# The Monoclonal Antibody Medications in inflammatory Arthritis: stopping or continuing in pregnancy (MAMA) trial

# Protocol

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**Conflict of interest:** There are no conflicts of interest to declare

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# 1 KEY TRIAL CONTACTS

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# 2 LAY SUMMARY

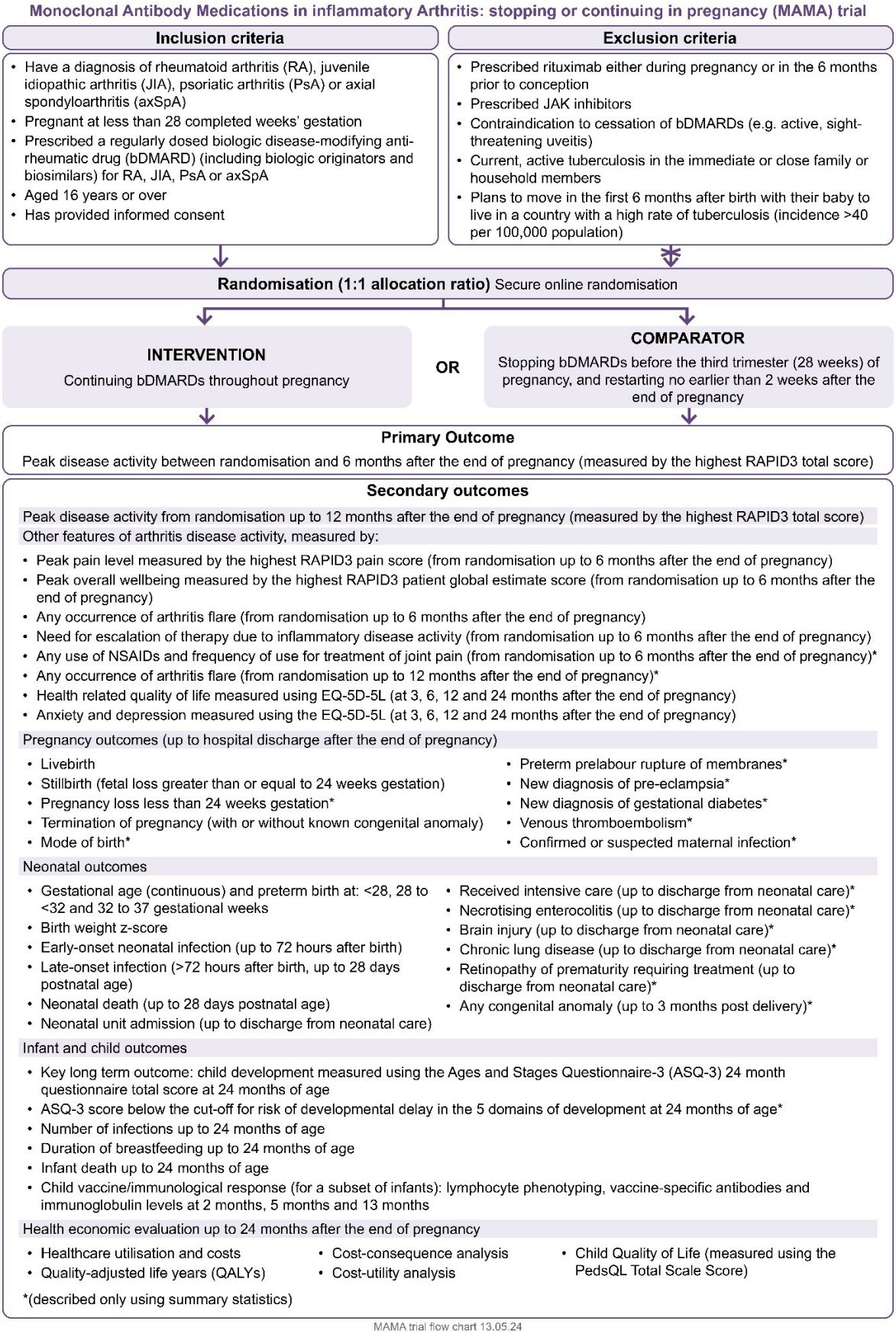
1–2% of women are affected by inflammatory arthritis such as rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis or juvenile idiopathic arthritis. Many are treated with new medications known as 'biologics'. More women with inflammatory arthritis are considering starting a family, because treatment with biologics means they are more able to manage their arthritis. They may need to make difficult decisions around treatments during pregnancy.

Uncontrolled arthritis can lead to worse outcomes in pregnancy, so managing arthritis well is very important. Biologics are often avoided during pregnancy because of limited understanding of how these drugs impact pregnancy or arthritis activity during this time. There are concerns about possible effects of these drugs on infants' immune systems, and some infant vaccinations are routinely delayed. Until recently, most women were advised that they should stop their biologic drugs during pregnancy and avoid these drugs in the second and third trimester; however, due to mounting evidence of their safety for women and babies during pregnancy, the 2022 national guidance now states that women can stay on biologics throughout pregnancy. It is currently unknown whether there is any benefit to this strategy in terms of arthritis disease control. We also know that certain other medicines used to treat arthritis flares in pregnancy, such as steroids, can pose potential harm.

The **M**onoclonal **A**ntibody **M**edications in inflammatory **A**rthritis (MAMA) trial aims to find out the effects of stopping or continuing biologics during pregnancy. It will compare whether women who continue their biologics throughout pregnancy have better arthritis control compared to those who stop, and assess the impact on their pregnancy, their infant, and the costs associated with this decision.

MAMA will recruit 328 women who will have an equal (random) chance to continue their biologic throughout pregnancy, or to stop by the end of the sixth month of pregnancy. During pregnancy women will be asked to complete a simple arthritis symptom severity questionnaire, known as RAPID3, monthly via an app (or in written format). After the baby is born, the woman will be asked to report her symptoms using the RAPID3 questionnaire at 3, 6 and 12 months. Women and infants will be followed up for up to 24 months after the end of pregnancy, to assess general health and their infant's development. A subset of infants, for whom their families have consented, will have blood tests to explore the impact of exposure to biologics during pregnancy on their developing immune system.

# 3 TRIAL FLOW CHART



# 4 SYNOPSIS

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|---|---|
| **Trial title** | The Monoclonal Antibody Medications in inflammatory Arthritis: stopping or continuing in pregnancy (MAMA) trial |
| **Short title** | The MAMA Trial |
| **Trial registration** | ISRCTN Ref: 89126536<br>Date of Registration: 23/10/2024 |
| **Sponsor** | University of Oxford |
| **Funder** | NIHR Health Technology Assessment (HTA) Programme (NIHR153577) |
| **Clinical Phase** | Phase III |
| **Trial Design** | Multicentre, pragmatic, two-arm, parallel-group, unblinded randomised controlled trial, with an internal pilot and an integrated health economic analysis, co-designed with lived experience contributors. |
| **Trial Participants** | Pregnant women less than 28 completed weeks of gestation prescribed a regularly dosed biologic disease-modifying anti-rheumatic drug (bDMARD) for Autoimmune Inflammatory Arthritis (AIA). |
| **Sample Size** | 328 women (164 per trial arm) individually randomised in approximately 35 obstetric units with a maternal medicine service in the UK. |
| **Planned Trial Period** | The total planned duration of the trial is 72 months: from 01/03/2024 (grant start) to 28/02/2030 (grant end).<br><br>Randomisation can occur any time up until the 28th week of gestation. The duration of participation will be up to 24 months after the end of pregnancy: all women and children will be followed up to 12 months after the end of pregnancy, with a reduced cohort followed up to 24 months after the end of pregnancy. |
| **Planned Recruitment period** | 48-month recruitment period including a 16-month internal pilot, planned for 01/09/2024 to 31/08/2028 |
| **Primary Objective** | To compare the peak of disease activity from trial entry up to 6 months after the end of pregnancy in pregnant women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs before the third trimester of pregnancy. |
| **Secondary Objectives** | In pregnant women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs before the third trimester of pregnancy:<br>To compare the peak of disease activity up to 12 months after the end of pregnancy<br>To compare other features of arthritis disease activity from randomisation up to 24 months after the end of pregnancy<br>To investigate pregnancy outcomes up to hospital discharge after the end of pregnancy<br>In babies born to women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs:<br>To compare neonatal outcomes up to 3 months post-delivery |

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|---|---|
| | To investigate infant and child outcomes including global development at 24 months of age, infection, infant death, and duration of breastfeeding up to 24 months of age, and in a subset of infants to investigate immune function (including response to vaccines) at 2, 5 and 13 months.<br>To examine using an economic evaluation, whether any additional benefits associated with continuing bDMARDs are justified by any additional health care resources needed up to 24 months after the end of pregnancy. |
| **Intervention** | Continuing bDMARDs throughout pregnancy.<br>The drug, dose and frequency of administration is at the discretion of the prescribing clinician, and all other aspects of clinical care are determined by the treating clinical team. |
| **Comparator** | Stopping bDMARDs before the third trimester (28 weeks) of pregnancy, and restarting no earlier than 2 weeks after the end of pregnancy. |

Assessment of acceptability to women and clinicians will be developed using co-applicants and patient and public involvement advisory group with amendments made to the protocol and study documentation as required.

# 5 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AIA | Autoimmune Inflammatory Arthritis |
| AR | Adverse reaction |
| ASQ-3 | Ages & Stages Questionnaires®, Third Edition |
| AxSpA | Axial spondyloarthritis |
| BCG | Bacillus Calmette-Guérin (vaccine against tuberculosis) |
| bDMARD | Biologic disease-modifying anti-rheumatic drug |
| CI | Chief Investigator |
| CRA | Clinical Research Associate (Monitor) |
| CRF | Case Report Form |
| CRN | Clinical Research Network |
| CRO | Contract Research Organisation |
| CTA | Clinical Trials Authorisation |
| CTU | Clinical Trials Unit |
| DMARD | Disease-modifying anti-rheumatic drug |
| DMC | Data Monitoring Committee |
| DSUR | Development Safety Update Report |
| EULAR | European Alliance of Associations for Rheumatology |
| FBC | Full blood count |
| GC | Glucocorticoid |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HIE | Hypoxic-ischaemic encephalopathy |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| Ig | Immunoglobulin |
| IMP | Investigational Medicinal Product |
| IRB | Independent Review Board |
| IQR | Interquartile range |
| JAK | Janus Kinase |
| JIA | Juvenile idiopathic arthritis |
| MAMA | Monoclonal Antibody Medications in inflammatory Arthritis |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NHS | National Health Service |
| NIHR | National Institute for Health and Care Research |
| NPEU | National Perinatal Epidemiology Unit |
| NSAID | Non-steroidal anti-inflammatory drugs |
| OVC | Oxford Vaccine Centre |
| OVG | Oxford Vaccine Group |
| OUH | Oxford University Hospitals |
| PedsQL | Paediatric Quality of Life |
| PI | Principal Investigator |
| PIL | Participant/Patient Information Leaflet |

| | |
|---|---|
| PBMC | Peripheral Blood Mononuclear Cell |
| PPIE | Patient and Public Involvement and Engagement |
| PsA | Psoriatic arthritis |
| QALYs | Quality-adjusted life years |
| R&D | NHS Trust R&D Department |
| RA | Rheumatoid arthritis |
| RAPID3 | Routine Assessment of Patient Index Data 3 |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| RGEA | Research Governance, Ethics and Assurance |
| CRSI | Collated Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SAM | Synthetic Absorptive Methods |
| SD | Standard deviation |
| SDV | Source Data Verification |
| SmPC | Summary of Medicinal Product Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| tsDMARD | Targeted synthetic disease-modifying anti-rheumatic drug |
| TMF | Trial Master File |
| TNF | Tumour Necrosis Factor |
| TNFi | Tumour Necrosis Factor Inhibitor |
| TSC | Trial Steering Committee |

# 6 BACKGROUND AND RATIONALE

## 6.1 The problem being addressed

Autoimmune inflammatory arthritides (AIA) are devastating, potentially joint destroying conditions, affecting 1-2% of people. AIA includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (AxSpA) and juvenile idiopathic arthritis (JIA). These AIA collectively affect many women during their reproductive years.

