American College of Rheumatology (ACR)
Vasculitis Guideline

Project Plan – Updated August 2019

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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This project of the American College of Rheumatology (ACR) has the broad objective of developing an evidence-based clinical practice guideline related to the treatment and management of systemic vasculitis.

BACKGROUND

The ACR has previously not developed guidelines for the management of systemic vasculitis. The diagnosis, treatment, and monitoring of these diseases can be challenging given their rarity and the paucity of large, randomized clinical trials to guide therapy. Therefore, the ACR convened the Vasculitis Guideline core leadership team to develop evidence-based guidelines for the management of systemic vasculitis. The group was encouraged to scope broadly, without mandate to cover a specific type of vasculitis. It was recognized that one set of guidelines could not cover the entire spectrum of vasculitic diseases, and that vasculitides not addressed in this initial effort could be covered in future guidelines.

At the group's first in-person meeting in June 2017, the Core Oversight Team, Voting Panel, and Expert Panel discussed the scope that should be covered in this initial guideline effort. The 2012 International Chapel Hill Consensus Conference Nomenclature (1) was used as the basis for categorizing the vasculitides to be considered. For this initial effort, the vasculitides in the major categories—large, medium, and small vessel vasculitis—were prioritized given their prevalence compared to other categories of vasculitis. After discussion, the group members elected to focus on large and medium vessel vasculitides, due to the need for clinical guidelines for these diseases and the available evidence upon which these guidelines could be based.

Using the Chapel Hill Consensus Conference nomenclature, the large vessel vasculitides covered in these guidelines are Takayasu arteritis and giant cell arteritis. The medium vessel vasculitides covered in this guideline are Kawasaki disease and polyarteritis nodosa. Of note, cutaneous polyarteritis nodosa and hepatitis B-related vasculitis will not be reviewed in this guideline since these two entities are included in other Chapel Hill Consensus Conference nomenclature categories (single-organ vasculitis and vasculitis associated with probable etiology, respectively). These vasculitides, and others not discussed in this guideline, can be considered for future guideline development efforts.

The Vasculitis Guideline group intends for these guidelines to be applicable to both adults and children affected by these diseases. Thus, the group is comprised of both adult and pediatric rheumatologists, and the questions addressed in this guideline apply to both adults and children.

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OBJECTIVES

The objective of this project is to develop recommendations informing the use of diagnostic testing, pharmacologic treatments, and non-pharmacologic interventions for the management of large vessel vasculitis (giant cell arteritis and Takayasu arteritis) and medium vessel vasculitis (non-hepatitis-related polyarteritis nodosa and Kawasaki disease).

Specifically, we aim to:

1. Develop recommendations for the use of clinical, laboratory, and imaging studies that contribute to the diagnosis and can be used to monitor large and medium vessel vasculitis.
2. Develop recommendations for the use of glucocorticoids, non-glucocorticoid and biologic immunosuppressive agents, and non-pharmacologic interventions for the management of large and medium vessel vasculitis based on considerations of both efficacy and safety.

METHODS

Identification of Studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) will be developed by the principal investigators, systematic literature review leader, and a research librarian, with input from the Core Team. The search strategies will be peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) (2). Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960s +).

The search strategies will be developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library; and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library.

Search Limits

Only English language articles will be retrieved.

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Grey Literature

The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), will be searched for peer-reviewed reports not indexed by electronic databases.

Literature Search Update

Literature searches will be updated just before the voting panel meeting to ensure completeness.

Inclusion/Exclusion Criteria

See PICO questions (*Appendix A*), which outline the defined patient population, interventions, comparators and outcomes.

Management of Studies and Data

References and abstracts will be imported into bibliographic management software (Reference Manager) (3), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (4). Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage defaulting to inclusion for full manuscript review. Following the same dual review process, disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature review leadership, if necessary.

Phases

1. A search for randomized controlled trials and observational studies about interventions aimed at the diagnostic testing, pharmacologic treatments, and non-pharmacologic interventions for the management of large vessel vasculitis (giant cell arteritis and Takayasu arteritis) and medium vessel vasculitis (non-hepatitis-related polyarteritis nodosa and Kawasaki disease) will be performed to determine existing studies covering outcomes of interest. Subsequently, identified studies will be assessed using the RevMan (5) and GRADE Pro tools (6).
2. Chosen studies will be assessed for risk of bias using modified versions of the Cochrane Risk of Bias tool (7) and the Newcastle-Ottawa Scale (8).
3. Additionally, recently published systematic reviews covering outcomes of interest will also be sought and used for reference cross-checking.

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GRADE Methodology

GRADE methodology (9) will be used in this project to grade available evidence and facilitate development of recommendations. The certainty in the evidence (also known as 'quality' of evidence) will be graded as high, moderate, low or very low. The strength of recommendations will be graded as strong or conditional. The strength of recommendations will not depend solely on the certainty in the evidence, but also on patient preferences and values, and the weight between benefits and harms. A series of articles that describe the GRADE methodology can be found on the GRADE working group's website: www.gradeworkinggroup.org.

Analysis and Synthesis

The literature review team will analyze and synthesize data from included studies that address the PICO questions. An evidence profile, including a GRADE Summary of Findings table, will be prepared for each PICO question using Review Manager (RevMan) (3) and GRADEprofiler (GRADEpro) software (6). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The evidence profile documents the overall certainty in the evidence for each critical and important outcome across studies and summarizes the rationale of the GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision and publication bias), or upgrading the certainty in a body of evidence (large magnitude of effect, dose-response gradient, and all plausible confounding that would reduce a demonstrated effect).

