SUPPLEMENTARY APPENDIX 12: Detailed background and justification for good practice statements and recommendations for medication use for men and women planning to conceive, and for women during pregnancy and lactation

2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases

Paternal medication use:

In rheumatic and musculoskeletal disease (RMD), the issues regarding medication use are different in men who are planning to conceive compared to those sexually active with a pregnant partner. Preconception, there may be concerns regarding effects of the medication on fertility or whether medication taken during spermatogenesis is teratogenic. A decision to discontinue a medication prior to conception must be weighed against the potential impact of stopping a medication on disease activity.

When his partner is pregnant, the primary concern is whether a medication taken by a male patient transfers through the vaginal mucosa, crosses the placenta, and is teratogenic, i.e., interferes with normal development of the embryo or fetus. The potential post-conception exposure of the embryo or fetus is thought to be minimal, the rationale being that the dose of medication transferred in semen is negligible because of the small volume of semen transferred (1) In support of this supposition, there are no published reports of male-mediated teratogenesis due to RMD medications used post conception.

There are limited data regarding either pre- or post-conception paternal use of rheumatology medications. Recommendation statements reflect three types of information quality: a) medications with at least some data on paternal exposure; b) medications for which accumulated clinical experience of paternal exposure guided the recommendation; or c) medications where there are no data on paternal exposure, but the medications are known to be teratogenic. No recommendations were developed for several newer medications with no class level or drug-specific data available.

In all cases, clinical decisions to continue or discontinue medications in males planning pregnancy should be individualized and be based on discussion and shared decision making in advance of a planned pregnancy. In most situations in which the father is being treated and his partner is pregnant, reassurance regarding lack of potential harm is warranted.

This guideline does not make specific recommendations regarding paternal exposure to prednisone, IVIG, aspirin, heparin, low-molecular weight heparin and warfarin. These medications – with the exception of warfarin and full dose aspirin – are commonly prescribed to pregnant women without concern. Review of relevant indirect literature for paternal exposure to these medications was beyond the scope of this analysis, but concerns about either fertility or pregnancy effects have not been raised over many years.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We strongly recommend discontinuing cyclophosphamide (GS133)	Not graded*

GS133. Justification for strong recommendation:

We recommend men planning to father a child discontinue cyclophosphamide (CYC) therapy before attempting to conceive. Based on compelling animal literature, the recommendation that potential fathers discontinue CYC in anticipation of pregnancy is strong. In mice, rats, and hamsters male exposure to cyclophosphamide induces genetic damage and alters structure and number of chromosomes. The animal literature suggests that these risks are reduced or eliminated 5-12 weeks after discontinuation of treatment. We recommend discontinuing this medication in men 12 weeks prior to attempting conception (2).

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing methotrexate (GS101)	Very low

GS101. Justification for conditional recommendation:

We recommend that men planning to father a child within the next three months continue methotrexate therapy. This recommendation is conditional based on several reassuring studies of pregnancy outcomes when fathers have been treated with low dose methotrexate. A German study that compared outcomes of pregnancies of 113 fathers exposed to low dose methotrexate (median dose 15

mg/week) within three months prior to conception to 412 pregnancies conceived by fathers not treated with this medication found no significant differences between groups in major birth defects or spontaneous abortion outcomes (3). Four additional studies may contain overlapping cases. The first two studies used nationwide administrative data from Denmark (4,5), comparing birth outcomes for 127 and 193 fathers exposed to methotrexate in the three months prior to conception to all other birth outcomes in the same period. No increased risks for major birth defects, stillbirth, preterm birth or small for gestational age infants were found in the exposed infants. Two studies from Norway (6,7) included 49 and 8 methotrexate-exposed fathers; and neither found increased risks for major birth defects.

The recommendation is conditional rather than strong because of compelling data that maternal use of methotrexate is associated with an increased risk of major birth defects and other adverse pregnancy outcomes. In addition, this guideline's recommendation disagrees with the methotrexate package label that recommends discontinuation of methotrexate in men three months prior to conception.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing leflunomide (GS108)	Not graded*

GS108. Justification for conditional recommendation:

We recommend that men planning to father a child within the next three months continue leflunomide therapy. The recommendation for potential fathers to continue leflunomide is conditional as there are only indirect data regarding the safety of leflunomide exposure. Teriflunomide, the metabolite of leflunomide, is used for the treatment of multiple sclerosis. No major birth defects were reported (8) in children fathered by 22 males being treated with teriflunomide during clinical trials. Although no data suggest an effect on sperm quality, if treated males experience difficulty conceiving, an evaluation of sperm may be warranted.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing mycophenolate mofetil/ mycophenolic acid (GS119)	Not graded*

GS119. Justification for conditional recommendation:

We recommend that potential fathers continue mycophenolate mofetil/ mycophenolic acid. Data on paternal exposure to mycophenolate mofetil/mycophenolic acid in non-RMD patient populations are reassuring. In a study of 350 Norwegian pregnancies fathered by 230 men, 155 were treated with mycophenolate mofetil and 195 were not (9).There were no significant differences between those whose fathers were treated and those who were not in rates of major birth defects or average birth weights. The U.S. National Transplantation Pregnancy Registry (10) published a descriptive analysis of 205 pregnancies fathered by 152 men treated with mycophenolic acid products . Although there was no comparison group, rates of major birth defects,

spontaneous abortion, and preterm delivery were similar to general population rates. The recommendation is conditional based on the lack of direct data regarding paternal exposure for treatment of RMD and the knowledge that maternal exposure to these drugs is associated with birth defects.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend <u>discontinuing</u> thalidomide (GS139)	No evidence

GS139. Justification for conditional recommendation:

We recommend that men planning to father a child discontinue thalidomide therapy at least four weeks prior to attempting conception. This recommendation is conditional because there are no direct data on paternal exposure to this drug in men with RMD. The Voting Panel discussed this recommendation extensively. While the risk of transmitting thalidomide to the developing fetus through seminal fluid is unlikely, there is concern about the high rate of teratogenicity after maternal exposure (limb reduction and other congenital anomalies occur in up to 50% of fetuses exposed in the critical gestational window of days 20-36 after conception; animal data suggest that exposures later in pregnancy may also be harmful) (11).