Disease-modifying anti-rheumatic drugs (DMARDs) are medications which treat AIA conditions, and work by reducing inflammation and improving symptoms such as pain and stiffness. There are various types of DMARDs; the “conventional” group which have been around for many years, and include medications such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, many of which have known harms to the developing fetus. Biologic DMARDS (bDMARDs) are a newer group of medical therapies. These medications block very specific aspects of the immune system involved in joint inflammation and therefore target the underlying drivers of the disease. They are estimated to be used by up to 25% of patients with AIA. These medications are often extremely effective, and have brought about disease control previously unachievable through conventional DMARDs alone.

Many women with these chronic conditions wish to plan pregnancy and it is known that poor control of AIA itself is associated with adverse pregnancy outcomes (1). Women with AIA often remain on a variety of treatments throughout pregnancy. Due to their structure, bDMARDs do not cross the placenta during the early stages of pregnancy, when the main foetal structural development is occurring, thus, have not been associated with an increase in miscarriage, stillbirth or fetal abnormalities (2); however despite the good fetal safety profile of these medications, it still remains uncertain whether bDMARDs should be continued throughout the entire pregnancy. The majority of bDMARDs are known to cross the placenta in the second and third trimester (2), hence historically, guidelines have been cautious and have recommended that women stop these drugs prior to the third trimester (week 28 of gestation).

However, there is a paucity of evidence on the impact of stopping bDMARDs on disease control and pregnancy outcomes, which runs the risk of AIA disease flare. Uncontrolled arthritis disease activity during pregnancy inevitably leads to increased use of glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) which have been associated with adverse outcomes for mothers and babies (3-5). In addition, women who cease bDMARD treatment and subsequently flare are at risk of experiencing secondary treatment failure, whereby upon restarting their bDMARD at completion of pregnancy, they experience no or only limited benefit compared to previously. In other specialities (6) it is now increasingly common to continue bDMARDs throughout pregnancy, but the true benefits and risks of this approach are unclear. Evidence of effectiveness of bDMARDs from other specialties cannot be relied upon, as to our knowledge, there are no randomised trials of bDMARDs in any disease systems in pregnancy. Disease behaviour and measures of outcomes in other specialities (for example, inflammatory bowel disease) are not comparable to those in AIA.

There are also concerns about the effects bDMARDs may have on infant immune response, particularly to vaccinations. Immunosuppressive bDMARDs that are known to cross the placenta may be found at concentrations several fold higher than in maternal blood. Despite this there is a growing body of evidence (particularly from mothers with Inflammatory Bowel Disease (IBD) on bDMARDs in pregnancy) supporting

the use of tumour necrosis factor inhibitors (TNFi), the oldest and most commonly used bDMARD in pregnancy, with this having little impact on the number of severe infections in infants and more limited data suggesting little impact on immune function or response to non-live vaccines in infants (7-9). However, there is little to no evidence about the impact of newer non-TNFi bDMARDs, particularly in the non-IBD context (10, 11). In addition, many of the studies looking at the impact of bDMARDs look at exposure during the first two trimesters rather than exposure throughout pregnancy: as the majority of transport of the biological agents across the placenta occurs in the third trimester of pregnancy this is an important distinction to make (12).

## 6.2 Current national guidance

With one exception (certolizumab), it was historically recommended that bDMARDs are stopped before the third trimester of pregnancy (13). However, the 2022 British Society of Rheumatology (BSR) guidelines (14) state that TNFi biologics (including infliximab, etanercept, adalimumab, certolizumab and golimumab), can be continued throughout pregnancy and breastfeeding, but may also be stopped if there are concerns about the effect of bDMARDs exposure in utero influencing the infant immune system, and subsequent outcomes following live vaccination i.e. rare cases of infant mortality following BCG vaccination against tuberculosis reported in the literature (14-17). Infant cellular and humoral immunity after in utero exposure to bDMARDs has not been adequately studied; with some observations of neutropenia (18), low IgG and IgM (19, 20), reduced vaccine responses (21) and defects in cellular immunity (7) in small case series or cohorts without adequate controls. In contrast, there are increasingly reassuring safety data from large retrospective cohorts of infants exposed to TNFi biologics in utero who have received live rotavirus and measles vaccinations (22). “Newer generation” biologics aimed at other cytokines have less overall safety data as they have been used less overall, but their monoclonal antibody structure and the data which are available, summarised in the 2022 BSR guidelines, do not suggest any increase in fetal harm (similar to TNF biologics) and can be continued through pregnancy in women with severe arthritis where this is desired. Guidance about neonatal care following in utero exposure to bDMARDs is currently lacking and not uniform. Most clinicians would follow the Green Book with regards to vaccination, which advises delaying live vaccines following in utero exposure.

## 6.3 Current practice

Despite the updated 2022 BSR guidelines, there remains wide variation in practice across the UK regarding the use of bDMARDs around the time of pregnancy and conception. In 2022, we conducted a national survey of obstetricians, rheumatologists and maternal medicine specialists and found that only 8% of clinicians routinely continue bDMARDs throughout pregnancy, with the exception of certolizumab (68% continue). Certolizumab is a pegolated TNF inhibitor and as such does not cross the placenta in any meaningful way and has historically been the preferred choice for women who are considering a pregnancy. Despite reassuring safety data for all five TNFi biologics, and the 2022 BSR guideline suggesting that all TNFi biologics may be continued, our survey reported that only 38% and 42% of clinicians would prescribe etanercept or adalimumab in pregnancy, respectively. There is also variation in when rheumatologists would advise their patients to stop biologics should they become pregnant, although many would “allow” their patients to continue the drug until at least the second trimester, stopping before week 28, to ensure that drug levels in the baby at birth were minimised. Pregnancy prescribing practices for newer generation bDMARD agents (such as abatacept, tocilizumab, sarilumab and ustekimumab) were guarded, with no clinicians likely to prescribe these agents routinely throughout pregnancy, although this is not contraindicated in women during pregnancy according to our most recent guidelines. That said, pregnant

women are, however, increasingly seen at obstetric units with a maternal medicine service, taking newer generation bDMARDs for conditions such as inflammatory bowel disease, eczema, asthma, and multiple sclerosis, with many continuing these drugs throughout pregnancy. Therefore, there is no single way that biologics are being prescribed during pregnancy in women with AIA in the UK, despite guidelines in place.

## 6.4 Study rationale

The Monoclonal Antibody Medications in inflammatory Arthritis (MAMA) trial is designed to address the significant uncertainty and resulting variation in practice surrounding the effects of continuing or stopping bDMARDs during pregnancy. There are no randomised trials which compare stopping or continuing bDMARDs in head-to-head studies in an AIA population. This study aims to fill the gap in evidence and enable evaluation of arthritis disease activity, pregnancy and infant outcomes in women randomly allocated to continuing their bDMARD medication throughout pregnancy, or to stopping their bDMARD medication prior to 28 completed weeks' gestation in a pragmatic, randomised controlled trial. The trial will assess arthritis disease activity, pregnancy and infant outcomes in each arm of the study. Exploring the infant immunological response to these agents will also add to the body of evidence regarding their safety and may provide valuable insights into the effect of in utero exposure to previously sparsely studied classes of bDMARDs.

This topic was a commissioned call from the NIHR Health Technology Assessment (HTA) Programme, to assess the significant evidence gap and variation in practice surrounding the use of bDMARDs in pregnancy in women with AIA. Robust evidence around benefits and risks of bDMARD treatment in pregnancy will enable evidence-based discussions with patients, helping them make informed decisions about treatment, and facilitate shared decision-making concerning treatment choice. Women have also described vividly the anxiety they faced at the time of pregnancy, and the difficult decisions around medication use. "…*deciding to take medication in pregnancy made me feel guilty… it was hard feeling like I was putting my health before my baby's…*", and "…*managing RA is like walking a tightrope… it takes so long to find a drug combination that works… coming off a drug that helped me manage my symptoms was a huge decision. We were so worried about how I would manage flare ups whilst also being pregnant. And if I came off the biologics, would I respond in the same way when I came back on them?*" emphasising the importance of this research to women and families.