Development of Recommendation Statements

PICO questions will be revised into drafted recommendation statements. Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of eight adult rheumatologists, four pediatric rheumatologists, and patient representatives, will consider the drafted recommendation statements in two stages. The first assessment will be done individually, and the results will be anonymous; this vote will only be used to determine where consensus might or might not already exist and develop the voting panel meeting agenda. At the face-to-face voting panel meeting, chaired by the principal investigator, the panelists will discuss the evidence in the context of their clinical experience and expertise to arrive at consensus on the final recommendations. The voting panel meeting

discussions will be supported by the literature review leader, the GRADE expert, and selected members of the literature review team, who will attend the meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will be informed by a separately convened patient panel, which will meet in the days before the voting panel meeting, to provide unique patient perspectives on the drafted recommendations based on their experiences and the available literature.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies
B. GRADE evidence profiles and summary of findings tables for each PICO question

AUTHORSHIP

Authorship of the guideline will include: principal investigator, Dr. Sharon Chung, as the lead author and voting panel leader; Dr. Hassan Murad, literature review leader; Drs. Gary Hoffman, Carol Langford, Mehrdad Maz, and Antoine Sreih, content experts; and Dr. Gordon Guyatt, GRADE expert. Members of the literature review team and voting panel will also be authors. The PI will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using international authorship standards as guidance.

DISCLOSURES/CONFLICTS OF INTEREST

The ACR's disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on this page of the ACR web site, under Policies & Procedures. *See Appendix B for participant disclosures.*

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APPENDIX A – PICO Questions

TAKAYASU ARTERITIS (TAK)

Definitions:

A. Disease states

1. Suspected disease: clinical symptoms or signs suggestive of TAK and not explained by other conditions
2. Active disease: new, persistent, or worsening clinical symptoms and/or signs attributed to TAK and not related to prior damage
3. Remission: absence of new or worsening clinical symptoms or signs attributed to TAK on or off immunosuppressive therapy
4. Refractory: persistent active disease despite an appropriate course of immunosuppressive therapy
5. Relapse: recurrence of active disease following a period of remission

B. Therapy

1. Pulse intravenous glucocorticoids:
   - Adults: methylprednisolone 500-1000 mg given intravenously for 3-5 days or equivalent
   - Children: methylprednisolone 30 mg/kg/day (maximum 1000 mg/day) for 3-5 days or equivalent
2. High dose oral glucocorticoids:
   - Adults: prednisone 1 mg/kg/day (generally up to 80 mg/day) or equivalent
   - Children: prednisone 1-2 mg/kg/day (generally up to 60 mg/day) or equivalent
3. Moderate dose oral glucocorticoids:
   - Adults: prednisone 0.25-0.5 mg/kg/day (generally between 10-40 mg/day) or equivalent

- Children: prednisone ~0.5 mg/kg/day (generally 10-30 mg/day) or equivalent

4. Low dose oral glucocorticoids:
   - Adults: prednisone ≤ 10 mg/day or equivalent
   - Children: prednisone ≤ 0.2 mg/kg/day (maximum 10 mg/day) or equivalent
5. Non-glucocorticoid immunosuppressive therapy: azathioprine (AZA), cyclophosphamide (CYC), leflunomide (LEF), methotrexate (MTX), mycophenolate mofetil/mycophenolate sulfate/mycophenolic acid (MMF)
6. Biologics: TNFα inhibitors, tocilizumab
7. Surgical intervention: angioplasty, stent placement, vascular bypass, or grafting

C. Disease assessments

1. Clinical monitoring: Assessing for clinical signs and symptoms of active disease (4 extremity blood pressure monitoring, pulse and bruit assessment, evaluation for valvular insufficiency murmurs) and obtaining clinical labs including inflammatory markers
2. Inflammatory markers: Sedimentation rate, C-reactive protein
3. Non-invasive imaging: CT angiogram, MR angiogram, PET, vascular ultrasound
4. Invasive imaging: Conventional catheter-based angiogram

D. Disease-related outcomes

1. Activity as determined by the Birmingham Vasculitis Activity Score (BVAS) or study-specific disease activity assessment
2. Damage as determined by the Vasculitis Damage Index (VDI) or study-specific disease damage measure
3. Clinical symptoms and organ damage attributable to disease
4. Relapse
5. Death
6. Patient-reported outcomes

i. SF36 (Short Form Health Surgery), or EQ-5D (Euroquol), or CHQ (Child Health Questionnaire)
ii. If above not available: Patient Global Assessment, PROMIS, RAPID3, or MDHAQ

E. Treatment-related adverse events

1. Serious adverse events
2. Infection
3. Malignancy
4. Any toxicity leading to drug discontinuation

F. Surgical intervention-related adverse events

1. Ischemic events
2. Need for additional intervention or immunosuppression
3. Complications of the intervention, such as bleeding or thrombotic events
4. Infection
5. Death

G. Diagnostic testing-related adverse effects/events

1. Non-invasive imaging-related adverse effects (if applicable):
    i. Adverse reaction to contrast exposure
2. Invasive imaging-related adverse events:
    i. Adverse reaction to contrast exposure including nephrotoxicity
    ii. Complications of the procedure, including bleeding, thrombotic events, and ischemic events
3. Adverse reaction to sedation needed to perform diagnostic testing

