Site Initiation Visit (SIV) - Training

The MAMA Trial

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

Presentation overview

Part 1: Background and Rationale

Part 2: The MAMA Study

Part 3: Study Logistics

FUNDED BY
NIHR | National Institute for Health and Care Research

NPEU Clinical Trials Unit
OXFORD POPULATION HEALTH
UNIVERSITY OF OXFORD
NPEU

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Reference Number NIHR151086).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

MAMA Trial Team

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NPEU CTU, based in Manchester

Background

The **M**onoclonal **A**ntibody **M**edications in inflammatory **A**rthritis: stopping or continuing in pregnancy (MAMA) trial

Co-applicants

- Professor Kimme Hyrich, Professor of Epidemiology and Honorary Consultant Rheumatologist
- Professor Jenny Myers, Professor of Obstetrics
- Professor Darren Ashcroft. Professor of Pharmacoepidemiology
- Professor Stuart Ralston, Versus Arthritis Professor of Rheumatology
- Ms Pollyanna Hardy, Clinical Trialist and Director of the NPEU Clinical Trials Unit
- Dr Helen Dakin, University Research Lecturer
- Dr Dominic Kelly, BRC consultant in Paediatrics and Vaccinology
- Professor Chris Gale, Professor of Neonatal Medicine
- Dr Charlotte Frise, Consultant Obstetric Physician and Lead for the NW London maternal medicine network
- Professor Samantha Johnson, Professor of Child Development
- Mrs Joanne Murphy, PPIE representative
- Dr Magdalena Skrybant, PPIE representative

Mama

The **M**onoclonal **A**ntibody **M**edications in inflammatory **A**rthritis: stopping or continuing in pregnancy (MAMA) trial

22/32 Biologic disease-modifying anti-rheumatic drugs in pregnancy

MAMA has been developed in response to a commissioned call from the NIHR Health Technology Assessment (HTA) Programme,

To assess the evidence gap and variation in practice surrounding the use of biologics in pregnancy in women with Autoimmune Inflammatory Arthritis (AIA).

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Difficult clinical decisions

Uncontrolled arthritis can lead to worse outcomes in pregnancy, so managing arthritis well is very important.

Concerns about possible effects of these drugs on infants' immune systems, and some infant vaccinations are routinely delayed.

Other medicines used to treat arthritis flares in pregnancy, such as steroids, can pose potential harm.

Despite a good fetal safety profile it still remains uncertain whether biologics should be continued throughout the entire pregnancy.

Until recently, most women were advised that they should stop their biologic drugs during pregnancy and avoid these drugs in the 2nd and 3rd trimester.

Many women, especially those with RA for example, find that their arthritis does not flare during pregnancy, some even say they feel a bit better, and no additional treatment is required.

BSR Guidance

Rheumatology, 2023, **62**, e48–e88
https://doi.org/10.1093/rheumatology/keac551
Advance access publication 2 November 2022
Guidelines

British Society for Rheumatology

RHEUMATOLOGY

OXFORD

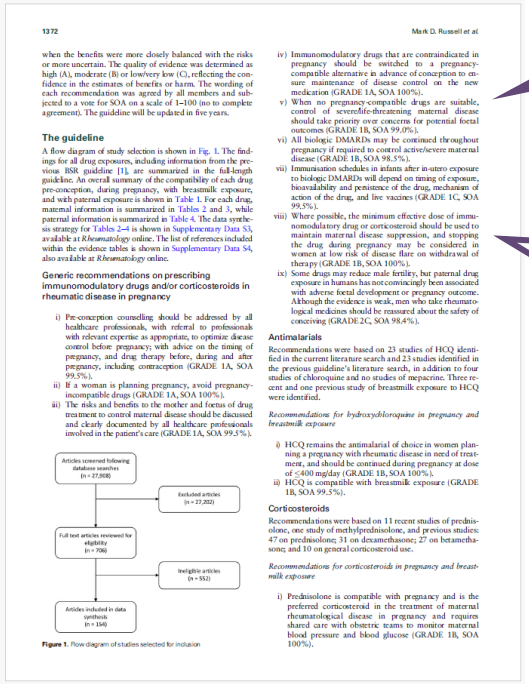
Guidelines

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids

Downloa

Due to mounting evidence of their safety for women and babies during pregnancy, **British Society for Rheumatology (BSR)** published updated guidance on the use of biologics in pregnancy in 2023