# 7 OBJECTIVES AND OUTCOME MEASURES

| Primary objective | Primary outcome measures | Time point of evaluation |
|---|---|---|
| To compare the peak of disease activity up to 6 months after the end of pregnancy in pregnant women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs before the third trimester of pregnancy. | Peak disease activity measured by the highest RAPID3 total score [self-report] | From randomisation up to 6 months after the end of pregnancy. |

| Secondary objectives | Secondary outcome measures | Time point(s) of evaluation |
|---|---|---|
| To compare the peak of disease activity up to 12 months after the end of pregnancy in pregnant women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs before the third trimester of pregnancy. | Peak disease activity measured by the highest RAPID3 total score [self-report] | From randomisation up to 12 months after the end of pregnancy. |
| To compare other features of arthritis disease activity in pregnant women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs before the third trimester of pregnancy | Peak pain level measured by the highest RAPID3 pain score [self-report] | From randomisation up to 6 months after the end of pregnancy. |
| | Peak overall wellbeing measured by the highest RAPID3 patient global estimate score [self-report] | |
| | Any occurrence of arthritis flare [self-report] | |
| | Need for escalation of therapy due to inflammatory disease activity [self-report], defined as:<br>• New or increased dose of any DMARD for arthritis;<br>• New or increased dose of systemic glucocorticoid (GC) for arthritis (oral or intramuscular injection); | |

| Secondary objectives | Secondary outcome measures | Time point(s) of evaluation |
|---|---|---|
| | • Received intra-articular GC joint injection | |
| | Any use of NSAIDs and frequency of use for treatment of joint pain [self-report] (described only using summary statistics) | |
| | Any occurrence of arthritis flare [maternal self-report] (described only using summary statistics) | From randomisation up to 12 months after the end of pregnancy |
| | Health related quality of life measured using the EQ-5D-5L | At 3, 6, 12 and 24 months after the end of pregnancy |
| | Anxiety and depression measured using the EQ-5D-5L | |
| To investigate pregnancy outcomes in women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs | Livebirth | Up to hospital discharge after the end of pregnancy |
| | Stillbirth (fetal loss greater than or equal to 24 weeks' gestation) | |
| | Pregnancy loss less than 24 weeks' gestation (described only using summary statistics) | |
| | Termination of pregnancy (with or without known congenital anomaly) | |
| | Mode of birth (described only using summary statistics) | |
| | Preterm prelabour rupture of membranes (described only using summary statistics) | |
| | New diagnosis of pre-eclampsia (described only using summary statistics) | |
| | New diagnosis of gestational diabetes (described only using summary statistics) | |
| | Venous thromboembolism (described only using summary statistics) | |
| | Confirmed or suspected maternal infection (defined as positive culture from a usually sterile site and/or maternal treatment with antibiotics) (23) (described only using summary statistics) | |
| To compare neonatal outcomes in babies born to | Gestational age (continuous) and preterm birth at: | At birth |

| Secondary objectives | Secondary outcome measures | Time point(s) of evaluation |
|---|---|---|
| women with AIA randomised to continue bDMARDs versus those randomised to stopping bDMARDs | <28<br>28 to <32 and<br>32 to 37 gestational weeks | |
| | Birth weight z-score | |
| | Early-onset neonatal infection: (<72 hours after birth), microbiologically-confirmed (24, 25) or clinically suspected infection (26) | Up to 72 hours after birth |
| | Late-onset infection (>72 hours after birth): microbiologically-confirmed (24, 25) or clinically suspected infection (26) | Up to 28 days postnatal age |
| | Neonatal death | |
| | Neonatal unit admission | Up to discharge from neonatal care |
| | Received intensive care<br>(described only using summary statistics) | |
| | Necrotising enterocolitis (NEC). [defined as babies born <$32^{+0}$ gestational weeks where NEC is diagnosed at surgery, post-mortem or based on the following clinical and radiographic signs:<br>At least one clinical feature from:<br>• Bilious gastric aspirate or emesis<br>• Abdominal distension<br>• Occult or gross blood in stool (no fissure)<br>And at least one radiographic feature from:<br>• Pneumatosis<br>• Hepato-biliary gas<br>• Pneumoperitoneum] (27)<br>(described only using summary statistics) | |
| | Brain injury [defined as any of neonatal seizures, intracranial haemorrhage (including intraventricular/periventricular haemorrhage grade 3 or 4), perinatal/neonatal stroke, hypoxic-ischaemic encephalopathy (28), central nervous system infection, bilirubin encephalopathy and among preterm infants only, cystic periventricular leukomalacia] (29)<br>(described only using summary statistics) | |

| Secondary objectives | Secondary outcome measures | Time point(s) of evaluation |
|---|---|---|
| | Chronic lung disease [defined as babies born <32$^{+0}$ gestational weeks who are alive and receiving any respiratory support at 36$^{+0}$ corrected gestational weeks] (27) (described only using summary statistics) | |
| | Retinopathy of prematurity requiring treatment [defined as babies born <32$^{+0}$ gestational weeks who received treatment with laser, cryotherapy or intravitreal injection for retinopathy of prematurity] (described only using summary statistics) | |
| | Any congenital anomaly [classified according to Eurocat] and to include congenital heart block as recommended by EULAR (30, 31) (described only using summary statistics) | Up to 3 months post delivery |
| To investigate infant and child outcomes including global development at 24 months of age, infection up to 24 months of age, and immune function (including response to vaccines) at 2, 5 and 13 months | Key long-term outcome:<br>Child development (measured using the parent-completed Ages and Stages Questionnaire-3 (ASQ-3) 24 month questionnaire (32) total score) | At 24 months of age |
| | ASQ-3 score below the cut-off for risk of developmental delay in the following domains:<br>• Communication skills<br>• Gross motor skills<br>• Fine motor skills<br>• Problem solving skills<br>• Personal social skills<br>(described only using summary statistics) | |
| | Number of infections (defined by admission to hospital for infection or prescribed antibiotic treatment for infection) | Up to 24 months of age |
| | Duration of breastfeeding | |
| | Infant death | |
| | For a subset of infants:<br>Child vaccine/immunological response:-<br>• Total IgG/A/M immunoglobulin levels<br>• Detailed lymphocyte phenotyping | At 2*. 5* and 13* months of age |

| Secondary objectives | Secondary outcome measures | Time point(s) of evaluation |
|---|---|---|
| | • Vaccine-specific antibodies (diphtheria, tetanus, pertussis antigens, Hib and measles antibody, and PCV13 at 13 months only) | (*See 11.8.1 for exact timings and ideal windows for these blood tests) |
| To examine using an economic evaluation, whether any additional benefits associated with continuing bDMARDs are justified by any additional health care resources needed | Healthcare utilisation and costs<br><br>Including neonatal unit admission level of care: intensive care, high dependency, special care, transitional care, including length of stay at different care levels | Up to 24 months after the end of pregnancy |
| | Quality-adjusted life years (QALYs) | |
| | Cost-consequence analysis | |
| | Cost-utility analysis | |
| | Child quality of life measured using the parent-completed PedsQL Total Scale Score (33) | |

Assessment of acceptability to women and clinicians will be developed using co-applicants and patient and public involvement advisory group with amendments made to the protocol and study documentation as required.

# 8 TRIAL DESIGN

MAMA is a multicentre, pragmatic, two-arm, parallel-group, unblinded randomised controlled trial, with an internal pilot and an integrated health economic analysis.

The research will take place in approximately 35 obstetric units with a maternal medicine service.

The trial flowchart and schedule of events are summarised in Section 3 and Appendix 1 respectively.

## 8.1 Internal pilot and progression criteria

A 16-month internal pilot will be conducted during which 35 centres are expected to be set up and 66 participants are expected to be recruited allowing for staggered site setup. The decision to progress from internal pilot to full trial will be based on a traffic light system with pre-defined stop-go criteria as presented in Table 1:

**Table 1: Internal pilot trial progression criteria**

| Progression criteria | Red | Amber | Green |
|---|---|---|---|

| *% Threshold* | *<60%* | *50–99%* | *100%* |
|---|---|---|---|
| Recruitment rate/site/month | <0.14 | 0.14–0.22 | ≥0.23 |
| Number of sites opened | <21 | 21–34 | ≥35 |
| Total number of participants recruited | <40 | 40–65 | ≥66 |
| | | | |
| Non-adherence to allocated trial arm (crossover) | >10% | 6%–10% | ≤5% |

Adherence will be captured by participant self-report. Biologic prescription data will also be obtained.

**Green**: continue into the main trial;

**Amber**: mitigation e.g.: open new sites, identify and address site specific issues through site visits, training and newsletters, review in 6 months;

**Red**: urgent detailed review of options with the TSC and HTA.

# 9 PARTICIPANT IDENTIFICATION

## 9.1 Trial participants

Pregnant women with Autoimmune Inflammatory Arthritis (AIA), satisfying the following criteria:

## 9.2 Inclusion criteria

- Have a diagnosis of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA)
- Pregnant at less than 28 completed weeks' gestation
- Prescribed one of the following regularly dosed bDMARDs (including the listed reference medicinal product and biosimilars) for RA, JIA, PsA or axSpA;

| **Class of drug** | **bDMARD** |
|---|---|
| **Biologics which block tumour necrosis factor (TNF)** | Humira and biosimilars<br>Active ingredient: Adalimumab |
| | Enbrel and biosimilars<br>Active ingredient: Etanercept |
| | Remicade and biosimilars<br>Active ingredient: Infliximab |
| | Simponi and biosimilars<br>Active ingredient: Golimumab |
| | Cimzia and biosimilars<br>Active ingredient: Certolizumab pegol |
| **Biologics which block CD80/86** | Orencia and biosimilars<br>Active ingredient: Abatacept |
| **Biologics which block interleukin 6** | RoActemra and biosimilars<br>Active ingredient: Tocilizumab |
| | Kevzara and biosimilars<br>Active ingredient: Sarilumab |

| | |
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| **Biologics which block interleukin 1** | Kineret and biosimilars<br>Active ingredient: Anakinra |
| | Ilarus and biosimilars<br>Active ingredient: Canakinumab |
| **Biologics which block interleukin 17** | Cosentyx and biosimilars<br>Active ingredient: Secukinumab |
| | Taltz and biosimilars<br>Active ingredient: Ixekizumab |
| | Bimzelx and biosimilars<br>Active ingredient: Bimekizumab |
| **Biologics which block interleukin 23** | Tremfya and biosimilars<br>Active ingredient: Guselkumab |
| | Skyrizi and biosimilars<br>Active ingredient: Risankizumab |
| **Biologics which block interleukin 12/23** | Stelara and biosimilars<br>Active ingredient: Ustekinumab |

- Aged 16 years or over
- Has provided informed consent

## 9.3 Exclusion criteria

- Prescribed rituximab either during pregnancy or in the 6 months prior to conception
- Prescribed JAK inhibitors
- Contraindication to cessation of bDMARDs (e.g. active, sight-threatening uveitis)
- Current, active tuberculosis in the immediate or close family or household members
- Plans to move in the first 6 months after birth with their infant to live in a country with a high rate of tuberculosis (incidence >40 per 100,000 population)

## 9.4 Infant immunological follow-up participants

A subset of up to 176 infants, where consent has been obtained, will have visits for specific immunological follow-up. The infants eligible for immunological follow-up will be determined based upon the required sample size using a pragmatic approach to geographical reach from the Oxford Vaccine Group (OVG) ("within geographical reach") in order to give an unbiased sample. Samples will be collected by a member of the clinical research team from OVG travelling to the participant's home. This and the requirement to return samples to the laboratory within a fixed time for sample processing will determine the geographical area within which participants can be enrolled into the infant immunology study. This therefore means that it will not be practical to follow up those infants the furthest distance away.

A member of the OVG will contact the parents of babies who fall within geographical reach who have consented to being considered for these blood tests in the weeks following birth and will confirm continued interest in sampling. There should be approximately equal numbers of infants who have immunological follow-up who were born to mothers from the intervention arm (i.e., have continued their bDMARD into the third trimester) and the comparator arm (those who have stopped prior to the third trimester).