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PICO Questions:

A. Imaging, laboratory tests, and monitoring:

1. In patients with TAK, what is the impact of utilizing non-invasive imaging vs. invasive imaging as a disease activity assessment tool on the development of disease-related outcomes and diagnostic testing-related adverse events?
2. In patients with TAK, what is the impact of adding inflammatory markers to clinical monitoring as a disease activity assessment tool vs. clinical monitoring alone on the development of disease-related outcomes and diagnostic testing-related adverse events?
3. In patients with known TAK, what is the impact of regularly scheduled non-invasive imaging (e.g., every 6 months) vs. routine clinical assessment on the development of disease-related outcomes and diagnostic testing-related adverse events?
4. In patients with TAK in apparent remission, what is the impact of long-term routine clinical monitoring (e.g., every 3 months) versus no routine clinical monitoring on disease-related outcomes?

B. Treatment:

5. In patients with TAK with active disease, what is the impact of treatment with high-dose glucocorticoids vs. low-dose glucocorticoids on disease-related outcomes and treatment-related adverse events?
6. In patients with active TAK not on immunosuppression, what is the impact of initiating treatment with pulse intravenous glucocorticoids followed by high dose oral glucocorticoids vs. high dose oral glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
7. UPDATED QUESTION In patients with active TAK, what is the impact of glucocorticoid + non-glucocorticoid non-biologic immunosuppressive therapy vs. glucocorticoid monotherapy on disease-related outcomes and treatment-related adverse events?
8. NEW QUESTION (added during literature review) In patients with active TAK, what is the impact of tocilizumab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

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9. NEW QUESTION (added during literature review) In patients with active TAK, what is the impact of anti-TNF inhibitors + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
10. NEW QUESTION (added during literature review) In patients with active TAK, what is the impact of abatacept + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
11. NEW QUESTION (added during literature review) In patients with active TAK, what is the impact of rituximab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
12. NEW QUESTION (added during literature review) In patients with active TAK, what is the impact of ustekinumab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
13. NEW QUESTION (added during literature review) In patients with active TAK, what is the impact of adding aspirin (any dose) or other anti-platelet therapy vs. not adding anti-platelet therapy on disease-related outcomes and treatment-related adverse events?
14. NEW QUESTION (added during literature review) In patients with refractory TAK on glucocorticoid therapy, what is the impact of adding anti-TNF therapy vs. adding tocilizumab on disease-related outcomes and treatment-related adverse events?
15. NEW QUESTION (added during literature review) In patients with TAK who achieved remission on glucocorticoids, what is the impact of low dose maintenance glucocorticoids vs. no maintenance glucocorticoids on disease-related outcomes and treatment-related adverse events?
16. In patients with TAK with asymptomatic progression of a previously identified vascular lesion, what is the impact of escalating or changing immunosuppression vs. continuing current therapy on disease-related outcomes and treatment-related adverse events?
17. In patients with known TAK who develop a new vascular lesion in a previously unaffected vascular territory, what is the impact of escalating or changing immunosuppression vs. continuing current therapy on disease-related outcomes and treatment-related adverse events?

18. NEW QUESTION (added during literature review) In patients with TAK in apparent clinical remission but with signs of active large vessel vascular inflammation on non-invasive imaging, what is the impact of treating with immunosuppressive therapy vs. not treating with immunosuppressive therapy on disease-related outcomes or treatment related adverse events?
19. NEW QUESTION (added during literature review) In patients with TAK in apparent clinical remission but with rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression versus escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?

C. Surgical intervention:

20. In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, what is the impact of surgical intervention with continued immunosuppression vs. continued immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
21. In patients with known TAK with worsening signs of limb/organ ischemia on immunosuppression, what is the impact of surgical intervention with escalating immunosuppression vs. escalating immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
22. In patients with TAK with stenosis of a cranial/cervical vessel without clinical symptoms, what is the impact of surgical intervention combined with continued immunosuppression vs. continued immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
23. In patients with TAK with worsening signs of limb/organ ischemia, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?
24. In patients with TAK with worsening signs of limb/organ ischemia, what is the impact of endovascular interventions (such as angioplasty or stent placement) versus vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?

25. NEW QUESTION (added during literature review) In patients with TAK undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure vs. not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?
26. NEW QUESTION (added during literature review) In patients with TAK with renovascular hypertension and renal artery stenosis, what is the impact of surgical intervention vs. treating with immunosuppression on hypertension, surgical intervention-related adverse events, and treatment-related adverse events?

D. Other:

27. UPDATED QUESTION In patients with known TAK and known cervicocranial stenotic lesions, what is the impact of maintaining blood pressure <130/80 (or ≤ 95 percentile in children <13 years old based on NIH/CDC values) vs. permitting blood pressure to remain above these levels on disease-related outcomes and treatment-related adverse events?

