American College of Rheumatology (ACR)
Reproductive Health in Rheumatic Disease Guidelines
Response to Public Comments
January 10, 2018

We greatly appreciate the thoughtful comments from members of the rheumatology community regarding the proposed ACR Reproductive Health in Rheumatic Disease Guidelines. The questions and our responses are summarized as follows:

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Position: Assistant Clinical Professor	
Disclosure (optional): Nothing to disclose	
Comments:	
Page 4, line 89, "Long-term issues in the offspring." I wonder if this could be worded differently to also include short-term recommendations for monitoring in the offspring? Such as recommendation for CBC after birth in a baby whose mother was on an anti-TNF, etc.	We agree that monitoring of offspring should be evaluated from birth onward given the potential for medication and other effects in both the short- and long-term; we will change the focus here to "short- and long-term issues in the offspring."
Page 31, section 3C, around line 709. "In a man with RD what is the impact of receiving rheumatology medications on paternal fertility outcomes?" I wonder if this should be worded differently so that it is clear that it means the impact on long-term fertility (even after going off the medications). For instance, I expected colchicine to be listed here, since it can decrease sperm count, but it was actually addressed later on in line 1457 with paternal medication exposures.	We did not specifically differentiate between immediate and long-term paternal fertility in this question; however, per our discussion with the Guidelines Group including the Expert Panel this PICO question was intended to reflect short-term changes in fertility. We agree that colchicine should be added to the list in question 3C. We can expand the question to include permanent infertility, although we felt that based on preliminary review cyclophosphamide (CYC) was the sole rheumatic drug likely to affect long term fertility; this is addressed in question 3B that focuses on potential benefit of testosterone co-therapy versus no therapy during CYC therapy.
Perhaps section 3C and section 7A should be closer to each other (in terms of printed proximity) in the actual guidelines.	While the Guidelines Group discussed a number of organizational strategies for the PICO questions at the Scoping Meeting, our decision was to group the questions and ultimately, the Guidelines, in terms of the reproductive lifespan: that is pre-pregnancy issues, pregnancy issues and post-pregnancy issues The organization of the Guidelines may change once we review the data, however, if a more logical order becomes apparent.
Page 51, line 1229. "Regular monitoring for rheumatic disease activity and rheumatic medication management during pregnancy." Can you define what "regular" means?	We debated suggesting specific intervals and tests in this PICO question (rather than using the term "regular") but felt this was something that might be better defined after the literature

	review was completed. In general, we would define "regular" monitoring as that appropriate to the mother's illness (including disease activity and severity) as well as specific fetal risks, and generally about once per trimester or more frequently as necessary.
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Comments:	
I sincerely hope that in addition to "Counseling in anticipation of pregnancy," the GL covers the teratogenicity of oral small molecules and biologics. This is only vaguely alluded to in the background and not mentioned in the outlined plan.	We agree that while intended to include a broad range of counseling issues, the summary statement provided did not explicitly convey our intentions. We would amend this as follows: Counseling will include discussion regarding teratogenicity of all medications for women and men as well as contraceptive use in this setting.
"Fertility preservation in the setting of cyclophosphamide therapy" is singled out…what about fertility preservation with other agents?	We can expand the question to include preservation of long-term infertility with other agents, however we felt that based on our preliminary review cyclophosphamide (CYC) was the sole rheumatic drug likely to affect long-term fertility. Inclusion of other medications was discussed and considered at the Scoping Meeting with the Guidelines Group including the Expert Panel: the consensus was that given the broad scope of our topic and the already large number of PICO questions, our focus should be on the agent that we know has a long-term effect. Evaluation of other agents could be addressed if necessary in future Guidelines.
This project plan seems to focus primarily on women's issues, as it should, but is somewhat neglectful of male issues. For example, the statement "contraceptive methods tend to be underutilized by reproductive-aged women with rheumatic disease" is certainly true, but why no mention about male use of contraceptives? What about data regarding sperm viability, etc.? The participants in this projects are disproportionately female (I'm glad to say!), but the relevant topics should be covered for males. As far as scoping is concerned, I hope more peripheral topics such as gynecomastia, libido, etc., are at least put on	We agree that contraception as a topic necessarily involves both males and females. We did not consider permanent methods of contraception such as vasectomy. We are not aware of published studies addressing contraceptive use by males with rheumatic disease, however, and reversible male contraception primarily involves use of barrier contraceptives (condoms) which are less effective and thus not recommended for use unless other options are contraindicated. This is of course separate from the role of condoms in preventing sexually transmitted