This will lead to an unbiased cohort assessment within a pragmatically defined geographical area.

### 9.4.1 Inclusion criteria

- Address “within geographical reach” from the OVG
- Ongoing consent from parents for infant immunological follow-up

### 9.4.2 Exclusion criteria

- Temporary exclusion criteria for taking immunology samples from the babies – fever in previous 72 hours (or felt to be systemically unwell)

# 10 TRIAL INTERVENTIONS

## 10.1 Pathways of care to be compared

This trial will compare two existing pathways of care for bDMARD use in pregnancy that are already being used in the UK, albeit with wide variation. MAMA is a pragmatic, comparative effectiveness trial of these two pathways of care.

The two pathways of care being assessed are:

1. Intervention: continuing bDMARDs throughout pregnancy.
   The woman’s current bDMARD, dose and frequency of administration will continue.
2. Comparator: stopping bDMARDs before the third trimester (week 28) of pregnancy and restarting no earlier than 2 weeks after the end of pregnancy.

For both groups, all other aspects of clinical care are determined by the treating clinical team.

## 10.2 Investigational Medicinal Product(s) (IMP) description

This is a trial of two treatment strategies relating to continuing or stopping prescribed bDMARDs. bDMARDs are a broad group of drugs which includes many classes and within each class, many marketed products which are largely similar with respect to their safety profile. The classes of bDMARDs included in this study are detailed in the inclusion criteria and the MAMA trial Collated Reference Safety Information. All drugs are licensed for use in inflammatory arthritis and are already prescribed in pregnancy. Additionally, their use in pregnancy is outlined in the 2022 BSR guidelines on use of medications in pregnancy (14).

As MAMA is an open label trial, healthcare teams and women will be aware of their allocation following randomisation. All women entering into the study will already be taking bDMARDs in their pregnancy, prescribed by their treating rheumatologist. In those randomised to continue treatment throughout pregnancy, their rheumatologist will continue to provide a prescription to be dispensed from a hospital pharmacy, with repeat prescriptions via hospital pharmacies, as per current standard of care. None of the drugs included in the trial is being modified or masked in any way, and are prescribed according to their indication for treatment of arthritis. The prescribed bDMARD will be taken from normal, non-trial stock and the standard NHS labelling for dispensed medicines will apply. Women will be provided with information that identifies their participation in the MAMA trial, with relevant contact details. Apart from the study arm allocated at randomisation, all other aspects of clinical management are entirely at the discretion of the local

healthcare team, including additional prescriptions or changes to the prescription provided, as required, throughout the pregnancy according to current clinical practice. Although a change in bDMARD during pregnancy is highly unlikely, were there to be a change the prescribing rheumatologist would not prescribe a bDMARD contraindicated in pregnancy as per normal medical practice.

To ensure this is a pragmatic trial, all current classes of bDMARDs which are dosed at regular intervals will be included. Rituximab is excluded due to the irregular dosing (which can range from treatment every 6–12 months). For clarity, the Janus Kinase (JAK) inhibitors, which are targeted synthetic (ts) DMARDs, not bDMARDs, and currently contraindicated in pregnancy for safety reasons, are excluded. All other aspects of obstetric management will be managed according to usual care. Rheumatology and obstetric medicine schedules of care will be decided by the treating clinician.

### 10.2.1 Dosage

The drug, dose and frequency of administration of a woman's bDMARD is at the discretion of the prescribing clinician, and all other aspects of clinical care are determined by the treating clinical team.

### 10.2.2 Storage of IMP

All drugs will be supplied by usual care pharmacies.

### 10.2.3 Accountability of the Trial Treatment

No stock recording will be undertaken as all biologic drugs will be dispensed from usual care pharmacies.

### 10.2.4 Post-trial Treatment

Provision of bDMARDs beyond the trial period would only take place as part of ongoing clinical management.

### 10.2.5 Concomitant Care

All other aspects of care for the woman and her infant will be determined by the treating clinician and remain the responsibility of the clinical team locally. Treating clinicians should refer to the current SmPC for the relevant bDMARD for interactions and incompatibilities when determining all other aspects of care. There is no capacity within this trial for baseline blood tests to be performed on any of the babies at birth, any additional blood sampling will need to be carried out by the clinical team caring for the mother and baby. Bloods will be arranged as felt appropriate locally.

### 10.2.6 Crossover between Allocated Care Pathways

Crossover will be captured by woman self-report using the trial app (see Section 15.3). Provision will be made for women unable to use the app. Reasons for missed doses if allocated to continuing treatment, or doses taken if allocated to stopping treatment, will also be captured (e.g., patient decision, forgot, advised to miss dose in setting of infection, etc.).

Crossover will be defined as:

For the continuing bDMARD allocation: Reported as missing all doses of bDMARD between 28 weeks of pregnancy until 2 weeks after the end of pregnancy unless clinically indicated;

For the stopping bDMARD allocation: Reported as taking at least one dose of bDMARD between 28 weeks of pregnancy until 2 weeks post-pregnancy unless clinically indicated.

Escalation of therapy for worsening disease would not be considered crossover for either trial arm.

## 10.3 Other Treatments (non-IMPs)

There are no non-IMPs in the trial.

## 10.4 Other Interventions

There are no additional interventions in the trial design. Clinicians may refer to the approved SmPC prior to prescribing concomitant medication.

# 11 TRIAL PROCEDURES

See APPENDIX 1: Schedule of procedures

## 11.1 Recruitment

Recruitment will be undertaken in approximately 35 obstetric units with a maternal medicine service in the 16 Maternal Medicine Networks in England and high risk antenatal clinics.

Although women will not be recruited directly from rheumatology departments, engagement of rheumatologists and specialist rheumatology nurses will be important for successful recruitment to the trial. Women are likely to contact rheumatology clinics when they become pregnant e.g. through the nurses' advice line. Rheumatology clinics will be equipped with information about the trial so that rheumatology nurses can signpost women appropriately. While there are no formal Patient Identification Centres (PICs), endorsement of the trial will take place through rheumatologist trial champions creating awareness of MAMA by writing to colleagues and providing training materials. The British Society for Rheumatology has also endorsed this trial and will support additional communications.

Brief information about the trial will be provided widely at rheumatology clinics and through rheumatology nurse specialists to women of child-bearing age, informing them about the trial. This will allow women the opportunities to discuss the trial before they become pregnant, and to consider the trial in the context of any pre-pregnancy discussions about medication choice during pregnancy. We are aware that some women choose to stop bDMARDs prior to pregnancy. Incorporating the opportunity for pre-pregnancy discussions could therefore enable a larger number of women to choose to continue bDMARDs into pregnancy and potentially participate in the trial although the ultimate decision will remain with the woman.

Women will be recruited through sites in several ways:

- Women who have discussed the trial pre-pregnancy may contact the maternal medicine service research team directly once they become pregnant. They will be provided with the Participant Information Leaflet (PIL) and the trial will be further discussed with them either remotely or in person.
- Women referred to the maternal medicine service for clinical advice who are already pregnant and who have not heard about the trial will also be provided with the PIL and will be offered a remote or in-person opportunity to discuss the trial with the maternal medicine service research team.
- The maternal medicine service research team will approach women who are being cared for directly by their service, provide the PIL and further discuss the trial.
- Women may contact the trial team at the National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU) directly, e.g. where women have heard about the trial but are not at a recruiting site for their care. The trial team at the NPEU CTU will direct women to a maternal medicine service research team.

## 11.2 Screening and Eligibility Assessment

Identification may be through referral letters, maternal medicine antenatal clinics, maternity booking appointments, general antenatal clinics or rheumatology services. Women potentially meeting the eligibility criteria will be screened for eligibility by their clinical care team at the recruiting site. All eligible women will be invited to participate.

Since the eligibility criteria do not require specific medical evaluation, assessment of eligibility is accepted to be within the scope of competency of appropriately trained and experienced doctors and nurses, as delegated by the Principal Investigator.

### 11.2.1 Recruitment to other studies

Co-recruitment of participating women to other non-interventional studies would generally be permitted. Co-recruitment to another CTIMP may be possible following discussion and agreement between Chief Investigators if perceived to not affect the outcome of either trial in any way. The burden to and risk to the safety of the woman of involvement in additional research will also be considered when making a decision.

## 11.3 Informed Consent

A trained and delegated individual must obtain appropriate informed consent from the woman prior to any trial related procedures being undertaken.

Women identified as being potentially eligible will be approached to discuss the trial and to request consent.

A Participant Information Leaflet (PIL) will be provided to women detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the woman is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

Women will be allowed as much time as wished to consider the information and the opportunity to ask questions of the research team or other independent parties to decide whether they will participate in the trial, including adequate time for discussion with their partner and/or relatives. Video materials will be

provided in addition to written materials to help inform discussions and to ensure consistency of the consent conversation.

There will be the option of remote consent (telephone or video call), in order to facilitate the extended time that might be required for a woman to decide to participate, to give potentially eligible women identified outside the recruiting site e.g. in a rheumatology clinic an opportunity to be in the trial, and to maximise the ease of recruitment for the women who may only visit the maternal medicine service infrequently. This will also facilitate consent for women who may require support for consent, such as language interpretation, or for those with visual impairment.

If consent is being taken in-person, written informed consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. If the consent discussion takes place remotely, the woman will be provided with a PIL either as a physical hard copy or as an electronic copy via an email or as a digital download. Virtual or remote consent (via telephone or video call) will be documented on the paper based Remote Consent Form and signed by the person taking consent.

Regardless of the method of consent, a copy of the signed Informed Consent Form will be given or emailed to the participant by the recruiting site. The original signed form will be retained at the trial site and a scanned copy will be sent via secure document transfer to NPEU CTU, University of Oxford for monitoring purposes.

Informed consent will also be requested at recruitment from women for storage of their NHS number and that of their newborns, for later data linkage to routine health and education data to assess children's longer term health, neurodevelopmental and educational outcome at school age (funding to be sought separately).

At the time of enrolment, there will be an option for women to consent to being contacted regarding their infant being considered for immunological follow-up with blood tests at three points in time (2 months, 5 months and 13 months of age). They will be made aware that there will not be capacity for all babies born to women in the trial to have immunological investigations. At the time of recruitment, they should be given access to the Infant Immune Response Information Leaflet.

### 11.3.1 Consent for infant immunological follow up

For the babies of women who have consented for whom there is no capacity for immunological follow up families will be notified by the study team.

For babies of women who have consented for whom there is capacity for immunological follow up: Study staff will contact parents/legal guardians of potential participants, either by phone or email, to discuss the study further, make sure they understand the study information, answer any questions, provide an electronic version of the Infant Immune Response Information Leaflet and book the first visit.