GIANT CELL ARTERITIS (GCA)

Definitions:

A. Disease states

1. Suspected disease: clinical signs and/or symptoms suggestive of GCA and not explained by other conditions
2. Active disease: new, persistent, or worsening clinical signs and/or symptoms attributed to GCA and not related to prior damage
3. Manifestations of cranial ischemia: visual loss, amaurosis fugax, and other signs and/or symptoms of impending visual loss
4. Severe disease: vascular involvement threatening organ function (e.g., visual loss, large vessel stenosis leading to limb ischemia, aortic aneurysm, and stroke)
5. Remission: absence of clinical signs or symptoms attributed to GCA on or off of immunosuppressive therapy

6. Relapse: recurrence of active disease following a period of remission

B. Therapy

1. Pulse intravenous glucocorticoids: methylprednisolone 500-1000 mg given intravenous daily for 3-5 days, or equivalent
2. High dose oral glucocorticoids: prednisone 1 mg/kg up to 80 mg daily or equivalent
3. Moderate dose oral glucocorticoids: prednisone 0.5 mg/kg/day (generally between 10-40 mg/day in adults) or equivalent
4. Low dose oral glucocorticoids: prednisone ≤ 10 mg daily or equivalent
5. Non-glucocorticoid immunosuppressive therapy: azathioprine (AZA), leflunomide (LEF), methotrexate (MTX)
6. Biologics: tocilizumab, abatacept
7. Surgical intervention: angioplasty, stent placement, vascular bypass, or grafting

C. Disease assessments

1. Clinical monitoring: Assessing for clinical signs and symptoms of active disease, obtaining 4 extremity blood pressures, and obtaining clinical labs including inflammatory markers
2. Inflammatory markers: Sedimentation rate (ESR), C-reactive protein (CRP)
3. Non-invasive imaging: CT angiogram, MR angiogram, PET scan, vascular ultrasound, MRI of temporal and scalp arteries
4. Invasive imaging: Conventional catheter-based angiogram

D. Disease-related outcomes

1. Activity as determined by the Birmingham Vasculitis Activity Score (BVAS) or study-specific disease activity assessment
2. Damage as determined by the Vasculitis Damage Index (VDI) or study-specific disease damage measure
3. Clinical symptoms and organ damage attributable to disease
4. Relapse
5. Death

6. Patient-Reported Outcomes
    i. SF36 or EQ-5D
    ii. If above not available: Patient Global Assessment, PROMIS, RAPID3, or MDHAQ

E. Treatment-related adverse events

1. Serious adverse events
2. Infection
3. Malignancy
4. Any toxicity leading to drug discontinuation

F. Surgical intervention-related adverse events

1. Ischemic events
2. Need for additional intervention or immunosuppression
3. Complications of intervention, such as bleeding, thrombotic events, and ischemic events
4. Infection
5. Death

G. Diagnostic testing-related adverse events

1. Non-invasive imaging-related adverse effects (if applicable):
    i. Adverse reaction to contrast exposure including nephrotoxicity
2. Invasive imaging-related adverse events:
    i. Adverse reaction to contrast exposure including nephrotoxicity
    ii. Complications of the procedure, such as bleeding, thrombotic events, and ischemic events
3. Tissue biopsy adverse effects

i. Pain
ii. Scarring
iii. Injury to tissue biopsied

PICO Questions:

A. Diagnosis, biopsy and imaging:

1. In patients with suspected GCA, what is the impact of unilateral versus bilateral temporal artery biopsy on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?
2. In patients with suspected GCA, what is the impact of a short segment temporal artery biopsy (less than 1 cm) versus a longer biopsy (greater than 1cm) on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?
3. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy within two weeks of starting oral glucocorticoids versus after two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?
4. In patients with suspected GCA, what is the impact of utilizing temporal artery ultrasound versus temporal artery biopsy on diagnostic accuracy, disease-related outcomes, and tissue biopsy related-adverse events?
5. In patients with suspected GCA, what is the impact of temporal artery MRI versus temporal artery biopsy on diagnostic accuracy, disease-related outcomes, diagnostic testing-related adverse events, and tissue biopsy-related adverse events?
6. In patients with suspected GCA, what is the impact of imaging the large vessels versus clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related complications?
7. In patients with suspected GCA and a negative temporal artery biopsy, what is the impact of large vessel imaging versus clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic-tested related adverse events?
8. In patients with suspected GCA what is impact of diagnostic confirmation by temporal artery biopsy versus clinical diagnosis alone on sustaining a diagnosis of GCA after one year of management and tissue biopsy-related adverse events?

9. In patients with GCA, what is the impact of routine monitoring (such as every 6-12 months) with non-invasive vascular imaging versus not performing routine monitoring with non-invasive vascular imaging on disease-related outcomes and diagnostic testing-related adverse events?
10. In patients with GCA in apparent remission off of immunosuppressive therapy what is the impact of long-term routine clinical monitoring (such as every 3-6 months) versus no routine clinical monitoring on disease-related outcomes?