Generic recommendations



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when the benefits were more closely balanced with the risks or more uncertain. The quality of evidence was determined as high (A), moderate (B) or low/very low (C), reflecting the confidence in the estimates of benefits or harm. The wording of each recommendation was agreed by all members and subjected to a vote for SOA on a scale of 1–100 (no to complete agreement). The guideline will be updated in five years.

The guideline

A flow diagram of study selection is shown in Fig. 1. The findings for all drug exposures, including information from the previous BSR guideline [1], are summarized in the full-length guideline. An overall summary of the compatibility of each drug pre-conception, during pregnancy, with breastmilk exposure, and with paternal exposure is shown in Table 1. For each drug, maternal information is summarized in Tables 2 and 3, while paternal information is summarized in Table 4. The data synthesis strategy for Tables 2–4 is shown in Supplementary Data S3, available at *Rheumatology* online. The list of references included within the evidence tables is shown in Supplementary Data S4, also available at *Rheumatology* online.

Generic recommendations on prescribing immunomodulatory drugs and/or corticosteroids in rheumatic disease in pregnancy

i) Pre-conception counselling should be addressed by all healthcare professionals, with referral to professionals with relevant expertise as appropriate, to optimize disease control before pregnancy; with advice on the timing of pregnancy, and drug therapy before, during and after pregnancy, including contraception (GRADE 1A, SOA 99.5%).
ii) If a woman is planning pregnancy, avoid pregnancy-incompatible drugs (GRADE 1A, SOA 100%).
iii) The risks and benefits to the mother and foetus of drug treatment to control maternal disease should be discussed and clearly documented by all healthcare professionals involved in the patient's care (GRADE 1A, SOA 99.5%).

Figure 1. Flow diagram of studies selected for inclusion

iv) Immunomodulatory drugs that are contraindicated in pregnancy should be switched to a pregnancy-compatible alternative in advance of conception to ensure maintenance of disease control on the new medication (GRADE 1A, SOA 100%).
v) When no pregnancy-compatible drugs are suitable, control of severe/life-threatening maternal disease should take priority over concerns for potential foetal outcomes (GRADE 1B, SOA 99.0%).
vi) All biologic DMARDs may be continued throughout pregnancy if required to control active/severe maternal disease (GRADE 1B, SOA 98.5%).
vii) Immunisation schedules in infants after in-utero exposure to biologic DMARDs will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccines (GRADE 1C, SOA 99.5%).
viii) Where possible, the minimum effective dose of immunomodulatory drug or corticosteroid should be used to maintain maternal disease suppression, and stopping the drug during pregnancy may be considered in women at low risk of disease flare on withdrawal of therapy (GRADE 1B, SOA 100%).
ix) Some drugs may reduce male fertility, but paternal drug exposure in humans has not convincingly been associated with adverse foetal development or pregnancy outcome. Although the evidence is weak, men who take rheumatological medicines should be reassured about the safety of conceiving (GRADE 2C, SOA 98.4%).

Antimalarials

Recommendations were based on 23 studies of HCQ identified in the current literature search and 23 studies identified in the previous guideline's literature search, in addition to four studies of chloroquine and no studies of mepacrine. Three recent and one previous study of breastmilk exposure to HCQ were identified.

