Nadia Luca, Clinical Research Fellow Hospital for Sick Children, Canada	Nothing to disclose.

1. Background: no comments

2. Project scope: agree with specific project objectives

3. Methodology: - consider also including studies/abstracts not published in English- may consider specifically indicating whether you will use registry data- consider how you will compare studies with different outcome measures (e.g. ACR response versus other outcomes)- re: evaluation of quality of studies: consider using CONSORT statement for RCTs, QUORUM statement for meta-analyses, STROBE statement for observational studies - these guidelines are more recently published compared with Jadad and NOS guidelines.

No other major issues identified.

Arun Chogle, Rheumatologist Arthritis care center, India	Nothing to disclose.

Comment on project protocol to be used for formulating 2013 ACR recommendations for the use of DMARDs and biologics in treatment of systemic onset JIA. As an international member of ACR and practicing Rheumatologist, I am submitting my comments on project scope specifically aim no 2 - to incorporate the use of anti IL1 and anti IL6 therapies in 2013 ACR recommendations.

With advancing knowledge about the pathogenesis of SOJIA, it has been shown that abnormalities in inate immunity plays a major role in categorizing SOJIA as a auto inflammatory disorder. Clinical experience has shown that anti IL1 and anti IL6 therapies are effective in SOJIA. I am referring to published data after October 2009. A double blind placebo control trial (ANAJIS trial)[1] showed efficacy of Anakinra in treating corticosteroid dependent patients with SOJIA as a significantly higher percentage of responders was observed after 1 month of treatment compared with placebo. However a loss of response was observed in most patients over time. In this trial patients who were naive for anti-pneumococcal vaccination received Pneumo23 immunization. Also Anakinra seemed less effective in arthritis and more effective for systemic features. As opposed to this, evidence from a recent retrospective study of 46 patients suggests that if given as a first-line drug rather than rescue therapy Anakinra leads to the resolution of both systemic symptoms and arthritis and protects the development of persistent arthritis in approximately 90% of patients and that the non-responders might have been under dosed.[2] .However the retrospective nature of this study and the lack of a control group make it difficult to draw firm conclusions. As regards newer IL1 blocking drugs, Canakinumab, a fully human anti-interleukin 1Beta (anti-IL-1beta) monoclonal antibody, has under gone phase II study and this has been published, [3] while results of a phase III trial should be available soon. Rilonacept (or IL-1Trap) is a fusion protein consisting of the human IL1 receptor extracellular domains and the Fc portion of human IgG1.It incorporates the extracellular domains of both receptor chains required for IL-1 signaling within a single molecule: the IL-1 type I receptor and the IL-1 receptor accessory protein. Due to this, the IL-1 Trap

molecule might be a more efficient inhibitor of in vivo IL-1 signaling than anakinra. Recently Rilonacept has been proven to be effective in familial cold auto-inflammatory syndromes.[4]

References

[1]Qurtier P, Allantaz F,Cimaz R,Pillet P,Messiaen C,Bardin C,et al. A mulicentre ,randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis.2011;70:747-54.

[2]Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE,van Rossum MA ,et al.Anakinra as first-line disease modifying therapy in systemic juvenile idiopathic arthritis.Arthritis Rheum.2011;63:545-55.

[3]Rupcrto N, Quarticr P,Wulffraat N,Woo P Ravelli A,Mouy R,et al. A phase II study to evaluate dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rhcum.2012;64:557-67

[4]Gillespie J, Mathews R, McDermott MF. Rilonacept in the management of cryopyrin-associated periodic syndromes (CAPS).J Inflamm Res.2010;3:1-8.

Based on the above four recent publications, the questions facing the practicing clinicians which 2013 ACR treatment recommendations are expected to cover are as follows:

1. Systemic JIA is diagnosed by excluding various mimicking conditions. What is the scope of diagnostic evaluation?
2. Once the diagnosis is established, how early should biologics like Anakinra be started?
3. Should all patients starting biologics receive prophylactic vaccination against pneumonia and influenza?
4. What is the best treatment approach in patient of SOJI with monocyclic course and polycyclic course?
5. What is the relationship between IL and IL6 production in SOJIA?
6. Tocilizumab (IL6 blocker) has received FDA approval for use in SOJIA.
7. When is Tocilizumab preferred over Anakinra?
8. What is the current status of newer IL1 antagonists in treatment of systemic JIA?
9. In patients receiving anti IL1 or anti IL6 therapy, what is risk of developing of macrophage activation syndrome?