The Infant Immune Response Information Leaflet will detail the exact nature of the infant immunology investigations, including the study schedule, what is involved, and any study procedures. It will be clearly stated that the parent/legal guardian is free to withdraw their child from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

During the first study visit written consent will be taken from the parent /legal guardians: the parent/legal guardian of the participant will personally sign and date the latest approved version of the MAMA Infant Immune Response Consent Form before any study procedures are performed.

The parent/legal guardian will be informed that samples will be processed at Oxford University Hospitals (OUH) laboratories, processed and stored at the OVG laboratory, and sent to other laboratories in the UK and Europe for analysis. Safety bloods will be labelled and processed according to local laboratory guidelines (Oxford University Hospitals NHS Foundation Trust). These samples will therefore be labelled with the information required by the OUH digital system for requesting and reviewing blood results, which includes personal identifiers.

The participant's parents/legal guardians will be allowed as much time as they wish to consider the information, and given the opportunity to question the Investigator, or other independent parties to decide whether to participate in the study, as long as the participant is still in the enrolment age window and the study is still open for recruitment. Written Informed Consent will then be obtained by means of a dated signature, together with the dated signature of the person who presented and obtained the Informed Consent. The person obtaining the consent must be suitably qualified and experienced, have been authorised to do so by the Chief/Principal Investigator and be listed on the delegation log. A copy of the signed MAMA Infant Immune Response Consent Form will be given to the participant's parents/ legal guardians.

Parents will also be given the opportunity to complete a separate consent form to have any leftover samples stored in the Biobank. Any left-over samples will be transferred to Oxford Vaccine Centre (OVC) Biobank (REC 21/SC/0161) for storage once the sample is no longer required for the study endpoints, if consent to do so has been obtained. The OVC Biobank study is covered by a separate study protocol and consent process. If parents/guardians do not consent to biobank storage, then all samples will be destroyed at the end of the study. Parents may consent to the Biobank during any of the study visits.

A copy of the separate Biobank consent form will also be given to the participant's parents/legal guardians (if applicable). The original signed forms will be retained at the study sites.

## 11.4 Randomisation

Randomisation of women to either continuing bDMARDs throughout pregnancy or to stopping bDMARDs before the third trimester will be managed securely via a secure web-based randomisation facility hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (University of Oxford) with telephone backup available at all times (365 days per year). A Senior Trials Programmer at the NPEU CTU will write the web-based randomisation program and hold the allocation codes. The Senior Trials Programmer and a Senior Statistician will monitor implementation of the randomisation procedure throughout the trial. Randomisation reports will be provided to the Data Monitoring Committee (DMC).

Randomisation will occur as soon as a woman becomes eligible and has given informed consent, using a 1:1 allocation ratio. This may be any time from first presentation with pregnancy up until the 28th week of gestation. Randomisation will use a probabilistic minimisation algorithm. To ensure balance between the randomised groups, minimisation criteria will comprise: recruiting site, rheumatological condition, trimester of pregnancy and class of bDMARD prescribed at randomisation.

## 11.5 Blinding and code-breaking

MAMA is an open label trial as blinding the woman or clinician to the treatment is not possible given the clinical pathways involved. The primary outcome is a participant-reported outcome assessing disease activity according to the woman's belief. The unblinded nature of the study will reflect real-world practice and allow ascertainment of the pragmatic treatment effect, based on women's experience of their disease activity (34). Other key clinical outcomes, such as need for escalation of therapy and neonatal unit admission are objective and unlikely to be influenced by knowledge of trial allocation.

## 11.6 Baseline Assessments

Some baseline maternal demographic and pregnancy data including ethnicity will be collected in order to accurately report on the demographics of the groups allocated to each pathway. Following randomisation, women will be asked to complete the following using electronic data capture (or via telephone or paper forms) wherever possible:

- RAPID3 score
- Details of hospital admissions or clinic attendance with arthritis or pregnancy complications
- EQ-5D-5L (Health-related quality of life)

## 11.7 Study Data Collection

Data collected will include further baseline demographic, arthritis and pregnancy characteristics, health related quality of life, arthritis disease activity, and maternal, birth and neonatal outcomes. Data will be entered onto a secure online study-specific database (Section 15.3). It is anticipated that the majority of babies may not be delivered in the unit where they are randomised; we will therefore utilise the NIHR Research Delivery Network (RDN) to locate many outcomes for women and babies. Women who are eligible for the MAMA Trial will have a multi-disciplinary team within the maternal medicine network who would be involved in their care regardless of place of birth. Recruiting site staff will be responsible for all CRF completion.

Data on bDMARDs and other arthritis medications including any alterations, will be captured from participant data entry. Provision will be made for women unable to use the app.

Disease activity, measured by RAPID3, will be collected via the app monthly in pregnancy, at 3, 6 and 12 months after the end of pregnancy, and ad hoc when women have an arthritis flare. Alternative completion options will be provided for the digitally excluded, disabled or those with language difficulties.

As well as self-reporting the disease activity scale, women will also be able to self-report adverse events, including certain serious adverse events, directly to the trial team via the MAMA trial app.

Other secondary maternal and infant outcomes will be collected by validated parent-reported questionnaire (Section 7). Respondents will be given the option of receiving and completing the questionnaire in paper copy by post, or electronically, at randomisation. All data will be entered on to the study database.

Neonatal outcomes recorded during neonatal unit admission (neonatal core outcomes) will be collected using a case report form completed by staff at the recruiting site using electronic patient records. If required continuing care sites will be set up according to NPEU procedures

### 11.7.1 Immunological data

IgG/A/M and lymphocyte phenotyping will be undertaken through the OUH NHS Foundation Trust immunology laboratory using assays routinely available in clinical practice.

Vaccine-specific antibodies will be measured at the National Institute for Public Health and the Environment (RIVM) laboratories in the Netherlands using a well-established high-throughput multiplex Luminex method (35).

Given the unique nature of the study with the potential for deeper immunological insight into the effect of maternal treatments during pregnancy on the developing infant immune system, some samples will be stored for consideration of further immunological analyses dependent on the nature of maternal biological agents to which infants have been exposed and the results of the initial immunophenotyping. These will include PBMCs, serum, plasma, mucosal lining fluid and blood spots on filter paper. Funding will be sought to undertake any such analyses that may include more detailed immunophenotyping (including cellular and serological assays and immune-repertoire sequencing) and measurement of the levels of DMARDs in infant blood samples.

## 11.8 Infant immunological follow-up

A subset of infants will be suitable for immunological follow-up in line with 9.4 above. This will involve blood tests being taken on three occasions during home visits (2 months, 5 months and 13 months of age).

During the first infant visit written consent for taking blood and handling of immunological data will be taken.

### 11.8.1 Trial Visits

A trained and experienced member of the clinical research staff from the OVG accompanied by a second person as an assistant will perform all of the home visits and obtain blood samples according to the following Standard Operating Procedures (SOPs):

- OVG009 - Venepuncture
- OVG012 - Safety of Research Staff in the Community and at CCVTM

**Visit 1** – Enrolment and blood sampling visit at 2 months of age

Window: 6–8 weeks after birth and should be prior to the first vaccinations.

At this visit study staff will:

- Provide an explanation of the study to parents/legal guardians
- Obtain written consent from the parents/legal guardians of the baby

**Visit 2** – Blood sampling visit at 5 months of age

Window: Ideal window = 28–35 days after primary vaccinations have been performed (will be approximately 5 months of age) but could be performed up to 42 days after primary vaccinations.

**Visit 3** – Blood sampling visit at 13 months of age

Window: Ideal window = 28–35 days after 12-month vaccinations have been administered (will be approximately 13 months of age) but could be performed up to 42 days after these vaccinations.

Visits should be scheduled to ensure that they fall within these time windows and participants contacted to confirm the dates of their vaccinations.

During each of the visits the clinical research staff will confirm whether the babies have required any courses of antibiotics or been admitted to hospital for an infection during the previous window of time from the visit. The red book will also be reviewed for the vaccination history.

Samples will be collected at each of the visits as described in the next section.

### 11.8.2 Sample handling

During each visit the following samples will be obtained to assess cellular and humoral immunity. These will include samples for:

- Lymphocyte subsets and other markers of cellular immunity
- Immunoglobulins – IgG, IgM, IgA
- Vaccine responses

During the visits we will also collect nasal mucosal samples using Synthetic Absorptive Methods (SAM) strips. In addition, serum will be collected to allow the possibility of studying *biologic agent drug levels* – although this is not part of the funded analysis and routine assays are not available for some of the biological agents this is an important sample set for which further funding will be sought in order to undertake assays for relevant agents. These levels may be taken according to which agent the mother was receiving in pregnancy. For some of these agents, particularly the newer agents, it may not be possible to obtain the drug level if the relevant assay is not available. We will also store PBMCs from samples where transport times allow this to be done.

Blood sampling will be carried out in line with SOP OVG009 - Venepuncture. A local anaesthetic cream will be sent to families and applied for an appropriate period of time prior to each venepuncture – at each visit study staff will ensure the cream has been applied with sufficient time between application and venepuncture. Venepuncture will be performed by an appropriately trained member of staff in conjunction with a second person whose role will be to help hold and distract the infant in order to reduce distress for participants (parent and infant).

The maximum blood volumes requested for each sample are in accordance with the NIHR Medicines for Children Research Network that states that “per individual, the trial-related blood loss should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90ml/kg body weight”, 3% is 2.7 ml blood per kg body weight considering a total estimated volume of 90ml/kg body weight.

For the calculation, we considered the WHO centile curves for girls and boys on the 5$^{th}$ centile as representative of the smallest participant. Based on this a maximum of 4mls of blood could be safely obtained during blood visits for laboratory analysis in participants up to 6 months of age, and a maximum of 6mls in participants at 12 months of age.

If the initial attempt at venepuncture is unsuccessful, verbal consent will be sought from the parents for a further attempt at that visit. No more than two attempts at venepuncture will be made during a single visit. If venepuncture is unsuccessful the visit may be rearranged on agreement from the parent within the defined timeline for that visit. A missing or incomplete blood draw from a visit will not mean that the participant needs to withdraw from the trial unless they choose to, and subsequent visits as per the schedule will be allowed.

Immunoglobulins and lymphocyte subsets will be reported back to parents and GPs as they are validated assays being analysed in an NHS clinical laboratory and should be reported in a contemporaneous fashion. It is not uncommon to have some values of immunoglobulins and lymphocyte subsets outside of the normal range even in otherwise healthy children. This can arise from variation in maturation of the immune system or minor intercurrent illnesses. These results will be reviewed with a consultant immunologist from the OUH clinical immunology team in order to decide whether any further action is needed based on the results or whether these are not of clinical significance. This will be communicated clearly in written correspondence and as needed verbally with the parents and GP. Results from the other blood tests taken will not all be available in real time and therefore will not be used for the contemporaneous clinical management of the babies: this responsibility rests with the local teams who should manage the babies clinically as required. Where abnormal results are identified during subsequent analysis this should be communicated to parents in collaboration with their GP/other medical professionals involved in their care.

