surgical setting, limiting the search to systematic literature reviews and meta-analyses for RA, SpA, and JIA, and including observational studies in SLE, as indicated?

QUESTION 6: Baseline risk of adverse events in patients with inflammatory arthritis undergoing THA or TKA who were not receiving the drugs of interest

What is the background risk for adverse events associated with THA or TKA in patients with RA, SpA, JIA, or SLE independent of the use of anti-rheumatic medications of interest?

SUPPLEMENTARY APPENDIX 2: Teams Involved

Core Leadership Team

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Voting Panel

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