In the semen of two men treated for 4-8 weeks with a dose of 100 mg/day, thalidomide levels ranged from 10-250 ng/g of semen (12). There is no known threshold dose for the teratogenic effect of thalidomide in humans. The current guidelines for males in the Risk Evaluation and Mitigation Strategies (REMS)

pregnancy prevention program for lenalidomide and thalidomide require that men treated with thalidomide consistently use barrier contraception (latex condoms) to prevent exposure through semen to a sexual partner of reproductive potential (13). When a man with RMD treated with thalidomide intends to father a pregnancy, the recommendation is to discontinue thalidomide treatment for at least 4 weeks or until there are no measurable levels of drug in semen. If treatment with thalidomide begins after conception, then latex condoms are required throughout pregnancy.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We strongly recommend continuing azathioprine/ 6-mercaptopurine (GS115)	Not graded*

GS115. Justification for strong recommendation:

We recommend that potential fathers continue azathioprine/ 6-mercaptopurine when required as RMD therapy. The recommendation is strong, based on indirect but reassuring evidence. No data regarding paternal exposure to azathioprine/6-mercaptopurine specifically for treatment of RMD are available, but a number of studies of paternal use of this medication are available for other patient populations. In six studies summarized in a pooled analysis, pregnancy outcomes resulting from 954 exposed men were compared to those from 1,070,487 unexposed men (14). No excess of major birth defects was found. A large Danish study found no increased risks for major birth defects, preterm birth or small for gestational age birth weight in children of 699 men treated with

azathioprine or 6-mercaptopurine within three months prior to conception, for various indications, compared to those of 1,012,624 untreated males (15).

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing classic non-steroidal anti-inflammatory drugs or Cox 2 inhibitors (GS85).	Very low

GS85. Justification for conditional recommendation:

We recommend that men planning to father a child within the next three months continue non-steroidal anti-inflammatory drug (NSAID) or Cox 2 inhibitor therapy. This recommendation for potential fathers is conditional because of very limited data. Nonetheless, these drugs have a long history of use in males without concern of teratogenicity. A Norwegian prescription database study of 705 children born to fathers exposed to non-selective NSAIDS showed no increase in incidence of major birth defects (6).

In men with RMD who are planning to father a child within three months:	Level of evidence
• We strongly recommend continuing hydroxychloroquine (GS90).	No evidence

GS90. Justification for strong recommendation:

We recommend men planning to father a child within the next three months continue hydroxychloroquine (HCQ) therapy. The recommendation is strong despite no direct data in men with RMD, based on the long history of paternal

exposure without reports of teratogenicity. The safety of this drug for maternal use and during lactation influenced the Voting Panel discussion, as did the benefits of continued HCQ on systemic lupus erythematosus (SLE) disease activity and damage accrual.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We strongly recommend continuing infliximab, etanercept, adalimumab, golimumab, certolizumab (GS143, GS146, GS149, GS152, GS155)	Very low/ Not graded*

GS143, GS146, GS149, GS152, and GS155. Justification for strong recommendation:

We recommend that potential fathers continue TNF-inhibitor therapy; the recommendation is strong is based on a combination of very low level direct evidence, indirect evidence, and the significant risk of flare if the drug were to be discontinued. A large cohort analysis, using administrative data from Denmark (16), compared outcomes of 372 singleton pregnancies that followed paternal exposure to a TNF-inhibitor to 399,498 children born to fathers not using a TNF-inhibitor and found no differences in rates of congenital anomalies, preterm delivery, or small for gestational age infants. Two other studies examined paternal exposure to TNF-inhibitors as a class in 46 (6) and 57 (7) pregnancies and found no increased risk for major birth defects. A study using the certolizumab global safety database described outcomes in 33 pregnancies with paternal exposure; outcomes were similar to that in the general population (17).

Two studies evaluated the impact of TNF-inhibitor medications as a class in seminal fluid among men with spondyloarthropathies. The first study compared semen of 23 men after 3-6 months of TNF-inhibitor therapy to that of 42 healthy controls (18). No differences in rates of oligospermia, semen volume, or sperm concentration were identified between groups. A second study compared sperm quality in 10 men with spondyloarthropathies after 12 months of treatment with TNF-inhibitors to 20 healthy control men (19). Sperm quality was no different between groups with the exception of a lower proportion of sperm aneuploidies among the TNF-inhibitor-treated men.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We strongly recommend continuing colchicine (GS97)	Not graded*

GS97. Justification for strong recommendation:

The recommendation for potential fathers to continue colchicine is based on extended Voter Panel discussion that included the long history of use of this medication without reports of teratogenicity, limited paternal data, reassuring maternal use data, and the risk of disease flare, especially for Familial Mediterranean Fever (FMF), if the drug were stopped. Limited human data on pregnancy outcome after paternal exposure to colchicine are reassuring. One observational study of 53 exposed men (222 pregnancies) with FMF suggests no increased risk of congenital malformations or pregnancy loss (20). While past reports had suggested decreased sperm motility after male exposure, recent

studies do not support a negative effect at doses used for treatment of FMF (21,22). Data supporting safety of the drug in maternal use influenced discussion and decision-making.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing sulfasalazine (GS94).	Very low

GS94. Justification for conditional recommendation:

We recommend that men planning to father a child within three months continue sulfasalazine therapy. The conditional nature of the recommendation is based on concerns regarding the documented reversible effects of this drug on sperm and the potential impact on male fertility, and not on concerns regarding teratogenicity. In men with inflammatory bowel disease, only those who continued treatment (23) had lowered sperm count, decreased motility and abnormal morphology. Semen analysis may be indicated for men taking sulfasalazine whose partners do not conceive promptly. No concerns have been raised regarding risk of major birth defects or adverse pregnancy outcomes after paternal exposure. One case series reported no birth defects in 17 children fathered by men with inflammatory joint disease treated with sulfasalazine (7).

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing cyclosporine (GS126)	Not graded*

GS126. Justification for conditional recommendation:

We recommend men planning to father a child within three months continue cyclosporine therapy. The recommendation is conditional, based on reassuring but indirect evidence from the transplantation literature that gives no adverse safety signal regarding paternal use of this medication (10). The literature supporting compatibility of the drug in pregnancy and lactation influenced discussion and decision-making.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing tacrolimus (GS130)	Not graded*

GS130. Justification for conditional recommendation:

We recommend that men planning to father a child within three months continue tacrolimus therapy. The recommendation is conditional, based on indirect evidence from the transplantation literature (10,24). There are no data on paternal exposure to tacrolimus use in RMD patients. Data supporting compatibility of the drug in pregnancy and lactation influenced discussion and decision-making.

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing anakinra (GS159)	Very low

GS159. Justification for conditional recommendation:

We recommend that men planning to father a child within three months continue anakinra. The recommendation is conditional as there are very limited data evaluating this drug's safety in men wanting to father a child. A single study included six men taking anakinra whose partners became pregnant; no adverse neonatal outcomes occurred (25).

In men with RMD who are planning to father a child within three months:	Level of evidence
• We conditionally recommend continuing rituximab (GS 163)	Very low

GS163. Justification for conditional recommendation:

We recommend men wanting to father a child within three months continue rituximab therapy. The recommendation is conditional, as it is based on very limited data. The manufacturer's global safety database described nine cases of paternal exposure to rituximab. Seven resulted in healthy offspring and two ended in spontaneous abortion (26).

Maternal medication use: conventional RMD medications

Methotrexate, mycophenolate mofetil/mycophenolic acid, cyclophosphamide, leflunomide and thalidomide are either known or suspected teratogens. The risk of congenital anomalies after in utero exposure to those medications that are known teratogens is significantly higher than the general population risk of 2-5%.