Recommendations for hydroxychloroquine in pregnancy and breastmilk exposure

i) HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment, and should be continued during pregnancy at dose of ≤400 mg/day (GRADE 1B, SOA 100%).
ii) HCQ is compatible with breastmilk exposure (GRADE 1B, SOA 99.5%).

Corticosteroids

Recommendations were based on 11 recent studies of prednisolone, one study of methylprednisolone, and previous studies: 47 on prednisolone; 31 on dexamethasone; 27 on betamethasone; and 10 on general corticosteroid use.

Recommendations for corticosteroids in pregnancy and breastmilk exposure

i) Prednisolone is compatible with pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatological disease in pregnancy and requires shared care with obstetric teams to monitor maternal blood pressure and blood glucose (GRADE 1B, SOA 100%).

> vi) All biologic DMARDs may be continued throughout pregnancy if required to control active/severe maternal disease (GRADE 1B, SOA 98.5%).

Biologics **<u>may</u>** be continued throughout pregnancy **<u>if</u>** required to control active/severe disease.

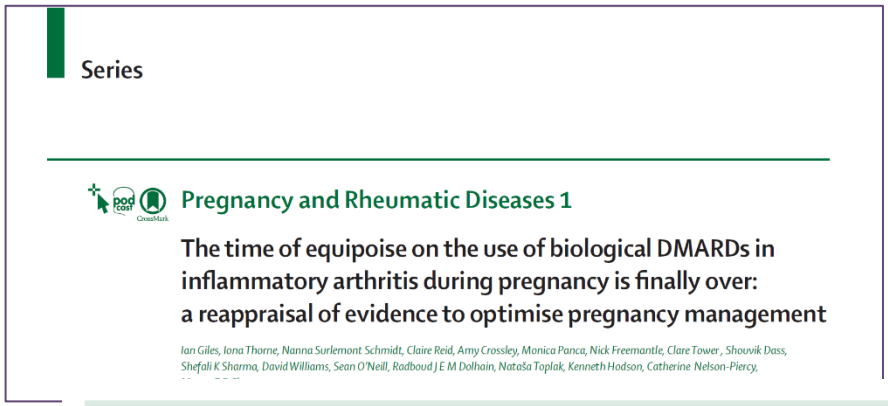
> viii) Where possible, the minimum effective dose of immunomodulatory drug or corticosteroid should be used to maintain maternal disease suppression, and stopping the drug during pregnancy may be considered in women at low risk of disease flare on withdrawal of therapy (GRADE 1B, SOA 100%).

Where possible, the **minimum effective dose** of immunomodulatory drug should be used to maintain maternal disease suppression.

Stopping during pregnancy may be considered for women at a low risk of disease flare on withdrawal of therapy.

The BSR guidelines indicate that women are safe to stay on biologics, but it does not confirm that women <u>should</u> stay on biologics.

Research agenda



Series

Pregnancy and Rheumatic Diseases 1

The time of equipoise on the use of biological DMARDs in inflammatory arthritis during pregnancy is finally over: a reappraisal of evidence to optimise pregnancy management

Ian Giles, Iona Thorne, Nanna Surlemont Schmidt, Claire Reid, Amy Crossley, Monica Panca, Nick Freemantle, Clare Tower, Shouvik Dass, Shefali K Sharma, David Williams, Sean O'Neill, Radboud J E M Dolhain, Nataša Toplak, Kenneth Hodson, Catherine Nelson-Piercy,

A RCT features in the proposed research agenda as a **requirement to improve certainty** around the use of biologics in inflammatory arthritis in pregnancy in a paper published in the Lancet Rheumatology in August 2024.