Participants will be informed that they may opt-in to the OVC Biobank study (REC16/SC/014) to allow long-term storage of biological samples collected under this protocol for use in possible future research. The OVC Biobank study is covered by a separate study protocol and consent process. Participants will be informed that declining to take part in the OVC Biobank study will not affect their participation in this study. If a participant does not wish to take part in the OVC Biobank, all their remaining samples will be destroyed after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

### 11.8.3 Sampling and storage requirements

Following study visits samples will be returned to Oxford, either with the researcher or via courier, where they will be either delivered to the OUH clinical immunology laboratory or processed and stored in the laboratory of the OVG according to SOP: OVG004 Transport of Samples. The exact details of sample handling will be documented in the Laboratory Analysis Plan.

Samples for transfer to the OUH clinical immunology laboratory: samples for lymphocyte subsets will be collected in an EDTA tube which will need to be stored at room temperature and processed by the lab within

24 hours; samples for immunoglobulins will be collected in a serum tube which can be stored at room temperature for 6 hours and refrigerated after this if not yet in the laboratory. The samples will be processed and stored according to the usually SOPs of the OUH clinical immunology laboratory.

Samples for processing and storage at the OVG: these will include serum for vaccine responses together with PBMCs (where return to laboratory within 6 hours is possible), mucosal lining fluid on SAM strips and blood spots on filter paper. Serum samples for vaccine responses will subsequently be transferred to National Institute for Public Health and the Environment (RIVM) laboratories in the Netherlands for testing vaccine antibody responses using a well-established high-throughput multiplex Luminex method (42).

Any samples left over following testing will be destroyed.

## 11.9 Early Discontinuation and participant change of consent

### 11.9.1 Change of consent

Women can request to change their consent to be involved with part or all of the trial at any point. Changing their level of involvement in the trial will not affect their ongoing clinical care. Change of consent may be indicated by a woman in-person or remotely, to a member of her healthcare team or to NPEU directly. In all cases a Change of consent eCRF will be completed on OpenClinica, which will notify NPEU to stop sending relevant questionnaires/reminders.

Women have the right to change consent to withdraw from some or all of the study data collection. Where women withdraw themselves and/or their child from some or all of the continued data collection (via any method), data and samples collected by that method up to the point of change of consent will be used in the trial. No further data or samples for that method would be collected after date of change of consent.

If a woman agrees to continue with all ongoing data collection but wishes to deviate from the allocated treatment this constitutes a discontinuation of the allocated trial pathway (as detailed in Section 11.9.2).

### 11.9.2 Discontinuation of the allocated trial pathway

Women have the right to request to discontinue from the allocated trial pathway. Following a discontinuation from the allocated trial pathway, care of the woman will revert to a care pathway based on usual shared decision-making between the woman and her clinical care team. In addition, the treating clinician may permanently discontinue the allocated trial pathway at any time, if they consider this to be in the best interest of the woman's health and well-being. Discontinuation from the allocated trial pathway will not affect their ongoing clinical care. Adherence will be captured by participant self-report via the trial app / questionnaires and data will continue to be collected unless the woman requests to withdraw from some or all data collection.

## 11.10 Definition of end of trial

The end of trial will be defined as the date when the trial database is locked after completion of follow-up.

# 12 SAFETY REPORTING

## 12.1 Adverse event definitions

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|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.<br><br>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.<br><br>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE),<br>Serious Adverse Reaction (SAR) | Any adverse event or adverse reaction respectively that:<br>• Results in death,<br>• Is life-threatening,<br>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.<br>Requires inpatient hospitalisation or prolongation of existing hospitalisation,<br>• NOTE: The term hospitalisation refers to any in-patient admission, regardless of length of stay, and does not need to be overnight. This includes precautionary measures for observation. It does not include hospital admission for elective procedures or for pre-existing conditions which have not worsened.<br>• Results in persistent or significant disability/incapacity, or<br>• Is a congenital anomaly/birth defect.<br>• Is another important medical event.<br>NOTE: May be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:<br>• in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product |

| | |
|---|---|
| | • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question. |

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

## 12.2 Assessment of causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified doctor according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the IMP
- **Possibly** – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP
- **Definitely** – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

## 12.3 Procedures for reporting adverse events

Safety reporting for MAMA is precautionary; the two pathways both represent standard care and converge to the identical care pathway two weeks post birth. Any reporting outside of this window therefore represents identification of expected outcomes in this population of women and their babies. We have included this additional reporting to ensure the severest outcomes are captured expeditiously. The safety reporting window for this trial will be from randomisation up to 12 months after the end of pregnancy for the woman and infant(s). All trials run by the National Perinatal Epidemiology Unit (NPEU) follow the Unit's safety reporting Standard Operating Procedure (SOP). Sites will be appropriately trained on the safety reporting requirements of the trial.

In this population we anticipate day-to-day fluctuations of pre-existing conditions, new conditions, and a small number of pregnancy losses. As a result, many adverse events are foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, only those adverse events or adverse reactions identified as serious (SAEs) and of special interest will require expedited reporting for the trial. During trial follow-up, mechanisms will be in place to capture details of other SAEs and safety outcomes of interest.

## 12.4 Reporting procedures for serious adverse events

The two pathways of care being compared in this trial are both used in standard clinical practice, as documented in the 2022 BSR guidelines on use of medications in pregnancy (14). Therefore, participation in the trial poses no greater risk than that of standard care. Safety events (as specified in section 7) are

being collected and reviewed by the DMC as part of the outcomes of the trial. Therefore, only those SAEs that are deemed to be of special interest (Section 12.4.1) will be reported as described in Section 12.4.2.

### 12.4.1 Serious Adverse Events of special interest

Although the following SAEs are known to occur in this population, they will be required to be reported immediately

- Maternal death
- Stillbirth (fetal loss greater than or equal to 24 weeks' gestation)
- Neonatal death up to 28 days of life
- All infant in-patient (>24 hours) hospitalisations that occur after neonatal/postnatal discharge

### 12.4.2 Procedure for immediate reporting of serious adverse events

All SAEs of special interest (Section 12.4.1) must be reported on the SAE Reporting Form to the NPEU CTU trial team immediately and within 24 hours of the site becoming aware of the event. Women will be able to self-report certain SAEs directly to the trial team via the trial app. When an SAE is reported via the app an alert will be sent to NPEU CTU and recruiting site to investigate if it requires onward reporting according to the protocol. Recruiting sites will be responsible for full onward reporting of SAEs to the NPEU CTU. In addition, recruiting sites will be prompted to check existing medical sources (e.g. medical records, MBRRACE-UK Perinatal and Maternal mortality data, NHS Spine) at pre-specified intervals for SAEs of special interest (i.e. maternal and neonatal deaths).

Sites may use one of the following SAE reporting methods:

1. Paper forms, with instructions, will be provided with the trial documentation to enable anyone to report an SAE. The completed SAE form must be uploaded to NPEU CTU via NPEU CTU systems or sent via other equally secure method.

2. Staff with access to the trial electronic database should complete the SAE form online. An automatic email notification to the NPEU CTU staff will be triggered for SAEs reported electronically.

3. Where the above routes are not possible, then the SAE may be reported to NPEU CTU by telephone and the SAE form will be completed by NPEU CTU staff in compliance with internal NPEU CTU safety reporting SOPs.

Follow-up SAE information should be reported as necessary by the site staff and sent back to the NPEU CTU electronically or by email.

### 12.4.3 Recording of other serious adverse events

Selected specific maternal and infant SAEs and Adverse Events (AEs) will be recorded as part of the study outcomes at regular intervals (see Section 7) and reviewed by the independent Data Monitoring Committee (DMC) who will review the progress of the trial and interim analysis at least annually, and provide advice on the conduct and safety of the trial.

In cases where women self-report an SAE through the app, the recruiting site will be responsible for full onward reporting of SAEs using the procedure described in section 12.4.2. Women will also be directed to ensure they have also reported the event to their clinical team if the team is not already aware.

## 12.5 Expectedness

The Chief Investigator, Co-Lead, or safety delegate will review all reported SAEs, assisted by the clinical co-investigators as appropriate, and assess the causality and expectedness. The expectedness assessment will be made in relation to the Collated Reference Safety Information (CRSI) document for the trial.

The CRSI used will be the current Sponsor and MHRA approved version at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see Section 12.7 below.

## 12.6 SUSAR Reporting

All SUSARs will be reported by the Sponsor or NPEU CTU delegate to the MHRA and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the NPEU CTU is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

NPEU CTU will ensure Sponsor are sent copies of all reports at the time of submission to REC.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

## 12.7 Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

For assessment of SAEs in the DSUR, the CRSI that was approved at the start of the safety reporting period will be used. When there has been approved changes to the CRSI by substantial amendment during the reporting period, the CRSI used for the DSUR will differ to the CRSI used to assess expectedness at the time of SAE occurrence for SAEs which require expedited reporting.

# 13 STATISTICS

## 13.1 Sample size determination

To detect a standardised effect size of 0.4 of a standard deviation between the two arms on the primary outcome, with 90% power and a 2-sided 5% significance, a total of 266 women are required. Inflating by 1.11 (36) to allow for 5% cross over would require approximately 295 women in total. It is anticipated that crossover will be low, as clinicians and women will be fully counselled about the implications of the trial arms prior to enrolment. Allowing for 10% loss to follow-up, will require a total of 328 women (295/0.9) (164 per arm). A ‘Minimal Clinically Important Improvement’ (MCII) of -3.8 has been published for the adult population

with active RA (n=250, mean RAPID3 score 16.3, SD 6.3) (2). This equates to a standardised effect size of 0.6, and reflects the improvement reported for adult patients with a high level of RA activity. Pregnant women on bDMARDs are more likely to have their symptoms controlled, and a smaller standardised effect size (0.4) is therefore important to detect (5). Lost to follow-up is defined as women for whom at least the 3-month postpartum RAPID3 data are not available, as disease activity in RA has been demonstrated as being higher in the first months post-pregnancy than during pregnancy (37).

A cohort of women randomised in the first 3 out of a total of 4 years will be followed up for 24 months after the end of pregnancy. We anticipate that 75% of women will be followed up to 24 months. For the 24-month key secondary child development outcome, total ASQ-3 score, assuming 75% are included in the follow-up and 20% non-response, an effective total sample size of 197 will provide 80% power to detect a standardised effect size of 0.40 (0.47 at 90% power).