Karen Kolba, Rheumatologist Pacific Arthritis Center Medical Group, USA	Nothing to disclose.
I agree with the proposed updates.	

Iona Szer, Professor, Attending MD UCSD, USA	Nothing to disclose.
I agree with this study. Systemic arthritis is not JIA and we need proper guidelines for treatment of the illness and of MAS.	

Brian Feldman, Professor Sick Kids, Canada	**Disclosure**: I sit on DSMBs for Pfizer and Novartis. I have research grants from Bayer and Baxter.
I am happy with the proposal as presented.	

Wafaa Suwairi, Consultant King Abdul Aziz Medical City/King Fahad National Guard Hospital, Riyadh, Saudi Arabia sewairiw@ngha.med.sa	Nothing to disclose.
I do approve the project as it is. However I would like to see some guidance on for how long I need to continue biologics after disease control. I liked very much considering Tocilizumab in the new guidelines and I believe it should be considered as an initial treatment in all systemic.	

Phillip Hashkes, Head, pediatric Rheumatology Unit Shaare Zedek Medical Center, Israel	**Disclosure:** Novartis 2 (speaking honoraria), 4 (research contracts)

I have several comments on the proposed important JIA treatment recommendation update project.

1. I think that other experts should be invited to either the core expert group or task force. These include experts in macrophage activation syndrome and international experts in JIA treatment particularly systemic disease (the international experts may have a somewhat different perspective) or experts in some of the new medications to be discussed. The 2011 recommendation team included several international experts. Specific potential names include: a. Nicola Ruperto (Genoa) b. Alexei Grom (Cincinnati) c. Nico Wulfraat (Utrecht) d. Angelo Ravelli (Genoa) e. Fabrizio DeBenedetti (Rome) f. Pierre Quartier (Paris) g. Myself (Jerusalem).

2. While it is correctly recognized that the main deficiency of the previous recommendations are in systemic JIA there are other smaller issues that were "tabled" in the 2011 recommendations and may be important to include in the current revision, particularly some safety issues. I don't believe the effort involved in some of these issues is huge. Since the ACR is already undertaking a major effort and assembling a large team for this effort adding several other issues may give additional value to this endeavor. Potential issues include: a. Vaccines b. Several issues related to methotrexate: a .Use of folic/folinic acid with methotrexate b.SC vs. PO methotrexate c. Liver biopsy indications for MTX d. Discontinuing methotrexate after attaining inactive disease c. Radiologic guidance for joint injections (for which joints).

3. The time line may be a little ambitious to be ready for a face to face meeting in November 2012.

4. I suggest an additional focused effort in the future (not for this effort) to develop recommendations for the treatment of JIA uveitis and TMJ arthritis and readdress the issue of early aggressive therapy for poly JIA.

Leonila Dans, Professor University of the Philippines, Philippines	**Disclosure:** I am presently doing a clinical trial on NSAIDs for JIA.
I suggest using the GRADE approach which already has been widely adopted even by the Cochrane Collaboration and World Health Organization in their clinical practice guideline development.	
Patricia Woo, Emeritus Professor in paediatric Rheumatology University college London, UK	Nothing to disclose.
I think the participant list being drawn entirely from North America ignores the fact that there is a wider group of paediatric rheumatologists in other parts of the world with huge amount of experience of this disease as well as the diversity of clinical manifestations and pathologies. Many of these are also ACR members/fellows. Moreover, the availability of the biological drugs are very much a problem in most parts of the world. ACR guideline should take into account such issues to be useful; especially patients are now very mixed in their origins. There is an excellent international trials organisation and also Scientific Society for paediatric rheumatology (PReS and PRINTO), from which experienced paediatric rheumatologists should be included in the drafting of the guideline. The previous publication of treatment recommendations is clearly an example where there was considerable disagreement expressed after the article appeared. My second comment is that the committee should take into account the experience of the registries now established, mainly in the western countries. So data from them should be actively sought and the committee should not rely only on publications as the latter will be around 2 years out of date. Post market safety and efficacy data is obviously critical to the formulation of any recommended treatment.	
L. Douglas Graham, Employed Rheumatologist Du Page Medical Group, USA	Nothing to disclose.
It is with some personal interest that I reviewed these guidelines. In the late l980's, I was involved in the care of a child with refractory systemic onset JIA. It was during the time when there was very little therapeutically available. It is heartening to seek the expansion of treatments for this challenging clinical condition. I have three areas of concern regarding this guideline: 1) the use of hydroxychloroquine in JIA, 2) the inclusion of sulfasalazine under the category of NSAID rather than DMARD, 3) the use of Remicade in JIA. It has been my experience in the ACR development of guidelines that information from specialties outside of rheumatology is seldom utilized. In 2011, the ophthalmologists have changed their guidelines	