Panel 2: Gaps in current knowledge and proposed research agenda

What we know

- Disease control in pregnancy is essential to reduce the risk of adverse outcomes
- Placental transfer of IgG subclasses can occur
- Extensive data show the safety of TNF inhibitors in pregnancy
- There is negligible transfer of biological disease-modifying antirheumatic drugs (DMARDs) in breastmilk

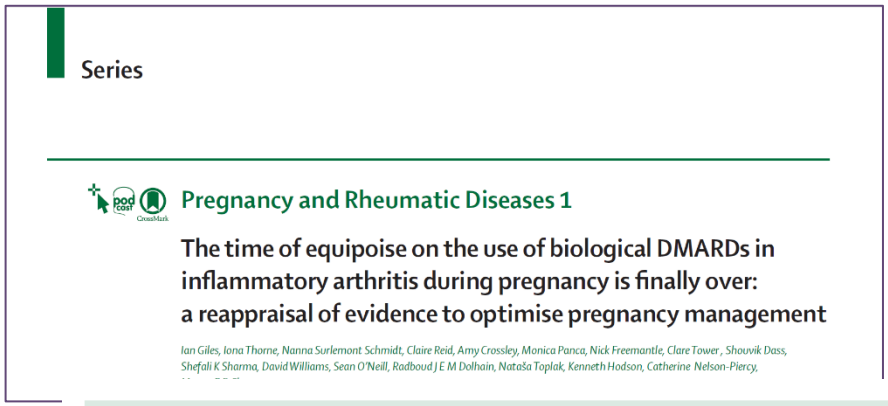
What we don't know

- Whether all biological DMARDs with high placental transfer should be stopped in mid-pregnancy or late pregnancy to allow live vaccination of infants in the first 6 months of life
- How biological DMARDs affect neonatal or infant immune development
- The long-term effects of biological DMARDs on children

Requirements to improve certainty

- Unified reporting systems and national registries documenting maternal, fetal, and infant outcomes following pregnancy in people with inflammatory arthritis
- Comparative studies of women treated with TNF inhibitors during pregnancy and those treated with sulfasalazine, hydroxychloroquine, or low-dose prednisolone
- Randomised controlled trials comparing the effects of stopping versus continuing biological DMARDs in pregnancy on maternal disease, pregnancy, and infant outcomes
- Long-term (ie, 10–20 years) studies of neurodevelopmental and immunological outcomes in children following in-utero exposure to biological DMARDs

Research agenda



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Difficult personal decision

"…deciding to take medication in pregnancy made me feel guilty… it was hard feeling like I was putting my health before my baby's…"

"…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.

Variation in practice

National survey of obstetricians, rheumatologists and maternal medicine specialists conducted in 2022.

Despite the updated 2022 national guidelines, there remained variation in:

- **Practice across the UK regarding the use of biologics in pregnancy.**
- **When rheumatologists would advise their patients to stop biologics should they become pregnant**

Newer generation biologics throughout pregnancy for conditions such as:

- Inflammatory bowel disease
  - Different clinical picture
  - Flares can cause be clinically dangerous

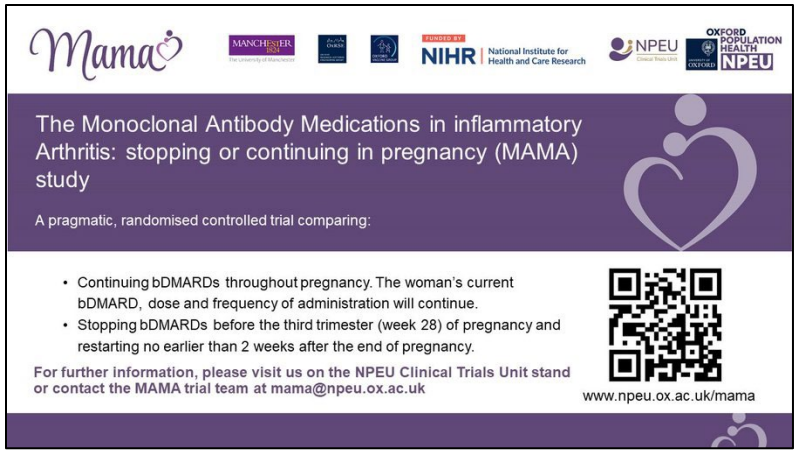
Therefore, there is no single way that biologics are being prescribed during pregnancy in women with inflammatory arthritis in the UK.