If pregnancy does occur while a patient is taking one of these medications, she should be referred to a maternal-fetal or genetics specialist for counseling.

This guideline does not make specific recommendations regarding the pregnancy compatibility of IVIG, heparin, and low-molecular weight heparin. In general, these medications are commonly used without discussion during pregnancy; review of the relevant literature was beyond the scope of this analysis. In general, no concerns have been raised with use of IVIG, low dose aspirin, heparin, or low molecular weight heparin over many years of use in pregnancy. Warfarin is teratogenic.

NSAID use:	Level of evidence
• If having difficulty conceiving, we conditionally recommend discontinuing NSAIDs while trying to conceive if disease control would not be compromised (GS86).	Very low
• If pregnant, we strongly recommend avoiding NSAIDs in the third trimester (GS87).	Not graded*
• If pregnant, we conditionally recommend non-selective NSAIDs over Cox2-specific inhibitors as compatible with pregnancy in the first two trimesters (GS88).	Not graded*

GS68. Justification for conditional recommendation:

We recommend discontinuing non-steroidal anti-inflammatory drugs (NSAIDs) if the patient is having difficulty conceiving because of concerns about risks of early miscarriage and luteinized unruptured follicle syndrome. The recommendation to

discontinue NSAIDs (if disease control would not be compromised) is conditional as it is based on conflicting and limited evidence. Two studies have shown an increased risk of miscarriage in women taking NSAIDs around conception or early pregnancy; however, the overall increase in risk was very low. Additionally, maternal age and disease, prior history of miscarriage, use of alcohol, smoking, other medication use, and differences in hot tub exposure between groups confound the results of these studies (27,28).

NSAIDs may inhibit ovulation, resulting in an increased risk for luteinized unruptured follicle syndrome (29,30)(29,30). In the prospective Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study of women with RA who wanted to conceive, NSAIDs were associated with subfertility and infertility (31). Tested as potential contraceptives due to their impact on ovulation, NSAIDs inhibit ovulation 30-50% of the time (32,33). If there is no delay in conceiving, we recommend continuing NSAIDS if necessary for disease or symptom control.

GS87. Justification for strong recommendation:

We recommend discontinuing NSAID use in the third trimester due to risk of premature closure of the ductus arteriosus. Justification for this strong recommendation is based on indirect evidence that third-trimester NSAID use may cause premature closure of the ductus arteriosus, leading to pulmonary hypertension in the fetus (34). Of note, while this is true for therapeutic doses of

aspirin, low dose aspirin (81- 162 mg daily) does not affect the ductus arteriosus and can be continued throughout pregnancy.

GS88. Justification for conditional recommendation:

We recommend continuing nonselective NSAIDs over Cox 2-inhibitors during the first two trimesters of pregnancy if clinically indicated for disease control. This is a conditional recommendation based on limited safety data regarding NSAID use during pregnancy. The conditional recommendation favoring classical NSAIDs is due to their longer and more extensive experience of use in early and mid-pregnancy. Most studies regarding NSAID safety in pregnancy involve women with a range of illnesses; these do not consistently show an increase in birth defects after NSAID exposure, but there have been reports of increased risk of ventricular septal defect or gastroschisis in offspring exposed to NSAIDs in the first trimester (35–37). One study compared 45 pregnancies with NSAID exposure and 43 pregnancies without NSAID exposure and found similar duration of pregnancy in both groups with one stillbirth in each group and two congenital anomalies in the control group (38). The data on Cox-2 inhibitors in pregnancy are limited (6,39).

In women who are pregnant or planning pregnancy:	Level of evidence
• We strongly recommend continuing hydroxychloroquine as compatible with pregnancy. (GS91).	Very low

GS91. Justification for strong recommendation:

We recommend continuing HCQ during pregnancy for potential beneficial effects on maternal and pregnancy outcome, along with data showing no risk of congenital defects in the fetus. The justification for the strong recommendation to continue HCQ prior to and during pregnancy is based on limited data that HCQ is not associated with an increased risk for congenital defects (40) and the understanding that cessation of HCQ in SLE patients during pregnancy is associated with lupus flare (41,42). Flare of SLE during pregnancy may result in organ- or life-threatening disease activity that endangers mother and fetus. Most pregnant women in published studies have taken 400 mg of HCQ daily; there are no data about the safety and efficacy of other HCQ doses. Reassuringly, small studies have not revealed ocular toxicity in infants exposed to HCQ in utero (43,44).

In women who are pregnant or planning pregnancy:	Level of evidence
• We strongly recommend continuing sulfasalazine as compatible with pregnancy (GS95).	Very low

GS95. Justification for strong recommendation:

We recommend continuation of sulfasalazine during pregnancy based on reassuring data suggesting no adverse pregnancy or neonatal outcomes. The justification for the strong recommendation is based on indirect evidence from patients with inflammatory bowel disease. One study in which sulfasalazine was used in combination with other drugs saw no adverse pregnancy outcomes (45). A theoretical increased risk of kernicterus in the newborn has not been seen at doses used in clinical practice (46,47). We recommend folic acid

supplementation prior to and during pregnancy for all women taking sulfasalazine because this drug is a dihydrofolate reductase inhibitor (48).

In women who are pregnant or planning pregnancy:	Level of evidence
• We strongly recommend continuing colchicine as compatible with pregnancy (GS98)	Not graded*

GS98. Justification for strong recommendation:

We recommend continuing colchicine during pregnancy based on reassuring pregnancy exposure data and the high risk of flare with discontinuation in certain disorders. Justification for the strong recommendation is based on recent data that suggest compatibility with pregnancy. Colchicine binds to tubulins, thereby blocking the assembly and polymerization of microtubules; it blocks mitotic cells in metaphase. While theoretically concerning, it does not appear that this effect causes human fetal anomalies (49). A systematic review and meta-analysis of 4 observational studies of 554 pregnancies in women with FMF treated with colchicine found a decrease in pregnancy loss and no increase in congenital anomalies (50). These data are reassuring for patients who rely on this drug for treatment, such as those with FMF, who do not have acceptable alternatives. Discontinuation of colchicine in these patients may lead to uncontrolled disease, which is likely to impact both maternal and pregnancy outcomes.

In women who are pregnant or planning pregnancy:	Level of evidence

• We strongly recommend discontinuing methotrexate prior to attempting conception (GS102).	Very low

GS102. Justification for strong recommendation:

We recommend discontinuing methotrexate one to three months prior to attempting conception. The recommendation to avoid methotrexate (MTX) during pregnancy is strong and based on the demonstrated teratogenicity of this drug. MTX exposure during the first trimester in doses used to treat rheumatologic disease is associated with spontaneous abortion and congenital anomalies (3). Weber-Schoendorfer et al. reported a 6.6% rate of congenital anomalies in methotrexate-exposed RA pregnancies, double the rate seen in pregnancies of women with RA without MTX exposure (3). The most critical weeks of exposure are between 6-8 weeks after fertilization (51). There is disagreement about the time between MTX exposure and conception that poses risk. The U.S. medication package insert recommends stopping MTX one ovulatory cycle prior to conception; most experts recommend 3 months (51–54). The data on pregnancies conceived within 3 months of MTX exposure for treatment of RMD or in a subsequent pregnancy following previous treatment with methotrexate for an ectopic pregnancy do not show higher rates of pregnancy loss or congenital anomalies (53,55). The Voting Panel was unable to agree on a specific time for discontinuation of MTX prior to pregnancy and recommends that the decision regarding when to stop MTX prior to conception be discussed between physician and patient after review of the limited, but reassuring, data.