for both dosage and monitoring of plaquenil retinal toxicity. (see Michaelides, M. et al. "Retinal Toxicity Associated with Hydroxychloroquine and Chloroquine. "Arch. or Ophthalmic. Vol 129, No. 1, January, 2011 and Marmor, M.F. et.al. "Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy." Ophthalmology, Vol 118, No.2, February, 2011) Given the potential for retinal toxicity in children due to their size and duration of treatment, it would be my sense that it would be prudent to incorporate these quidelines. I am unsure why sulfasalazine was placed in the section on NSAIDS rather than DMARDS. Sulfasalazine appears in the Arthritis Foundation pamphlet on DMARDS and on the ACR website in the medication section on medications separate from NSAIDS, so it would be my impression that many rheumatologists consider it a DMARD rather than an NSAID, although it contains an NSAID. An explanation in the guideline, from my perspective would be useful. Finally, while the committee may be concerned with the short-term data for effficacy of Infliximab, from my perspective as an adult rheumatologist who inherits children with JIA when they become older, the long term outcome and consequences of intravenous treatment are more important. I no longer use Remicade for adults. There are reasonable in vitro studies that demonstrate that it is among the weakest binders of TNF-alpha which mirror my clinical experience. There is the documented problem of tachyphylaxis, which in my experience represents a therapeutic failure. I was never able to achieve long term control by escalating the dose, but was able to achieve control when I switched products or mechanism of action. It exposures children to an avoidable risk of disease progression with loss of function that is critical to their physical and psychological development. It would be hard for me to prescribe the regimen of intravenous treatment for a child, recognizing the impact on the child and family, given the time commitment for Infliximab. Sitting still for long periods of time can only re-enforce the illness self-image and affect other aspects of family dynamics. And, as in adults, I believe that it is imprudent to exhaust venous access while treating a disease that can last 30-50 years when there are alternative treatments available. It jeopardizes venous access if needed for transfusions, antibiotics, or IV fluids during surgery.

Kara Schmidt, Assistant Professor of Pediatrics Department of Pediatrics, Section of Pediatric Rheumatology, University of Louisville School of Medicine, USA	Nothing to disclose.

Recommend including elevated Soluble IL2R consistent with prolonged activation of T cells in the definition of "macrophage activation syndrome, a life-threatening condition characterized by fever, organomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, hepatitis, coagulopathy, low or absent natural killer cell activity, and hyperferritinemia" and noting that NK cell activity may not be low or absent.

Peter Tugwell, Faculty UNIVERSITY OF OTTAWA, Canada	Nothing to disclose.

THE MAJORITY OF GUIDELINE GROUPS IN THE MEDICAL WORLD INCLUDING AHRQ AND UpToDate AND

THE WORLD HEALTH ORGANISATION NOW USE THE 'GRADE' APPROACH [http://www.gradeworkinggroup.org/publications/ - SEE BELOW-THESE ARE COMPLEMENTARY TO THE RAND APPROACH - ACR SHOULD USE GRADE TOO!

1.Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Sch?nemann HJ, for the GRADE Working Group. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-926 or [pdf]

2.Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Sch?nemann HJ; GRADE Working Group.Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians? BMJ. 2008 May 3;336(7651):995-83.Sch?nemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams JW Jr, Kunz R, Craig J, Montori VM, Bossuyt P, Guyatt GH; GRADE Working Group. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008 May 17;336(7653):1106-104.Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, Vist GE, Sch?nemann HJ; GRADE working group. Rating quality of evidence and strength of recommendations: Incorporating considerations of resources use into grading recommendations.BMJ. 2008 May 24;336(7654):1170-35.Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Sch?nemann HJ; GRADE Working Group. Rating quality of evidence and strength of recommendations: Going from evidence to recommendations. BMJ. 2008 May 10;336(7652):1049-51Organizations that have endorsed or that are using GRADE*