B. Medical treatment:

11. In patients with newly-diagnosed GCA without manifestations of cranial ischemia, what is the impact of pulse IV glucocorticoids versus high dose oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
12. In patients with newly-diagnosed GCA with manifestations of cranial ischemia, what is the impact of treatment with pulse IV glucocorticoids versus high dose oral glucocorticoids on, cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
13. In patients with newly-diagnosed GCA, what is the impact of using daily aspirin (81 to 325 mg) versus not using aspirin on disease-related outcomes and treatment-related adverse events?
14. In patients with newly-diagnosed GCA without cranial ischemic manifestations, what is the impact of initial high dose oral glucocorticoids versus moderate dose oral glucocorticoids on disease-related outcomes, cumulative glucocorticoid dose, and treatment-related adverse events?
15. In patients with newly-diagnosed GCA, what is the impact of oral glucocorticoids with non-glucocorticoid immunosuppressive therapy versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
16. In patients with newly-diagnosed GCA, what is the impact of oral glucocorticoids with tocilizumab versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
17. In patients with newly-diagnosed GCA, what is the impact of oral glucocorticoids with abatacept versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

18. In patients with newly-diagnosed GCA, what is the impact of alternate day oral glucocorticoids versus daily oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
19. In patients with newly diagnosed GCA, what is the impact of statin use versus not using a statin on cardiovascular events, disease-related outcomes, and treatment-related adverse events?
20. In patients with GCA on glucocorticoids, what is the impact of tapering glucocorticoids off by 6 months versus tapering glucocorticoids off over a period longer than 6 months on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
21. In patients with GCA with extra-cranial large vessel involvement, what is the impact of oral glucocorticoids with a non-glucocorticoid immunosuppressive agent versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?
22. In patients with GCA who are in remission off of glucocorticoids and on non-glucocorticoid immunosuppressive therapy for 1 year, what is the effect of discontinuing non-glucocorticoid immunosuppressive therapy versus continuing non-glucocorticoid immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
23. In asymptomatic patients with GCA who have rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression versus escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?

C. Surgical interventions:

24. In patients with GCA with severe disease, what is the impact of surgical intervention with immunosuppression versus immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
25. In patients with GCA and severe disease, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?

26. In patients with GCA with severe disease, what is the impact of endovascular interventions (such as angioplasty or stent placement) versus vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?
27. NEW QUESTION (added during literature review) In patients with GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure vs. not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?

POLYARTERITIS NODOSA (PAN)

Definitions:

A. Disease states

1. Suspected disease: clinical signs and/or symptoms suggestive of PAN and not explained by other conditions
2. Active disease: new, persistent, or worsening clinical signs and/or symptoms attributed to PAN and not related to prior damage
3. Severe disease: vasculitis with life/organ-threatening manifestations (e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia)
4. Non-severe disease: vasculitis without life/organ-threatening manifestations (e.g. mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
5. Remission: absence of clinical signs or symptoms attributed to PAN on or off of immunosuppressive therapy
6. Refractory: persistent active disease despite an appropriate course of immunosuppressive therapy
7. Relapse: recurrence of active disease following a period of remission

B. Therapy

1. Pulse intravenous glucocorticoids:
    i. Adults: methylprednisolone 500-1000 mg given intravenously for 3-5 days or equivalent
    ii. Children: methylprednisolone 30 mg/kg/day (maximum 1000 mg/day) for 3-5 days or equivalent
2. High dose oral glucocorticoids:
    i. Adults: prednisone 1 mg/kg/day (generally up to 80 mg/day) or equivalent
    ii. Children: prednisone 1-2 mg/kg/day (generally up to 60 mg/day) or equivalent
3. Moderate dose oral glucocorticoids:
    i. Adults: prednisone 0.25-0.5 mg/kg/day (generally between 10-40 mg/day) or equivalent
    ii. Children: prednisone ~0.5 mg/kg/day (generally 10-30 mg/day) or equivalent
4. Low dose oral glucocorticoids:
    i. Adults: prednisone ≤ 10 mg/day or equivalent
    ii. Children: prednisone ≤ 0.2 mg/kg/day (maximum 10 mg/day) or equivalent
5. Non-glucocorticoid immunosuppressive therapy: Azathioprine (AZA), cyclophosphamide (CYC), leflunomide (LEF), methotrexate (MTX), mycophenolate mofetil/mycophenolate sulfate/mycophenolic acid (MMF)

C. Disease assessments

1. Clinical monitoring: Assessing for clinical signs and symptoms of active disease and obtaining clinical labs including inflammatory markers
2. Inflammatory markers: Sedimentation rate (ESR), C-reactive protein (CRP)
3. Non-invasive imaging: CT angiogram, MR angiogram,
4. Invasive imaging: Conventional catheter-based angiogram

D. Disease-related outcomes

1. Activity as determined by the Birmingham Vasculitis Activity Score (BVAS) or study-specific disease activity assessment

2. Damage as determined by the Vasculitis Damage Index (VDI) or study-specific disease damage measure
3. Clinical symptoms and organ damage attributable to disease
4. Relapse
5. Death
6. Patient-Reported Outcomes
    i. SF36 (Short Form Health Survey), EQ-5D (Euroqol), or CHQ (Child Health Questionnaire)
    ii. If above not available: Patient Global Assessment, PROMIS, RAPID3, or MDHAQ

E. Treatment-related adverse events

1. Serious adverse events
2. Infection
3. Malignancy
4. Any toxicity leading to drug/treatment discontinuation

F. Diagnostic testing-related adverse events

1. Non-invasive imaging-related adverse effects:
    i. Adverse reaction to contrast exposure
2. Invasive imaging-related adverse events:
    i. Adverse reaction to contrast exposure including nephrotoxicity
    ii. Complications of the procedure, such as bleeding, thrombotic events, and ischemic events
3. Tissue biopsy adverse effects
    i. Pain
    ii. Scarring
    iii. Injury to tissue biopsied

4. EMG/NCS related harmful effects
    i. Adverse reaction to testing procedure
5. Adverse reaction to sedation needed to perform diagnostic testing