In women who are pregnant or planning pregnancy:	Level of evidence
• If treated with leflunomide within 24 months, we strongly recommend demonstrating that blood levels are undetectable, or initiating a cholestyramine washout until drug levels are undetectable, prior to attempting conception (GS109).	Very low
• If an inadvertent pregnancy occurs while using leflunomide, we strongly recommend discontinuing leflunomide and initiating a cholestyramine washout until drug levels are undetectable (GS110).	Very low

GS109 and GS110. Justification for strong recommendation:

We recommend stopping leflunomide prior to pregnancy and initiating an appropriate washout with cholestyramine; the recommendation is strong based on very low-level data regarding teratogenicity in rodents, an appreciation of the prolonged half-life of this drug, and the potential long-term adverse effects of major congenital anomalies on both child and parent. Reassuringly, when washed out with cholestyramine, use of leflunomide prior to and very early in pregnancy is not associated with a specific pattern of congenital anomalies or pregnancy loss in humans (56–59). We suggest discontinuing leflunomide prior to attempting conception, and checking the metabolite (teriflunomide) level; if it is detectable, administer cholestyramine 8g for a total of 33 doses, generally 3 times per day for 11 days. Once washout is completed, repeat measurement of the teriflunomide level (consider further cholestyramine dosing if there is still a detectable drug level). If leflunomide has been taken during conception and early pregnancy, we suggest immediate discontinuation of leflunomide and prompt cholestyramine washout to confirm an undetectable teriflunomide level.

Referral to maternal fetal medicine and/or genetic counseling is recommended after inadvertent exposure.

In women who are pregnant or planning pregnancy:	Level of evidence
• We strongly recommend continuing azathioprine/6-mercaptopurine as compatible with pregnancy. (GS116).	Very low

GS116. Justification for strong recommendation:

We recommend continuing azathioprine (AZA), and 6-mercaptopurine, its major metabolite, during pregnancy when immunosuppressive therapy is required. The recommendation is strong, based on indirect but reassuring evidence from use in non-RMD pregnant populations. Transplacental transfer of these drugs is limited, with infants having serum levels that are <5% of maternal levels of metabolites; including the inactive metabolite thiouric acid, the main metabolite that transfers (60,61). AZA is widely used in the management of pregnancy in women with solid organ transplantation, inflammatory bowel disease (IBD), and rheumatologic disease. Some, but not all, observational studies found increases in preterm birth with AZA use; it is not clear if this is due to a drug effect or underlying maternal disease (62–64). A meta-analysis of 3045 IBD pregnancies found no increase in congenital anomalies or low birth weight but an increase in preterm deliveries (65). A single study has suggested an increase in need for special education services in offspring of women with lupus who took AZA during pregnancy (66).

In women who are pregnant or planning pregnancy:	Level of evidence
• We strongly recommend discontinuing mycophenolate mofetil/mycophenolic acid at least six weeks prior to attempting conception (GS120).	I

GS120. Justification for strong recommendation:

We recommend discontinuing mycophenolate mofetil/mycophenolic acid 3 – 6 months prior to pregnancy to avoid risk of teratogenicity and to document stable disease off drug before conception. The recommendation is strong based on data that suggest that mycophenolate is teratogenic. Exposure in utero produces a specific pattern of congenital anomalies including facial clefts, abnormal ear development, and cardiac defects (67). Due to concerns regarding teratogenicity, the FDA initiated a Risk Evaluation and Mitigation Strategy (REMS) program. This program (https://www.mycophenolaterems.com/) provides useful information to aid in pregnancy prevention while taking these drugs and provides an opportunity to report newly exposed pregnancies. The REMS program recommends discontinuation of mycophenolate medications at least 6 weeks prior to conception to avoid birth defects. However, because of the risk of flare with discontinuation, the we suggest that mycophenolate medications be discontinued 3-6 months prior to conception, to allow monitoring of disease activity after discontinuation or change to a pregnancy compatible immunosuppressive therapy.

In women who are pregnant or planning pregnancy:	

• We conditionally recommend continuing cyclosporine as compatible with pregnancy (GS127).	Not graded*

GS127. Justification for conditional recommendation:

We recommend continuing cyclosporine during pregnancy when immunosuppressive therapy is required. The recommendation to continue cyclosporine in RMD pregnancy is conditional, based on indirect evidence from use of this medication in non-RMD conditions suggesting low fetal risk and an appreciation of the risk of maternal hypertension including preeclampsia with this drug. Reassuringly, cyclosporine is not associated with congenital anomalies or pregnancy loss in extensive reports from women with solid organ transplants, inflammatory bowel disease, and rheumatologic disease (68). Cyclosporine does cross the placenta, with the fetal level 30-60% of the maternal level (69,70). Preterm delivery and low birth weight infants are more common in pregnancies exposed to this drug, but it is unclear whether this is related to the drug itself or underlying maternal disease. An estimated 10% of patients who take cyclosporine develop hypertension; maternal hypertension related to cyclosporine use should be considered and monitored for during pregnancy (68). Cyclosporine can be used after discussion with patients regarding relative risks and benefits, if alternative therapy is unsuccessful or is not tolerated.

In women who are pregnant or planning pregnancy:	
• We conditionally recommend continuing tacrolimus as compatible with pregnancy. (GS131).	Not graded*

GS131. Justification for conditional recommendation:

We recommend continuing tacrolimus therapy through pregnancy when immunosuppressive therapy is required. Justification for the conditional recommendation of pregnancy compatibility is based on limited evidence, most but not all from the transplantation population. Tacrolimus has not been associated with birth defects, but observational cohorts have identified higher rates of preterm birth, maternal hypertension, and neonatal hyperkalemia with tacrolimus use (71). Tacrolimus does cross the placenta, with the fetal concentration being roughly half the maternal level (72). Two retrospective case series of pregnant women with SLE taking tacrolimus during pregnancy demonstrated expected rates of adverse pregnancy outcomes, and no birth defects (73,74). The recommendation for use in pregnancy is conditional due to the limited evidence; tacrolimus may be used, after discussion of risks and benefits, if alternative therapy (usually azathioprine) is unsuccessful or not tolerated.