Between 2010 and 2019 the British Society for Rheumatology Biologics Register registered 805 women aged 40 or under, within which 170 pregnancies were recorded in 86 women. The data in this registry represents ~20% of UK RA patients on biologics, with 85–90% follow-up. Therefore, there are approximately 85–100 pregnancies per year in women affected by RA receiving biologics. Psoriatic arthritis (prevalence 113/100,000 women) (38), axial spondyloarthritis (190/100,000 women) (39) and adult juvenile idiopathic arthritis (19.4/100,000 women) (28, 40) all individually have lower prevalence than RA, but a younger age of onset. We therefore estimate that there would be around 150–200 pregnancies per year in the UK among the women in these populations in total. We have therefore allowed a 4-year recruitment period to reach our sample size of 328 (recruitment rate 7–8/month at steady state), overall duration 6 years.

For the infant immunology study the sample size is pragmatic and centred on a conservative estimate of the proportion of participants likely to be within geographic reach for blood sampling of the Oxford-based clinical research team of 60%. This is based on travel times and the distribution of the population within the UK. Although not the primary outcome of the study we have calculated a sample size to inform infant recruitment. The sample size calculations are based on non-inferiority of the proportion of participants achieving anti-PRP concentrations ≥ 1.0 µg/mL in the Intervention *vs* comparator group.

The calculations are based on the assumptions of:

- Seroprotection rate in the homologous arms of 95% (41)
- Non-inferiority margin of 10%
- Power of 80%
- Type I error of two-sided 0.05

The effective sample would be 75 in each arm and allowing for up to 15% drop-out rate then 75/0.85*2= 176 participants would be required. This would be 54% of total participants (176/328) which is within the estimate of the participants likely to be within geographic reach.

## 13.2 Statistical Analysis Plan (SAP)

The statistical aspects of the trial are summarised here with details fully described in a statistical analysis plan that will be available prior to the first DMC review of interim data. The SAP will be finalised before final data lock takes place.

## 13.3 Description of statistical methods

### 13.3.1 Descriptive statistics

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram (42). The number and percentage of participants lost to follow-up will be reported with the reasons recorded. Demographic factors and clinical characteristics at baseline will be summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile [IQR] or entire range) for other continuous variables. There will be no tests of statistical significance performed for differences between randomised groups on any baseline variable.

### 13.3.2 Comparative statistics

The primary analysis will be based on an intention-to-treat approach; participants with outcome data will be analysed in the groups to which they are assigned, regardless of deviation from the protocol. The stop bDMARDs group will be used as the reference group in all analyses.

For binary outcomes, risk ratios and confidence intervals will be calculated using a mixed effects log binomial or Poisson model with a log link. Risk differences will also be calculated using a mixed effects log binomial model with an identity link. The primary outcome will be analysed as a continuous outcome using mixed effects linear regression with mean differences and confidence intervals presented, where model assumptions are satisfied, and adjusting for baseline RAPID3 score. Skewed continuous outcomes will be analysed using multi-level quantile regression models, with median differences and confidence intervals presented.

Analyses will be adjusted for the minimisation factors (recruiting site, rheumatological condition, class of bDMARD prescribed at randomisation, trimester of pregnancy at recruitment). Recruiting site will be treated as a random effect in the model, and all other factors as fixed effects. Both crude and adjusted effect estimates will be presented, but the primary inference will be based on the adjusted estimates. Pre-specified exploratory subgroup analyses will investigate whether the treatment effect for the primary outcome and the key secondary child development outcome differs according to rheumatological condition and class of biologic. 95% confidence intervals will be used for all pre-specified outcome comparisons including subgroup analysis.

### 13.3.3 Analysis of immunological data

Geometric mean concentrations for vaccine-specific antibodies and mean absolute cell frequencies for each lymphocyte population will be calculated with 95% confidence intervals. The proportion with vaccine-specific antibody responses above the protective threshold will be calculated for each time-point along with the geometric mean antibody concentration and 95% confidence interval. For each outcome at each time-point comparison will be made between infants of mothers continuing bDMARDs compared with stopping before the third trimester. The use of multiple time-points (2, 5 and 13 months) will allow a descriptive comparison of immune ontogeny over the first year of life between these two groups.

Exploratory analyses will be undertaken stratifying by specific biological agents or classes of agent between exposure at 28 weeks and greater gestation and stopping before 28 weeks gestation where there are sufficient participants using these agents.

## 13.4 Data monitoring

Accumulating data from the trial will be reviewed by an independent Data Monitoring Committee (DMC) at least annually during the recruitment period of the trial, or as requested. The DMC will make recommendations to the Trial Steering Committee based on their findings (see 13.5 below).

## 13.5 Stopping rules

A recommendation may be made by the DMC to the TSC to stop the trial early following review of accumulating data, or evidence from other relevant studies becoming available. In addition to the internal pilot progression criteria (see 8.1), guidelines for the early cessation of the trial will be agreed with the DMC and documented in the DMC Charter.

## 13.6 The level of statistical significance

Two-sided statistical testing will be performed for the primary and key long-term outcomes, adopting a 5% level of statistical significance. Treatment effects for all outcomes will be presented with two-sided 95% confidence intervals.

## 13.7 Procedures for reporting any deviation(s) from the original statistical plan

Any deviations from the original statistical analysis plan will be described and justified in the final report, as appropriate.

# 14 HEALTH ECONOMICS

## 14.1 Health economic analysis and justification

A trial-based economic evaluation will assess the cost-effectiveness of continuing bDMARDs in pregnancy compared with stopping before the third trimester. The base case analysis will take a NHS perspective, following the NICE reference case (43). A secondary analysis will take a societal perspective, including costs incurred by parents and families.

Women will complete EQ-5D-5L alongside RAPID3 at randomisation and at 3, 6, 12 and 24 months' post-partum (43). RAPID3 will be mapped onto EQ-5D-5L by estimating a mapping algorithm on trial data to obtain additional estimates of EQ-5D-5L utility at intermediate time points, while minimising the questionnaire burden on women. The mapping algorithm will adjust for gestation and postpartum time point. We will use the EQ-5D-5L tariff recommended by the NICE reference case at the time of analysis (currently a crosswalk) (44).

Data on all NHS resources used by the mother and infant up to 2 years post-partum and all health-related out-of-pocket expenses will be included in the analysis. This approach avoids the need to distinguish between resources related to pregnancy or inflammatory arthritis and unrelated resource use; most healthcare resources in this population will be related to either pregnancy or inflammatory arthritis. A case report form completed by the team at the site where baby was born will provide data on the type of labour, length of hospital stay and level of care for mother and baby. Women will provide data on bDMARD medication use and complete resource use questionnaires providing data on all hospitalisations,

procedures, outpatient consultations, primary care and maternal and infant community contacts throughout the study period. Healthcare resource use will be valued using standard unit cost tariffs (45-47).

Cost-consequence analysis will tabulate disaggregated resource use, costs, RAPID3, key secondary endpoints (including adverse neonatal and maternal outcomes), mothers' EQ-5D utility over the trial period and infants' PedsQL quality of life at two years. This will provide decision-makers with a comparison of the costs, risks and benefits of continuing bDMARDs compared with stopping before the third trimester.

Cost-utility analysis will estimate the cost per Quality Adjusted Life Years (QALYs) gained using a maternal perspective for outcomes. QALYs will be estimated as the area under the quality-of-life profile with linear interpolation, including mapped and directly measured values. The base case analysis will include the costs and QALYs accrued from randomisation to 2.75 years after conception for all women regardless of the timing of delivery. This will exclude the QALYs for the infant since the primary research question focuses on disease activity for the mother. This will enable the cost-effectiveness of continuing bDMARDs during pregnancy to be compared against other healthcare technologies.

Costs and QALYs will be discounted at 3.5% per annum (43). Multiple imputation will be used to impute missing data. Bootstrapping will be used to quantify uncertainty around resource use, costs, outcomes within the cost-consequence table, QALYs and cost-effectiveness ratios, adjusting for baseline confounders. The analysis and reporting will follow the NICE reference case (43) and best practice guidelines (48).

Extensive sensitivity and subgroup analyses will test the impact of alternative methods or assumptions and explore the extent to which the results are sensitive to healthcare decisions, such as when bDMARDs are stopped/restarted, escalation treatment and the bDMARD used. A sensitivity analysis will extrapolate over the mother's lifetime, taking a maternal perspective for outcomes. This will use general population life tables and published studies on excess mortality for inflammatory arthritis to estimate QALYs for each mother in the study. We will assume that the mean cost of arthritis drugs and monitoring in each trial arm will remain constant and that after the trial period, mean EQ-5D utility within each arm will remain constant (other than age-related decline in quality of life observed in the general population). A further sensitivity analysis will combine QALYs for the infant and mother and use published data to extrapolate the trial results over the infant's lifetime to capture any long-term impact of stopping/continuing biologics on long-term progression of inflammatory arthritis, fetal loss and neonatal/maternal mortality/morbidity.

# 15 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

## 15.1 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). Participant reported data (for example, data collected via the app, quality of life data and 24-month questionnaires) will be considered source data.

## 15.2 Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Recruiting site staff will have authenticated and restricted access to the secure Clinical Database Management System (OpenClinica), ensuring they are only able to see data on participants recruited at their site. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

## 15.3 Data recording and record keeping

Data for the primary outcome will be collected via a smartphone app created for the trial to capture participants' data and to provide support materials. The app will integrate with the Clinical Database Management System (OpenClinica) and the trial administrative database application. Provision will be made for the digitally excluded and non-English speakers.

The majority of trial-specific data will be collected using electronic CRFs (eCRFs) and either entered directly into the secure Clinical Database Management System (OpenClinica) or automatically transferred into it from the bespoke randomisation database.

The clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data will be entered and at the point of entry will undergo a number of validation checks to verify the validity and completeness of the data captured. A separate administrative database application will be used to store the participant's name and any other identifiable details. Trial participants will be identified by a unique trial number, which is used to link the clinical and administrative database applications.

Consent forms containing the women's names will be sent securely electronically (using encryption) or in pre-addressed envelopes to the NPEU CTU. All data will be processed in line with the NPEU CTU Data Management SOPs. It is the responsibility of all parties involved (Sponsor, NPEU CTU, and the NHS organisations) to ensure confidentiality of participant information is maintained.

Electronic files, such as eCRFs and other electronic or scanned documents containing personal/sensitive information, will be stored on a restricted access (named individuals) server held in a secure location. Authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Authorised staff will process data via a secure network which requires individual login name and password (changed regularly). No data are stored on individual workstations. The data are backed up automatically overnight to an offsite storage area accessed by authorised personnel via electronic tag and key-pad systems.

All paper and electronic data will be stored securely in strict compliance with data protection regulations.

# 16 QUALITY ASSURANCE PROCEDURES

## 16.1 Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and Standard Operating Procedures (SOPs). A risk assessment (RA) and monitoring plan (7) will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

## 16.2 Monitoring

The Principal Investigator (PI) will be responsible for the running of the trial at their site. This will include ensuring successful recruitment, staff education and training, and trial data completeness and quality.