PICO Questions:

A. Diagnosis:

1. In patients with suspected PAN with and without gastrointestinal symptoms, what is the impact of non-invasive vascular imaging vs. conventional catheter-based imaging on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
2. In patients with suspected cutaneous or systemic PAN involving the skin, what is the impact of a deep skin biopsy vs. skin punch biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
3. In patients with suspected PAN and peripheral neuropathy (motor and/or sensory), what is the impact of nerve and muscle biopsy vs. nerve biopsy alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

B. Treatment:

4. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of pulse intravenous glucocorticoids compared to high dose oral glucocorticoids disease-related outcomes and treatment-related adverse events?
5. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide with high dose glucocorticoids vs. high dose glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
6. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide vs. other non-glucocorticoid immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
7. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of plasmapheresis combined with cyclophosphamide and glucocorticoids vs. cyclophosphamide and glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

8. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of using non-glucocorticoid immunosuppressive therapy (excluding cyclophosphamide) with glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
9. In patients with newly-diagnosed PAN who has achieved remission with cyclophosphamide, what is the impact of transitioning to another non-glucocorticoid immunosuppressive agent vs. continuing with cyclophosphamide on disease-related outcomes and treatment-related adverse events?
10. In patients with newly-diagnosed PAN with active disease and severe manifestations, what is the impact of cyclophosphamide vs. rituximab on disease-related outcomes and treatment-related adverse events?
11. In patients with newly-diagnosed PAN in remission after remission induction therapy, what is the impact of a rapid taper of glucocorticoids (<6 months) vs. a slow taper (≥ 6 months) on disease-related outcomes and treatment-related adverse events?
12. In patients with newly diagnosed PAN with active and non-severe disease, what is the impact of adding of non-glucocorticoid immunosuppressive therapy to glucocorticoids vs. using glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
13. In patients with PAN in remission on non-glucocorticoid immunosuppressive therapy, what is the impact of discontinuation of non-glucocorticoid immunosuppressive therapy after 18 months vs. continued treatment on disease-related outcomes and treatment-related adverse events?
14. In patients with PAN who has nerve and/or muscle involvement, what is the impact of physical therapy vs. no physical therapy on disease-related outcomes?
15. In patients with PAN with refractory disease on glucocorticoids alone, what is the impact of adding of cyclophosphamide vs. increasing the glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?
16. In patients with PAN with refractory disease on glucocorticoids and cyclophosphamide, what is the impact of adding plasmapheresis vs. increasing immunosuppression on disease-related outcomes and treatment-related adverse events?

17. UPDATED QUESTION In patients with PAN with refractory disease on glucocorticoids and non-glucocorticoid immunosuppressive therapy (excluding cyclophosphamide), what is the impact of switching to cyclophosphamide vs. increasing glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?
18. NEW QUESTION (added during literature review) In patients with PAN and Adenosine Deaminase 2 deficiency what is the impact of TNF-alpha inhibitors (e.g., infliximab, etanercept, adalimumab) versus glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

C. Monitoring:

19. In patients with a history of severe PAN who is clinically asymptomatic but has newly elevated inflammatory markers without a clear etiology, what is the impact of vascular imaging (both invasive and non-invasive) vs. clinical assessment alone on disease-related outcomes and diagnostic testing-related adverse events?
20. In patients with a history of severe PAN who is clinically asymptomatic, what is the impact of routine vascular imaging (both invasive and non-invasive) every 6 months vs. vascular imaging only prompted by clinical symptoms/signs on disease-related outcomes and diagnostic testing-related adverse events?
21. In patients with a history of peripheral motor neuropathy secondary to PAN, what is the effect of routine EMG/NCS every 6 months vs. routine neurologic exam alone on disease-related outcomes and treatment-related adverse events?

KAWASAKI DISEASE (KD)

Definitions:

A. Disease states

1. KD: Fever lasting at least five days without any other explanation combined with at least four of the five principal clinical findings below. The diagnosis may be made with only 4 days of fever if > 4 principal clinical findings are present. Principal clinical findings:
    i. Bilateral bulbar conjunctival injection
    ii. Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
    iii. Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase)
    iv. Polymorphous rash
    v. Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter)
2. Incomplete KD: Defined according to the algorithm in Newburger JW et al. Circulation 2004 Oct 26;110(17):2747-71 and McCrindle et al. Circulation 2017 Apr 25;135(17):e927-e999. More specifically, any infant or child with prolonged unexplained fever, fewer than 4 of the principal clinical findings of KD (see above), and compatible laboratory studies (elevated ESR/CRP, elevated transaminases, UA with leukocyte esterase negative WBC) or echocardiographic findings (coronary artery dilatation).
3. KD with high risk scores: child with KD at high risk of inadequate response to IVIG therapy based on risk-scoring systems such as the Kobayashi score (Kobayashi T et al., Circulation 2006; 113: 2606–2612) , Egami score (Egami K et al., J Pediatr. 2006;149:237–240), Sano score (Sano T et al. , Eur J Pediatr. 2007;166:131–137), or Harada score (Harada K., Acta Paediatr Jpn. 1991;33:805–810).
4. Acute phase KD: initial febrile phase of KD
5. Resolved KD: previously diagnosed KD with resolution of fevers and principal clinical findings, normalization of inflammatory markers, and stable coronary artery aneurysms if present