In women who are pregnant or planning pregnancy:	
• We strongly recommend <u>discontinuing</u> cyclophosphamide prior to attempting conception (GS134)	Very low
• In the case of life- or organ- threatening maternal disease in which there are no alternative therapies we conditionally recommend initiating cyclophosphamide in the second or third trimester (GS136).	Very low

GS134. Justification for strong recommendation:

We recommend discontinuing cyclophosphamide (CYC) 3 – 6 months prior to attempting conception in RMD women who are planning pregnancy. The recommendation is strong, based on limited data and indirect evidence that suggest increased risk of major birth defects in the infant. The risk for congenital anomalies is increased first trimester CYC exposure with reported limb malformations, eye abnormalities, and defects in the skeleton and palate (75). Although the level of evidence with use in RMD patients is very low (63,76) the recommendation to discontinue CYC prior to conception is strong based on evidence of its teratogenicity in other human studies and animal models. Women with RMD taking CYC often have high disease activity with life- or organ-threatening manifestations, which itself confers an increased risk for adverse pregnancy outcomes. Therefore, after extended discussion, the ACR suggests that CYC be discontinued at 3-6 months prior to conception, to allow both clearance of the medication and appropriate monitoring of disease activity after discontinuation or change to a pregnancy compatible immunosuppressive therapy.

GS136. Justification for conditional recommendation:

We recommend using CYC in women with life-threatening RMD disease activity in the second or third trimesters, and for which no alternative therapies are available. The recommendation is conditional, based on very low-level evidence suggesting limited risk of fetal harm and the high risk of maternal mortality with

untreated severe disease. In utero exposure to CYC in the second and third trimesters does not appear to be as potentially harmful to the fetus as is first trimester exposure. Women diagnosed with cancer in pregnancy are treated with chemotherapy during these trimesters, including CYC, without an increase in pregnancy loss or birth defects. However, infants are at risk for pancytopenia and impaired fetal growth (77). Available case reports of CYC in late pregnancy for women with SLE suggest a high rate of stillbirth, though this is strongly confounded by the severity of maternal disease. When a woman has severe organ- or life-threatening RMD during the second or third trimesters, intravenous CYC can be considered as a life-saving measure.

In women who are pregnant or planning pregnancy:	
• We strongly recommend <u>discontinuing</u> thalidomide prior to attempting conception (GS140).	Not graded*

GS140. Justification for strong recommendation:

The recommendation to discontinue thalidomide at least 4 weeks prior to conception is based on the drug's compelling history of teratogenicity. The recommendation is strong, based on the knowledge that thalidomide is a known teratogen that can lead to severe craniofacial and limb defects in exposed fetuses (11). While there are no human pregnancy data available on the thalidomide analog lenalidomide, it has been demonstrated to cause malformations in monkeys similar to those induced by thalidomide. As per the

package insert, lenalidomide should also be discontinued at least 4 weeks prior to pregnancy.

Maternal medication use: biologic RMD medications

TNF-inhibitor therapy:	Level of evidence
• We conditionally recommend continuing TNF-inhibitor therapy (infliximab, etanercept, adalimumab, golimumab) prior to and during pregnancy (GS144, GS147, GS150, GS153).	Very low
• We strongly recommend continuing certolizumab therapy prior to and during pregnancy (GS156).	Very low

GS 144, GS147, GS150, GS153. Justification for conditional recommendation.

We recommend continuing infliximab, etanercept, adalimumab and golimumab prior to and during pregnancy although if or when to stop these medications is controversial. The recommendation is conditional due to limited but reassuring data from RMD and inflammatory bowel disease populations. Concerns regarding potential teratogenicity and adverse effects of this class of drugs on the fetus must be balanced against the risk of uncontrolled disease activity during pregnancy and its consequences for both mother and infant. A single study addresses this specific question (78) and shows increased flare rates of inflammatory arthritis among women who discontinued TNF-inhibitor therapy compared to those who continued therapy (OR 4.95, 95% CI 2.19-11.22).

However the total number of pregnancies observed was low, and there are no other published studies.

Given that most of these molecules are IgG1 subclass constructs, there is little to no transfer during the first trimester as the placental neonatal Fc-receptors have not yet developed (79). Thus, continuation of these medications during the first trimester is conditionally recommended and is supported by a low level of evidence from observational studies of early pregnancy exposure to TNF-inhibitors that demonstrate no increase in major birth defects or other adverse outcomes compared to unexposed pregnancies (80,81). Etanercept does not contain the CH1 domain of IgG1, so placental transfer is lower than with other IgG1 subclass molecules (82). An administrative claims-based study demonstrated no increased risk of major birth defects in pregnancies exposed to etanercept (83).

Active transport of IgG1 antibodies increases during the second trimester to supersede maternal levels by delivery, resulting in a theoretical concern about neonatal immunosuppression, with susceptibility to infections and live vaccines, during the first 6 months of extrauterine life. There are no data published as of the cut-off date for this review evaluating infection risk in infants exposed to these drugs in late pregnancy. One case report described an infant antenatally exposed to infliximab who developed fatal bacille Calmette-Guérin (BCG) infection following vaccination for tuberculosis (84). Based on this case, many

experts suggest stopping TNF-inhibitors in the late second or early third trimester. Because most studies evaluate TNF-inhibitors as a class, outcomes are not available for specific agents. Observational data do not suggest an increased risk of major birth defects among infants exposed to various TNF-inhibitors during pregnancy, but controversy remains if and when to discontinue TNF-inhibitors (particularly infliximab, adalimumab, and golimumab based on their molecular structures and higher levels of placental transfer in late pregnancy) prior to delivery for fear of excessive immunosuppression in the infant.

Justification for the strong recommendation to continue certolizumab therapy during pregnancy:

We recommend continuing certolizumab prior to and during pregnancy. The recommendation to continue certolizumab therapy during pregnancy is strong due to data that support very minimal placental transfer of this drug. Certolizumab contains a polyethylene glycol (PEG) moiety rather than an Fc domain and so is not actively transported across the placenta via Fc receptors. A small placental transfer study of certolizumab has shown negligible amounts of drug transfer (85). Based on this reassuring data, the recommendation is strong to continue this medication throughout pregnancy if needed. There is no strong evidence of an increase in major birth defects or neonatal infections for any commercially available TNF-inhibitors to date, and so the risks and/or benefits of

switching a stable patient from a currently effective TNF-inhibitor for the sole purpose of lowered placental transfer during the third trimester are not known.

Rituximab:	Level of evidence
• We conditionally recommend continuing rituximab through conception (GS164)	Very low
• We conditionally recommend using rituximab during pregnancy in the setting of severe, life or organ threatening maternal disease (GS165)	Very low

GS 164 and GS 165. Justification for recommendations:

We recommend continuing rituximab prior to pregnancy until conception, and during pregnancy in the presence of severe life- or organ-threatening maternal disease. These recommendations are conditional, based on a low level of data. Like TNF-inhibitors, rituximab is a monoclonal antibody structure with an IgG1 construct, with minimal to very low transplacental transfer during the first trimester of pregnancy. Therefore, it is felt to be compatible with use through conception.