the list of possible PICO questions, even if not addressed in the initial iteration of these guidelines.	disease, a subject we had initially included in our scope but which was deleted upon discussion at the Scoping Meeting due to the already broad scope of our topic. (We did, as mentioned, consider other related issues for both males and females in our initial outline, including HPV infection, treatment and vaccination and reproductive malignancies. These can perhaps be considered in future Guidelines updates.)
Please disregard my prior comment re: male issues. I did not see the appendix with PICOs initially and it does appear that male issues are addressed in PICO 3C and 3B and 7A.	
Line 243 ("7. Safety of paternal medication exposure") probably belongs in pre-pregnancy.	We discussed the organization of the questions a great deal and agree that it is difficult to "place" the medication discussion since this obviously needs to be considered both before and during pregnancy. We ultimately tried to place specific and common questions about discontinuation (or substitution) of medications in the pre-pregnancy section. The medication effects during pregnancy would be included in pre-pregnancy counseling and considered throughout pregnancy as well.
Line 849 PICO 4E does not identify an intervention…it is not in PICO format, as best as I can tell. A PICO question that does require the project to address the issue of disease risks might be "in pts with RD, does counselling (versus no counselling) recommended for certain diseases or levels of disease activity lead to better outcomes?" That's a rough sketch out, but hopefully it leads somewhere.	We agree that question 4E is atypical compared to the other PICO questions: the intention was to allow us to identify what effect, if any, underlying rheumatic disease in the parent has on the long-term outcome of offspring in terms of neuro-developmental issues and eventual development of autoimmune disease. This is a frequent question asked by patients during pre-pregnancy / pregnancy counseling and we hoped to provide information to be used by the general rheumatologist when counseling their patients.
While mycophenolate and non-TNFi garner specific PICOs around relative safety of one agent versus another, I hope that PICOs were constructed for other agents that will be addressed in the future (MTX, for instance).	Due to the broad scope of the project, we eliminated some proposed specific PICO questions regarding agents that are currently considered to be contraindicated during pregnancy and lactation. We tried to focus on common clinical issues of medication substitution in the specific questions but we will be commenting on all rheumatic medications in the Guidelines. We agree that these agents merit further evaluation, especially as new data become available, and would hope to include this in a future Guidelines update

There needs to be some general comment about the relative dangers of DMARDs in pregnancy…perhaps a table that lists agents in terms of most dangerous to least dangerous as a way to address the innumerable potential agent-to-agent comparisons.	We hope to effectively convey the both the risks and benefits of DMARD / immunosuppressive use during pregnancy. Question 5C attempts to specifically address this issue (5C: In women with RD with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy [listed] versus no immunosuppressive therapy on maternal and pregnancy outcomes?) In general, our goal is to help the general rheumatologist balance the very real risk of untreated active disease against the risk of the medication and we will convey this as clearly as possible in the Guidelines. We agree that the use of Tables will be very helpful for the broad topic of reproductive health and do plan to include these where appropriate to simplify what might otherwise be lengthy text. The risk of medications cannot be presented in a rank order, however, since our intention is to present the data for each drug and allow the treating rheumatologist to weigh the relative differences for each individual patient. As new data become available, we would plan to include this information in future Guidelines updates.
Maybe I missed it, but the other practice that is frequently done for which I see no PICO is continuing DMARD/TNFi vs. switching to low-dose prednisone.	Again, due to the very broad nature of this particular Guidelines topic we eliminated some questions on which we felt there was general consensus. Most authorities are comfortable continuing TNFi during pregnancy through the first or second trimester, as detailed in the EULAR and British Society of Rheumatology guidelines on medication use in pregnancy. Skorpen CG, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the rheumatic diseases. 2016 Feb 17:annrheumdis-2015. Flint J, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology. 2016 Sep 1;55(9):1693-7.

Another question around reproductive health is the question of genetic testing (HLAB27, for example, in unaffected children of adults with axSpA)…more PICOs to file away on the "eventually we will get there" list. Thanks for all your hard work on this.	As alluded to above, the broad scope of the topic of reproductive health in rheumatic diseases gave rise to much spirited discussion during our Scoping Meeting in August 2017. This particular topic, as well as others mentioned above, may be addressed in future guidelines/updates. We have tried to address what we felt were the most pressing questions in this initial project; in fact, several of the Core Team members polled colleagues within their respective rheumatology divisions prior to PICO question development in an attempt to help focus our questions on those topics for which general rheumatologists most commonly requested guidance.