The NPEU CTU will develop an appropriate central monitoring plan (7) for the trial, based on the RA. Recruitment patterns at sites and within the data will be monitored. Any unexpected patterns, issues, or outlier data will be investigated and may trigger 'for cause' site monitoring. No other routine monitoring or auditing will be conducted unless the central monitoring triggers cause to do so.

## 16.3 Trial committees

The trial will be run on a day-to-day basis by the Project Management Group (PMG), which reports to the Trial Steering Committee (TSC), which in turn is responsible to the NIHR HTA programme. The PMG will consist of the Chief Investigator, CTU Director, Clinical CTU Director, Head of Operations, Senior Trials Manager, Trial Statistician, Trials IT Development and Data Management Team and other project staff. The PMG will meet every month.

The Co-Investigator Group (CIG), an extended PMG, will comprise all members of the co-applicant group and the members of the PMG, and will review progress, troubleshoot and plan strategically.

The trial will be overseen by a TSC consisting of an independent chair and other members, to include clinicians, statisticians and PPI representatives. Committee members will be deemed independent if they are not involved in trial recruitment. The chair and members of the TSC will be nominated as per the guidance outlined by the NIHR HTA for their approval. The TSC will aim to meet at least annually.

The Patient and Public Involvement and Engagement (PPIE) Advisory Group will comprise up to 20 public members identified through working with the National Rheumatoid Arthritis Society (NRAS) and their JIA subgroup, JIA@NRAS, the National Axial Spondyloarthritis Society (NASS), Arthur's Place (a charity for young adults with arthritis), the Musculoskeletal user group within VOCAL (the Greater Manchester PPIE working group), as well as lived experience co-investigators for MAMA. The group will meet at least annually to advise on key aspects of study design, parent information materials, study conduct, promotion and dissemination.

The TSC will monitor the progress of the trial and its conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carry the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy. Details

about the roles, responsibilities and conduct of the committee with be set out in a TSC Charter, which will be agreed at the first meeting.

The DMC members will be independent of the trial team and the TSC, and will include a chair, clinician and statistician. During the recruitment phase, the committee will meet annually or more often as appropriate, review trial conduct, progress, and accumulating data, and make recommendations to the TSC. Details about the roles, responsibilities and conduct of the committee with be set out in a DMC Charter, which will be agreed at the first meeting.

# 17 PROTOCOL DEVIATIONS

A trial-related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in incident forms and where applicable the relevant corrective and preventative action completed. All incidents will be recorded in an Incident Log database.

# 18 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

# 19 ETHICAL AND REGULATORY CONSIDERATIONS

## 19.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

## 19.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

## 19.3 Approvals

Following Sponsor approval the protocol, Participant Information Leaflet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The NPEU CTU will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## 19.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

## 19.5 Transparency in research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

## 19.6 Participant confidentiality

The trial will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

All personal identifiers will be stored in a separate database also held at the NPEU CTU. These databases will only be linked by the participant's trial number. After the trial has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

## 19.7 Expenses and benefits

No financial or material incentive or compensation will be provided to women for enrolling in this trial. As a thank you for their participation women will be provided with a £15 high street voucher when they are sent the final questionnaire at 24 months after the end of pregnancy.

# 20 FINANCE AND INSURANCE

## 20.1 Funding

This trial is funded by the NIHR Health Technology Assessment (HTA) programme Funder Reference: NIHR153577. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

## 20.2 Insurance

University of Oxford is the sponsor for the trial. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

## 20.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

# 21 PUBLICATION POLICY

The success of the trial depends on a large number of health professionals and parents. Credit for the trial findings will be given to all who have collaborated and participated in the trial, including all local co-ordinators and collaborators, members of the trial committees, the MAMA Coordinating Centre and trial staff.

Authorship at the head of the primary results paper will take the form "[name], [name] and [name] on behalf of the MAMA Collaborative Group". The drafting of the paper will be the responsibility of a writing committee. All contributors to the trial will be listed at the end of the main paper, with their contribution identified. It is the intention of the MAMA Collaborative Group to publish the protocol and peer-reviewed articles including the analysis of key outcomes. All published material will contain an acknowledgement of funding, as required by the NIHR HTA.

The results will be published in a high-impact peer-reviewed general medical journal. Full details of the trial will be made available through the trial website: https://www.npeu.ox.ac.uk/mama.

A wide range of routes will be used to disseminate the results of the study to both women and professionals. It is NPEU policy to send results to all trial participants, unless they have opted out.

We will present the study results at national and international maternity and rheumatology conferences. We will also disseminate study results through local Maternity Services Liaison Committees (MSLCs), through the NIHR Reproductive Health and Childbirth Research Network Midwife Champions, and the Academic Health Sciences Network (AHSN).

The National Perinatal Epidemiology Unit (NPEU) reports directly to the Department of Health and has a distinguished record for influencing policy both in the UK and worldwide. The results will be reported back to the Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists (RCOG), the Royal College of Physicians (RCP), the Royal College of Paediatrics and Child Health (RCPCH), the British Association of Perinatal Medicine (BAPM), and the Royal College of Midwives (RCM). We will present the findings of this study at key conferences such as the British Maternal and Fetal Medicine Society (BMFMS) and the British Society of Rheumatology. We will discuss the results directly with the UK Teratology Information Service (UKTIS) who are commissioned nationally to provide advice to women and health professionals on medication use in pregnancy, in order to enable updates to their materials as rapidly as possible. Results will be disseminated to professional groups through the maternal medicine networks, and via the International Society of Obstetric Medicine.

A full dissemination plan will be developed by the PMG.

# 22 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

# 23 ARCHIVING

Archiving of research data will follow the completion of the trial and publication of results for an initial period of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

Archiving of identifiable data will follow the completion of the trial and publication of results for a maximum of 25 years, to allow for contact in the unlikely event of very long-term treatment effects being discovered. Participants are aware that we will hold identifiable data for long-term use.

# 24 REFERENCES


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# 25 APPENDICES

**APPENDIX 1: Schedule of procedures**

| PROCEDURES | BEFORE TRIAL ENTRY | AT TRIAL ENTRY | | AFTER TRIAL ENTRY | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention and Data collection | | | | | | | | |
| | | | | | | Number of months after the end of pregnancy | | | | | | |
| | Screening | Random-isation | Baseline | Antenatal | Labour and delivery | 0 | 2 | 3 | 5 | 6 | 12 | 13 | 24 |
| Eligibility assessment | X | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | |
| Continuing bDMARDs throughout pregnancy / Stopping bDMARDs before the third trimester (28 weeks) of pregnancy, and restarting no earlier than 2 weeks after the end of pregnancy. | | | | X | | | | | | | | | |
| Disease activity reported via RAPID3 (primary outcome up to 6 months and secondary outcome up to 12 months after the end of pregnancy)* [self-reported] | | | X | X Monthly in pregnancy | | | | X | | X | X | | |
| Arthritis flares [self-reported] | | | Women can self-report a RAPID3 score at any time whilst participating in the trial | | | | | | | | | | |
| Changes or additions to antirheumatic therapies including change to DMARDs and/or GC use [self-reported] | | | | X | | | | X | | X | X HealthEconomics only | | X Health Economics only |
| Pregnancy outcomes [CRF completion/clinical data extraction] | | | | | | X** | | | | | | | |
| Neonatal outcomes [CRF completion/clinical data extraction] | | | | | | X | | X | | | | | |
| Infant developmental outcomes: ASQ-3 [parent-reported] | | | | | | | | | | | | | X*** |
| Infant infections and breastfeeding duration up to 24 months [parent-reported] | | | | | | | | X | | X | X | | X*** |

| PROCEDURES | BEFORE TRIAL ENTRY | AT TRIAL ENTRY | | AFTER TRIAL ENTRY | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Random -isation | Baseline | Intervention and Data collection | | | | | | | | |
| | | | | Antenatal | Labour and delivery | Number of months after the end of pregnancy | | | | | | |
| | | | | | | 0 | 2 | 3 | 5 | 6 | 12 | 13 | 24 |
| Infant death up to 24 months [site-reported] | | | | | | | | | | | | | X*** |
| Health economic outcome: EQ-5D-5L [self-reported] | | | X | | | | | X | | X | X | | X*** |
| Health economic outcome: NHS resource use by mother and infant [self/parent reported])*** | | | X | | | | | X | | X | X | | X*** |
| Health economic outcome: non-NHS resource use by mother and infant [self/parent reported] | | | | | | | | X | | | X | | X*** |
| Safety reporting window | | From randomisation up to 12 months after the end of pregnancy for the woman and infant(s) | | | | | | | | | | | |
| SAEs of special interest/mortality check [site-reported]**** | | | | | | | | X | | X | X | | X |
| **Infant immunology (optional)** | | | | | | | | | | | | | |
| Child vaccine/immunological response (infant blood sampling)(optional)***** | | | | | | | X | | X | | | X | |

* Time points for evaluation of the RAPID3 outcome measure are: monthly in pregnancy, at 3, 6 and 12 months after the end of pregnancy, during a disease flare plus the option to self-report a score at any time whilst participating in the trial

** Pregnancy outcomes will be collected up to hospital discharge after the end of pregnancy

*** A cohort of women randomised in the first 3 out of a total of 4 years will be followed up for 24 months after the end of pregnancy. We anticipate that 75% of women and their infants will be followed up to 24 months

**** Recruiting sites will be prompted to check existing medical sources (e.g., medical records, MBRRACE-UK Perinatal and Maternal mortality data, NHS Spine) for SAEs of special interest (i.e. maternal and neonatal deaths) prior to contacting participants at 3, 6, 12, and 24 months after the end of pregnancy

***** A subset of infants where consent has been obtained and the participant's home is within geographical reach will have visits for immunological follow-up

**APPENDIX 2: Amendment history**

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| Non-substantial amendment 1 (NSA1) | 1.1 | 06/11/2024 | Shan Gray, Trial Manager | Correction of typographical error in Table 1: Internal pilot trial progression criteria (no change to sample size or recruitment rate):<br>From: Recruitment rate/site/month<br>To: Recruitment rate/site/6 months |
| Substantial amendment 3 (SA3) | 2.0 | 22/09/2025 | Shan Gray, Trial Manager | Amendment of Table 1 from Recruitment rate/site/6 months to Recruitment rate/ site/ month, as per funder request. Additional Information added to the definition of SAE/SAR to ensure compliance with sponsor SOP. Minor typographical amendments to improve clarity. Update of Co-Lead Dr Kate Duhig's change from University of Manchester to King's College London in protocol - this change was approved in Minor Amendment 3. |

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / MHRA / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.

# MAMA Protocol v2.0 22Sep2025

Final Audit Report 2025-10-31

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