Continued use during pregnancy is more controversial. A single study documenting pregnancy outcomes following antenatal exposure to rituximab (86) showed no increase in adverse pregnancy outcomes among exposed women; however, no comparator group was studied, and many of the pregnancies were complicated by concomitant exposure to potential teratogens including methotrexate and mycophenolate mofetil. Similar to the concerns regarding

neonatal immunosuppression with antenatal TNF-inhibitor exposures in the second and third trimesters, theoretical concerns remain about persistent B-cell depletion in exposed neonates.

Because rituximab is given at 6-month intervals, or periodically for moderate to severe disease activity, a conditional recommendation for use during an established pregnancy, even in the second or third trimester, is suggested for life- or organ-threatening disease but not for stable disease.

Non-TNFi biologic agents: Including anakinra (GS160), belimumab (GS169), abatacept (GS173), tocilizumab (GS177), secukinumab (GS181), and ustekinumab (GS185)	
• We conditionally recommend continuing therapy through conception.	No evidence
• We conditionally recommend discontinuing therapy during pregnancy.	No evidence

GS160, GS169, GS173, GS177, GS181, and GS185. Justification for conditional recommendations:

We recommend women planning pregnancy continue anakinra, belimumab, abatacept, tocilizumab, secukinumab and ustekinumab through conception but discontinue these medications during pregnancy. The recommendations to continue non-TNF-inhibitor biologic therapies through conception but to discontinue these during pregnancy are conditional, as there are little or no published data. As with other biologics, these molecules contain the IgG1

component, thus placental transfer is negligible during the first trimester. Administration of drug beyond conception is not recommended, as there are no data to confirm safety of these medications.

For novel, small molecule targeted therapies: Including tofacitinib (GS189), baracitinib (GS 193), and apremilast (GS197), the committee was unable to offer recommendations regarding use during pregnancy due to lack of data.	No evidence

GS189, GS193, GS197. Justification for no recommendations:

The Voting Panel declined to vote on recommendations regarding use in pregnancy of targeted and small molecule therapies including tofacitinib, baracitinib, and apremilast. There is no evidence of their use in pregnancy outside of case reports. Furthermore, these molecules are of low molecular weight, and so are expected to cross the placenta via diffusion throughout all stages of pregnancy. Until data are available to better guide decision-making, attempts should be made to use alternative therapies for which data suggest compatibility with pregnancy. If patients choose to take these medications for any time in pregnancy or are inadvertently exposed in an unplanned pregnancy, we suggest enrollment in an FDA-approved pregnancy registry.

Maternal medication use: corticosteroids.

Use of non-fluorinated glucocorticoids during pregnancy:	Level of Evidence
• We conditionally recommend continuing chronic low dose (<10 mg daily of prednisone or non-fluorinated equivalent) during pregnancy if clinically indicated. (GS201)	Low
• We strongly recommend tapering higher doses of non-fluorinated steroids to < 20mg daily of prednisone with the addition of a pregnancy-compatible immunosuppressive agent if needed. (GS202)	Low

GS201. Justification for conditional recommendation:

We recommend continuing low dose steroid during pregnancy, if clinically indicated, because of evidence that disease control during pregnancy is important for good pregnancy outcome for mother and fetus in most RMDs (87–89). We distinguish between non-fluorinated (prednisone, prednisolone) and fluorinated corticosteroids (dexamethasone, betamethasone) because the former do not cross the placenta at low to moderate doses, so are unlikely to affect the fetus, whereas the latter do. The recommendation is conditional due to a low level of evidence, but abrupt discontinuation of glucocorticoid may precipitate a disease flare and data support the safety of glucocorticoids during pregnancy with low risk of congenital anomalies (90–92). Nonetheless, attempts should be made to carefully taper glucocorticoid dose if possible given the known risks of chronic high dose corticosteroid therapy.

GS202. Justification for strong recommendation:

We recommend tapering prednisone dose to 20 mg or less daily for pregnant women with RMD, with addition of a pregnancy-compatible immunosuppressive drug if necessary. The recommendation to taper prednisone doses of >20mg (or non-fluorinated steroid equivalent) in women with RMD is strong, based on indirect evidence suggesting that doses higher than this level increase the risk of pregnancy complications including small-for-gestational age (SGA) infants and premature rupture of the membranes (93,94). Higher doses of glucocorticoids during pregnancy also predispose to increased risk of gestational diabetes and hypertension. The addition of an alternative immunosuppressive agent compatible with pregnancy is suggested to permit safe taper of higher dose glucocorticoids, mitigating these risks.

In women using chronic low dose steroids during pregnancy: • We conditionally <u>do not</u> recommend treating with stress dose steroids at the time of vaginal delivery (GS206)	No evidence
• We conditionally recommend treating with stress dose steroids at the time of Cesarean delivery. (GS207)	Low

GS206. Justification for conditional recommendation:

We do not recommend use of stress dose steroids at the time of delivery in RMS women on chronic low dose steroids. The recommendation against use of stress

dose steroids for routine vaginal delivery in women on prednisone of >5mg a day (or non-fluorinated glucocorticoid equivalent) is based on the lack of data to either support or negate the utility of stress dose steroid in this scenario. The recommendation is conditional as individual patient scenarios vary greatly, and stress steroids may be considered in specific situations, for example, a patient on long-term high dose steroid with multiple comorbidities.

GS207. Justification for conditional recommendation:

We recommend use of stress dose steroids at the time of Cesarean section in RMD women on chronic low dose steroids. The recommendation to use stress dose steroids during Cesarean section in women who have been on prednisone >5mg a day (or non-fluorinated steroid equivalent) for more than three weeks in the six months prior to delivery is conditional, based on indirect and low level data. Adrenal suppression occurs at the aforementioned dosing regimens (95) and, in general, stress dose steroids are given for surgical procedures. Details of the patient's clinical situation will weigh heavily in this decision, which is ultimately made by the anesthesiology and obstetrics teams.

Medication use in breastfeeding:

The benefits of breastfeeding include higher quality nutrition for the infant, improved gastrointestinal function, enhanced immunity to pathogens, and reduced subsequent risk of obesity, diabetes, heart disease and cancer (96–

102). The American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months of life and continued breast feeding until age one (103) (104). Women with RMD are at risk for disease flare during the post-partum period, thus continuation, resumption or initiation of anti-rheumatic drugs is often desired. Balancing benefits of disease control with the potential risk of infant exposure through breast milk are important considerations for management decisions in breastfeeding women.

Maternal medications are transferred as unbound drug. Lipid soluble, low molecular weight, non-ionized and non-protein bound medications will readily cross into breast milk. Peak drug levels in breast milk occur several hours after the lactating woman ingests medication and vary with medication half-life (105). Drug level in breast milk less than 10% the infant therapeutic dose or the maternal weight-adjusted dose is considered safe.

Infant serum levels are a function not only of drug concentration in breast milk and the quantity of breast milk ingested but also a function of drug absorption through the infant gastrointestinal tract. Thus, premature infants and infants with poorly developed gastrointestinal tracts may absorb more undigested medication into the blood stream than do full term infants.