B. Therapy

1. Intravenous immunoglobulin (IVIG): 2g/kg administered as a single dose
2. Aspirin:
    i. Low dose aspirin: 3-5 mg/kg/day
    ii. Moderate dose aspirin: 30-50 mg/kg/day

iii. High dose aspirin 80-100 mg/kg/day

3. Glucocorticoids:
   i. Pulse-dose glucocorticoids: methylprednisolone 30 mg/kg IV daily for 1-3 days, or equivalent
   ii. Oral glucocorticoids: prednisone 2 mg/kg daily for 5-10 days followed by ~25% reduction every 5-7 days, or equivalent
4. Non-glucocorticoid immunosuppressive therapy: cyclophosphamide, cyclosporine, TNF inhibitors, anakinra
5. Anti-coagulation therapy: warfarin, heparin, low molecular weight heparin
6. Anti-platelet therapy: aspirin, clopidogrel, dipyridamole

C. Disease assessments

1. Clinical monitoring: Assessing for clinical signs and symptoms of active disease including fever and obtaining clinical labs including inflammatory markers
2. Imaging: echocardiogram

D. Disease-related outcomes

1. Clinical symptoms and organ damage attributable to disease, including coronary artery aneurysms and myocardial infarction
2. Relapse
3. Death
4. Patient-Reported Outcomes
   i. SF36, (Short Form Health Survey), EQ-5D (Euroqol), or CHQ (Child Health Questionnaire)
   ii. If above not available: Patient Global Assessment, PROMIS, RAPID3, or MDHAQ

E. Treatment-related adverse events

1. Serious adverse events
2. Infection

3. Malignancy
4. Any toxicity leading to drug/treatment discontinuation

F. Diagnostic testing-related adverse events

1. Adverse events related to sedation needed for diagnostic testing
2. Non-invasive imaging-related adverse events (if applicable):
    i. Adverse events related to contrast exposure including nephrotoxicity

PICO Questions:

A. Treatment:

1. In children with incomplete KD with unexplained fever ≥7 days, what is the impact of treatment with IVIG therapy before day 10 vs. after day 10 on the development of disease-related outcomes and treatment-related adverse events?
2. In children with acute KD and features of macrophage activation syndrome (MAS), what is the impact of treatment with IVIG with glucocorticoids or anakinra vs. IVIG alone on the development of disease-related outcomes, treatment-related adverse events, and persistence of MAS?
3. In children with acute KD, what is the impact of initial treatment with glucocorticoids vs. IVIG on the development of disease-related outcomes and treatment-related adverse events?
4. In children with acute KD with high risk scores, what is the impact of initial treatment with IVIG and glucocorticoids vs. IVIG alone on the development of disease-related outcomes and treatment-related adverse events?
5. In children with acute KD with high risk scores, what is the impact of initial therapy with IVIG and other non-glucocorticoid immunosuppressive agents vs. IVIG alone on the development of disease-related outcomes and treatment-related adverse events?
6. In children with acute KD, what is the impact of treatment with any dose of aspirin vs. no aspirin on the development of disease-related outcomes and treatment-related adverse events?

7. In children with acute KD, what is the impact of initial treatment with high-dose or moderate dose aspirin vs. low-dose aspirin on the development of disease-related outcomes and treatment-related adverse events?
8. In children with KD and coronary artery aneurysms, what is the impact of treatment with anti-coagulation vs. no anti-coagulation on the development of disease-related outcomes and treatment-related adverse events?
9. In children with KD and coronary artery aneurysms, what is the impact of treatment with anti-platelet agents besides aspirin vs. low dose aspirin on the development of disease-related outcomes and adverse effects of anti-platelet therapy?
10. In children with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids vs. another course of IVIG on the development of disease-related outcomes and treatment-related adverse events?
11. In children with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids in combination with non-glucocorticoid immunosuppressive therapy vs. treatment with glucocorticoids alone on the development of disease-related outcomes and treatment-related adverse events?
12. In children on treatment for acute KD with resolution of fevers, what is the impact of continued daily monitoring for fevers for 2 weeks vs. no monitoring for fevers on the development of disease-related outcomes?
13. In children with KD and arthritis that persists after IVIG treatment, what is the impact of treatment with NSAIDs vs. no NSAIDS on the persistence of arthritis, development of disease-related outcomes, and development of treatment-related adverse events?

B. Additional diagnostic testing:

1. In children with suspected incomplete KD and fever for over 7 days, what is the impact of obtaining an echocardiogram before day 10 of fever vs. not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
2. In children with unexplained shock physiology, what is the impact of obtaining an echocardiogram vs. not obtaining an echocardiogram on the diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?

3. In children with fever and unexplained macrophage activation syndrome, what is the impact of obtaining an echocardiogram vs. not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?