http://www.gradeworkinggroup.org/society/index.htm World Health Organization – International Example Endocrine Society - USA Example American College of Chest Physicians - USA Example UpToDate - Putting Clinical Information Into Practice - USAUTD GRADE tutorial Agenzia sanitaria regionale, Bologna - Italia Ministry of Health and Long-Term Care, Ontario – Canada Example Surviving Sepsis - International ?rztliches Zentrum f?r Qualit?t in der Medizin - Germany American Thoracic Society - USA Example American College of Physicians - USA Example The Cochrane Collaboration - International Kidney Disease: Improving Global Outcome - International Example European Society of Thoracic Surgeons - International British Medical Journal - UK** JIDC Journal of Infection in Developing Countries - International Agency for Healthcare Research and Quality (AHRQ) - USA Example Society of Critical Care Medicine (SCCM) - USA National Institute for Clinical Excellence (NICE) - UK Norwegian Knowledge Centre for the Health Services - Norway The University of Pennsylvania Health System Center for Evidence-based Practice - USA Example German Center for Evidence-based Nursing "sapere aude" - Germany Evidence-based Nursing S? dtirol, Alto Adige ? Italy Society for Vascular Surgery - USA Example Example BMJ Clinical Evidence - UK EBM Guidelines - Finland/International Polish Institute for EBM - Poland European Respiratory Society (ERS) - Europe Japanese Society for Temporomandibular Joint – Japan Example Example National Board of Health and Welfare - Sweden ExampleCOMPUS at The Canadian Agency for Drugs and Technologies in Health (CADTH) - Canada ExampleInfectious Diseases Society of America - USA Spanish Society for Family and Community Medicine - Spain Emergency Medical Services for Children National Resource Center - USA SBU ? The Swedish Council on Technology Assessment in Health Care - Sweden The Scottish Intercollegiate

Guidelines Network (SIGN) - UK Evidence-Based Tuberculosis Diagnosis (tbevidence.org) - Canada National & Gulf Center for Evidence Based Health Practice (NGCEBHP) - Saudi Arabia American Society for Gastrointestinal Endoscopy – USA Example European Association for the Study of the Liver - Europe CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC) – USA Example Finnish Office for Health Technology Assessment – Finland Example NHS Quality Improvement Scotland - UK The American Association for the Study of Liver Diseases - USA The Canadian Cardiovascular Society - CanadaLa Soci?t? Canadienne de Cardiologie - Canada The World Allergy Organization (WAO) – International Example Kaiser Permanente - USA The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) - Europe World Interactive Network Focused On Critical UltraSound - International Critical Ultrasound Journal - Italy American Society for Colposcopy and Cervical Pathology - USA The Dutch Institute for Healthcare Improvement CBO - The Netherlands Kleijnen Systematic Reviews Ltd - UK American Gastroenterological Association - USA Ludwig Boltzmann Institut – Austria Example Canadian Task Force on Preventive Health Care – Canada Example Canadian Society of Nephrology - Canada The National Kidney Foundation / KDOQI - USA ICSI - Institute for Clinical Systems Improvement - USA World Society of the Abdominal Compartment Syndrome (WSACS) - International CDC's Advisory Committee on Immunization Practices (ACIP) – USA About ACIP GRADE The American Society of Colon and Rectal Surgeons - USA The American Academy of Sleep Medicine - USA The Belgian Health Care Knowledge Centre (KCE) - Belgium Robert Koch Institute - Germany Oficina de Evaluaci?n de Medicamentos (Servicio Extreme?o de Salud) - Spain Royal Dutch Society for Physical Therapy (KNGF) - The Netherlands American Urogynecologic Society

Arnulfo Nava, Researcher / Research Director UIEC UMAE Hosp. Especialidades CMNO IMSS / Universidad Autonoma de Guadalajara, Mexico	I have nothing to disclose.

Update of the 2011 ACR JIA Guidelines. Comments on the Project Protocol. This project properly addresses major issues regarding the use of DMARDs in Systemic JIA, such as the role of new biological agents anti-interleukin (IL)-1 and anti-IL6.The proposal of modification of treatment recommendations for Systemic JIA by defining patients into 3 main groups deserves special consideration including:

a) To define both significant systemic features and significant arthritis issues, and to clarify if these definitions correspond better to a construct.
b) This approach also requires mentioning the level for the clinical competence involved (are they considering pediatricians, rheumatologists, or general practitioners?)

Janalee Taylor, Nurse Practitioner, Assoc. Clinical Director Cincinnati Children's Hospital, USA	**Disclosure:** Was on the Original Task Force for guideline development as ARHP rep. Member of QIC Committee for ACR/ARHP Executive Committee and Board of Directors of Arthritis Foundation

Utilize guidelines in current practice also utilize as guiding document for part of quality improvement

work will be valuable for national JIA quality improvement collaborative	
No information provided.	I refuse to provide disclosure.
Tx recommendations are not phase specific enough!	