These guidelines do not make specific recommendations regarding the maternal use during pregnancy and lactation of IVIG, aspirin, heparin, low-molecular

weight heparin and warfarin. Review of these medications was beyond the scope of these guidelines, although these medications are used commonly in the postpartum setting without concern. High dose aspirin should be avoided in breastfeeding mothers due to the risk of Reye's syndrome in the infant (106).

No recommendations regarding use of small molecule therapies during breastfeeding are offered due to lack of any data on the safety of the small molecules tofacitanib, baracitanib, and apremilast in breastfeeding infants. However, given that these molecules have a low molecular weight they will likely readily pass into breast milk; we suggest avoiding these medications in breastfeeding women.

In women who are breastfeeding:	Level of evidence
• We conditionally recommend that NSAIDs are compatible with breastfeeding (GS89)	Not graded*

GS89. Justification for conditional recommendation:

We recommend that women with RMD who are breastfeeding can initiate NSAID therapy, preferably ibuprofen, if needed for control of RMD symptoms. The recommendation is conditional, based on the low level of evidence. There are no randomized clinical trials to evaluate safety of NSAIDs in lactation and the remainder of the literature is limited. One study on piroxicam in lactating women suggested that a nursing infant would receive under 10% of the therapeutic dose through breast milk and thus concluded that this medication was compatible with

lactation (107). LactMed lists ibuprofen as a preferred choice of NSAID in nursing mothers given its short half-life and safety in infants (108). There are no data on Cox-2 inhibitor compatibility with breast-feeding. Low dose aspirin in considered compatible with lactation. At higher aspirin doses, Reye's syndrome has been reported, thus high dose aspirin therapy should be avoided in lactating women (106).

In women who are breastfeeding:	Level of evidence
• We strongly recommend that hydroxychloroquine is compatible with breastfeeding (GS 92)	Low

GS92. Justification for strong recommendation:

We recommend that women with RMD who are breastfeeding can initiate or continue HCQ therapy. HCQ is compatible with breastfeeding, based on limited data. One case series of 13 infants exposed to HCQ in breast milk reported normal ophthalmologic exams in these children (109). The recommendation to continue HCQ in breastfeeding mothers is strong because the risk of flare of rheumatic disease is high in the post-partum period, and HCQ has been shown to protect against flares of SLE with no reported adverse effects in offspring.

In women who are breastfeeding:	Level of evidence
• We conditionally recommend that sulfasalazine is compatible with breastfeeding (GS96)	Low

GS96. **Justification for conditional recommendation:**

We recommend that women with RMD who are breastfeeding can initiate or continue sulfasalazine therapy. The recommendation that sulfasalazine is compatible with breastfeeding is conditional, based on low level evidence, data showing significant transfer of its metabolite sulfapyridine into breast milk, and low possibility of diarrhea in the offspring. Sulfasalazine is secreted at low concentrations in breast milk although its metabolite sulfapyridine is transferred at levels that reach 30-60% of those in the maternal serum (110,111). There has been one case of bloody diarrhea reported in a breast fed infant whose mother was taking full dose sulfasalazine (3grams/day) (112). In infants having diarrhea, discontinuation of sulfasalazine in the lactating mother should be considered. The American Academy of Pediatrics recommends caution in using sulfasalazine in lactating women (103).

In women who are breastfeeding:	Level of evidence
We conditionally recommend that colchicine is compatible with breastfeeding. (GS99)	Low

GS99. Justification for conditional recommendation:

We recommend that women with RMD who are breastfeeding can initiate or continue colchicine therapy. The recommendation that colchicine is compatible with breastfeeding is conditional, based on a low level of reassuring evidence. Colchicine levels in breast milk are under 10% of maternal serum levels (113). The highest level occurs 2 to 4 hours after dosing, thus avoiding nursing during

this period may be prudent. There are case reports of breastfed infants of mothers taking colchicine who have had no untoward effects (21). The American Academy of Pediatrics considers colchicine compatible with breastfeeding (103).

In women who are breastfeeding:	Level of evidence
• We conditionally recommend against using methotrexate in breastfeeding women (GS106)	Low

GS106. Justification for conditional recommendation:

We recommend that RMD women do not use methotrexate therapy while breastfeeding. The recommendation against using methotrexate in lactating women is conditional, based on indirect and low level evidence. While the level of methotrexate secreted in breast milk is low, and the resulting infant exposure is well below the threshold of 10% of maternal dose (114), the hypothetical concern that this medication may accumulate in neonatal tissue has led the American Academy of Pediatrics to recommend avoiding methotrexate in breastfeeding women (103). Further study is needed to clarify this issue, as methotrexate is a mainstay of treatment for inflammatory arthritis patients, and no clinical data supporting neonatal tissue accumulation could be identified.

In women who are breastfeeding:	Level of evidence
• We strongly recommend against using leflunomide in breastfeeding women (GS113)	No evidence

GS113. Justification for strong recommendation:

We recommend that RMD women do not use leflunomide therapy while breastfeeding. The recommendation against using leflunomide in breastfeeding women is strong, based on a lack of data, extrapolation from the strong recommendation to avoid this medication during pregnancy, and the drug's known long half-life. There are no data on leflunomide transfer to breast milk, or regarding its safety in breastfed infants. We recommend against use during lactation until more data are available.

In women who are breastfeeding:	Level of evidence
• We conditionally recommend that azathioprine and 6-mercaptopurine are compatible with breastfeeding (GS117)	Low

GS117. Justification for conditional recommendation:

We recommend that women with RMD who are breastfeeding can initiate or continue AZA (or its metabolite 6-mercaptopurine). The recommendation that AZA and 6-mercaptopurine are compatible with breastfeeding is a conditional one, based on a low level of reassuring evidence. AZA is metabolized to 6-mercaptopurine. This metabolite's level in breast milk is under 1% of the maternal weight-adjusted dose (115–117). Given the potential theoretical risk for fetal immunosuppression, concerned patients may wish to either avoid breastfeeding or to pump and discard breast milk for the first four hours after

taking this medication. In cases of frequent infant infections, one should consider checking TPMT levels as well as a complete blood count in the child.

In women who are breastfeeding:	Level of evidence
• We strongly recommend <u>against</u> using mycophenolate mofetil/ mycophenolic acid while breastfeeding (GS124)	No evidence

GS124. Justification for strong recommendation:

We recommend that RMD women do not use mycophenolate mofetil or mycophenolic acid therapy while breastfeeding. The recommendation against using mycophenolate therapies in breastfeeding women is strong and based on indirect evidence and theoretical concerns. There are no data on the transfer of mycophenolate to breast milk or its safety in breastfed infants. Given its small size and long half-life there are theoretical concerns regarding its transfer and accumulation in breast milk. We recommend against use during lactation until further data are available.