APPENDIX B – Participant Disclosures

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts. The purpose of the ACR's Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

Participants	Role	Primary Employer	Sources of Personal Income (salary information from primary employer is not required):	Research Grants/Contracts	Investments to Include Medical Industry and Nonmedical Industry	Organizational Benefit	Activities with Other Organizations
Sharon Chung	Core Team/PI	University of California, San Francisco	N/A	NIH; UCSF; UCSF School of Medicine	N/A	N/A	N/A
Antoine G. Sreih	Core Team/Content Expert	The University of Pennsylvania	Krogg and Partners; Rupert Case Management ; Naxion	PCORI; NIH/NIAMS; NIH/NHLBI; Genentech-Investigator-Initiated Clinical Trial	Alexion	N/A	The Vasculitis Foundation; Philadelphia Rheumatism Society; The Vasculitis Clinical Research Consortium; The Vasculitis Patient Powered Research Network
Carol Langford	Core Team/Content Expert	Cleveland Clinic	McGraw Hill	NIH; FDA; Genentech; Genentech, NIH; GlaxoSmith Kline; Bristol-Myers Squibb	N/A	N/A	N/A
Mehrdad Maz	Core Team/Content Expert	Kansas University	N/A	Glaxo-Smith-Kline	N/A	N/A	N/A
Gary Hoffman	Core Team/Content Expert	Self employed	N/A	Philanthropy (study)	N/A	N/A	N/A
Gordon Guyatt	Core Team/GRADE Expert	McMaster University	N/A	N/A	N/A	N/A	N/A
Reem Mustafa	Core Team/Lit Review Lead	University of Kansas Medical Center	N/A	PCORI (2); American Society of Hematology	N/A	N/A	American College of Physicians; US GRADE Netwrok; Canadian Society of Nephrology; The Institute for Clinical and Economic Review (ICEF)
Gary Firestein	ACR Board of Directors Liaison	UCSD	Astra Zeneca; Eli Lilly; Elsevier; Roche	Arthritis Foundation; NIH; Janssen; Gilead; RRF	Ignyta; Sialix	N/A	N/A
Eric Matteson	Expert Panel	Mayo Clinic College of Medicine	Up To Date	NIH; Janssen/Amgen/Roche//Mesoblast/Novartis; Pfizer; Novartis, Roche/Bristol-Myers-Squibb/Genentech//Pfizer	N/A	Pfizer	Vasculitis Foundation
Kenneth J. Warrington	Expert Panel	Mayo Clinic	American College of Physicians	GSK; Eli Lilly	N/A	N/A	N/A
Linda Wagner-Weiner	Expert Panel	The University of Chicago	American Academy of Pediatrics	Abbott Pharmaceuticals; UCB Pharmaceuticals; Bristol-Myers Squibb Company ; Alliance for Lupus Research; Pfizer Pharmaceuticals	N/A	N/A	Lupus Society of Illinois; Pediatric Rheumatology Journal
Ora Gewurz-Singer	Expert Panel	University of Michigan	N/A	univ. of Pennsylvania; Clev. Clinic Foundation; Univ. of Oxford	N/A	N/A	N/A
Robert Spiera	Expert Panel	Hospital for Special Surgery	Roche-Genetech; GSK	Roche Genetech; Corbus; Chemocentryx; Cytori; GSK	N/A	N/A	N/A
Rula Hajj-Ali	Expert Panel	Cleveland Clinic	Novartis; Abbvie	N/A	N/A	N/A	N/A
Amy Archer	Voting Panel	Northwestern Medicine/Northwestern University	N/A	N/A	N/A	Vasculitis Foundation	Vasculitis Foundation
Ann Warner	Voting Panel	Self Employed	Best Doctors	N/A	N/A	N/A	N/A
John H. Stone	Voting Panel	Massachusetts General Hospital	Roche/Genentech	Roche; Genentech	N/A	N/A	N/A
Peter A. Merkel	Voting Panel	University of Pennsylvania	Various Academic Institutions; Actelion; BMS; Genentech/Roche; GSK; ChemoCentryx; PrincipiaBio, InflaRx, Boston Pharmaceuticals	NIH: NIAMS, NCATS, NHLBI; FDA; PCORI; BMS, Celegene, ChemoCentryx, Genentech/Roche, GSK; Kypha	N/A	N/A	N/A
Peter Grayson	Voting Panel	National Institute of Health	N/A	N/A	N/A	N/A	N/A
Phil Seo	Voting Panel	Johns Hopkins University	Daniel Lee English, Esq.; Genentech; GSK; UptoDate; Oxford University Press	NIAMS	N/A	Centocor	N/A
Rennie Rhee	Voting Panel	University of Pennsylvania	N/A	Rheumatology Research Foundation; Vasculitis Foundation; Gilead Sciencies	N/A	N/A	N/A
Robert Sundel	Voting Panel	Boston Children's Hospital	UpToDate; Paul Hastings (Law Firm); Conway, Homer & Chin-Caplan, P.C.; Medical Education Resources; Misc Legal Firms	Pfizer	Bristol Myers Squibb; BIB (Biotech ETF); XLV (Medical ETF)	N/A	N/A
Susan Kim	Voting Panel	UCSF Benioff Children's Hospital	N/A	CARRA	N/A	N/A	CARRA
Sangeeta Sule	Voting Panel	Johns Hopkins University	Springer Healthcare Medicine Matters Rheumatology	N/A	N/A	N/A	Lupus Foundation DC/MD/VA Chapter
Maria Ibarra	Voting Panel	Children's Mercy Hospital	N/A	N/A	N/A	N/A	N/A
Lisa Imundo	Voting Panel	Columbia University	N/A	Sobi; Pfizer; PROPEL; PASCAL	N/A	N/A	Athritis Foundation; AAP; ABP
Doyt Conn	Voting Panel	Emory University	N/A	N/A	N/A	N/A	N/A