In women who are breastfeeding:	Level of evidence
• We conditionally recommend that cyclosporine is compatible with breastfeeding(GS128)	Low

GS128. **Justification for conditional recommendation:**

We recommend that women with RMD who are breastfeeding can initiate or continue cyclosporine. The recommendation that cyclosporine is compatible with

breastfeeding is conditional, based on limited data and concern about possible variability in infant levels, with some studies reporting levels well below the recommended 10% of maternal dose and other studies suggesting that the infant level is much higher (118,119). Given this finding, infants exposed to cyclosporine in breast milk should be monitored clinically and if an infant develops recurrent infections one should consider checking drug level in the infant.

In women who are breastfeeding:	Level of evidence
• We conditionally recommend that tacrolimus is compatible with breastfeeding (GS132)	Low

GS132. **Justification for conditional recommendation:**

We recommend that women with RMD who are breastfeeding can initiate or continue tacrolimus therapy. The recommendation that tacrolimus is compatible with breastfeeding is conditional, based on low level but reassuring data. This medication is highly protein bound and thus little is likely to be transmitted into breast milk. One study has shown the maximal absorption from breast milk to be < 0.23% of the maternal weight-adjusted dose (120–122).

In women who are breastfeeding:	Level of evidence
• We strongly recommend <u>against</u> using cyclophosphamide while breastfeeding (GS137)	Low

GS137. Justification for strong recommendation:

We recommend that RMD women do not use cyclophosphamide while breastfeeding. The recommendation against using cyclophosphamide in breastfeeding women is strong based on limited data with significant clinical effects noted in breastfed infants. Cyclophosphamide is transferred into breast milk (123) and there are case reports of neutropenia in infants exposed to cyclophosphamide during breastfeeding (124,125).

In women who are breastfeeding:	Level of evidence
• We strongly recommend <u>against</u> using thalidomide while breastfeeding (GS142)	No evidence

GS142. Justification for strong recommendation:

We recommend that RMD women do not use thalidomide while breastfeeding. The recommendation against using thalidomide in breastfeeding women is strong based on the concern that given thalidomide's strong teratogenicity, it could potentially affect infant development. There are no data on thalidomide transfer to breast milk or its safety in breastfed infants.

In women who are breastfeeding:	Level of evidence
• We strongly recommend that TNF-inhibitors as a class: infliximab, etanercept, adalimumab, golimumab (no-data), certolizumab are compatible with breastfeeding (GS143, GS146, GS149, GS152, GS155)	Low

GS145, GS148, GS151, GS154, and GS155. Justification for strong recommendations:

We recommend that women with RMD who are breastfeeding can initiate or continue therapy with infliximab, etanercept, adalimumab, certolizumab and golimumab. The recommendation that TNF-inhibitors are compatible with breastfeeding is strong based on limited but reassuring data as well as breast milk physiology. These molecules are large and protein bound so that little, if any, will be transferred to breast milk. Moreover, any small amount of drug that is transferred to breast milk is unlikely to be absorbed by the infant's gastrointestinal tract. However, there are no data regarding absorption in preterm infants who may not have a fully developed gastrointestinal tract. Minimal to no levels of infliximab have been detected in breast milk of lactating women (79,126). Infant levels in breastfed infants are well below the 10% maternal dose (127). Minimal to no levels of etanercept or adalimumab have been detected in breast milk of lactating women (128–132). Similarly, data show no detectable certolizumab levels in breast milk (133). While there are no data available on the use of golimumab during breastfeeding, its large size (MW 150,000) suggests that the amount transferred into breast milk is likely to be minimal.

In women who are breastfeeding:	Level of evidence
• We conditionally recommend that anakinra is compatible with breastfeeding (GS161)	No evidence

• We strongly recommend that rituximab is compatible with breastfeeding (GS166)	Low/ Not graded*
• We conditionally recommend that belimumab is compatible with breastfeeding (GS170)	Low/ Not graded*
• We conditionally recommend that abatacept is compatible with breastfeeding (GS174)	No evidence
• We conditionally recommend that tocilizumab is compatible with breastfeeding (GS178)	Low
• We conditionally recommend that sekukinumab is compatible with breastfeeding (GS182)	No evidence
• We conditionally recommend that ustekinumab is compatible with breastfeeding (GS186)	No evidence

GS161. Justification for conditional recommendation:

We recommend that women with RMD who are breastfeeding can initiate therapy with anakinra. The recommendation that anakinra is compatible with breastfeeding is conditional based on indirect evidence and breast milk physiology. While there are no data on the transfer of anakinra into breast milk, or corresponding infant levels, given the large size of this molecule it is unlikely that significant amounts will be transferred. Moreover, any small amount of drug that is transferred to breast milk is unlikely to be absorbed by the infant's gastrointestinal tract.

GS166. Justification for strong recommendation:

We recommend that women with RMD who are breastfeeding can initiate or continue therapy with rituximab. The recommendation that rituximab is

compatible with breastfeeding is strong, based on data that show that transmission of rituximab into breast milk is very low (134,135). Any small amount of drug that is transferred to breast milk is unlikely to be absorbed by the infant's gastrointestinal tract. Given that rituximab is used for severe RMD, if the mother requires rituximab for disease control, breastfeeding can be continued.

GS170, GS174, GS178, GS182, and GS186. Justification for conditional recommendations:

We recommend that women with RMD who are breastfeeding can initiate or continue therapy with belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab. The recommendation to use these non-TNF-inhibitor biologic therapies is conditional and based on indirect evidence and breast milk physiology. The large molecular weight of these protein bound molecules suggests that little drug will be transferred to breast milk. Moreover, any small amount of drug that is transferred to breast milk is unlikely to be absorbed by the infant's gastrointestinal tract. In support of this supposition, very low amounts of tocilizumab (136) and ustekinumab (137), well below the recommended 10% of maternal weight adjusted dose, have been found in breast milk.

In women who are breastfeeding:	Level of evidence
• We strongly recommend that prednisone <20mg a day (or non-fluorinated equivalent) is compatible with breastfeeding (GS204)	Low
• We strongly recommend that women using prednisone >20mg a day (or non-fluorinated steroid	Low

	equivalent) delay breastfeeding or discard breast milk for the four hours following steroid administration (GS205)	

GS204. Justification for strong recommendation:

We recommend that women with RMD who are breastfeeding can initiate or continue low dose non-fluorinated corticosteroid. The recommendation that <20 mg daily prednisone (or equivalent) are compatible with breastfeeding is strong, based on evidence that glucocorticoid exposure through breast milk does not cause untoward effects in the infant (138,139). Women with RMD are at risk for flare in the post partum period, thus good disease control is essential.

GS205. Justification for strong recommendation:

We recommend that women with RMD who are breastfeeding can initiate or continue higher dose non-fluorinated corticosteroid but avoid feeding the infant within four hours of steroid dose. The recommendation that women using prednisone ≥20mg a day (or non-fluorinated steroid equivalent) either delay breastfeeding or discard breast milk for the first four hours following steroid administration in order to reduce the risk of infant exposure is strong and based on data suggesting peak drug levels occur during this time period (138).

*Not graded: Evidence was indirect and derived from additional informal literature reviews of medications and procedures in non-RMD populations, as detailed in Methods (Appendix 1).

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