Mama Support for MAMA

nras
National Rheumatoid Arthritis Society

Arthur's Place
AWARD WINNING

NASS



The **M**onoclonal **A**ntibody **M**edications in inflammatory **A**rthritis: stopping or continuing in pregnancy (MAMA) trial

- The 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**.

Site Initiation Visit (SIV) - Training

Part 2: The MAMA Trial

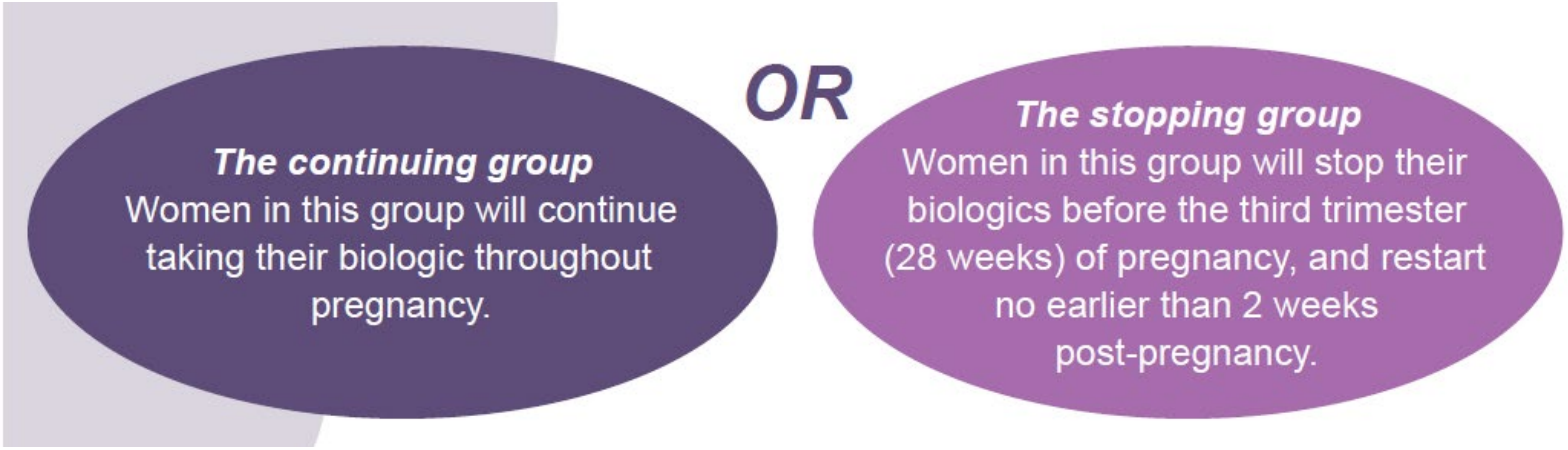
Study information relevant for all site staff

Trial design

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 for Autoimmune Inflammatory Arthritis (AIA).
Sample Size	328 women (164 per trial arm) individually randomised
Sites	35 obstetric units with a maternal medicine service in the UK.
Planned Recruitment period	48-month recruitment period including a 12-month internal pilot

Intervention and comparator

- MAMA will compare two existing pathways of care for biologic use in pregnancy.
- Women will be randomised to either:



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

MAMA is a CTIMP, but there is no requirement for pharmacy input, no changes to existing prescriptions or dispensing of medication.

Inclusion criteria

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

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
- Aged 16 years or over
- Has provided informed consent
- Prescribed one of the following regularly dosed biologics (including the listed reference medicinal product and biosimilars) for RA, JIA, PsA or axSpA;

Class of drug	Biologic
Biologic drugs which block Tumour necrosis factor (TNF)	Humira and biosimilars Active ingredient: Adalimumab
	Enbrel and biosimilars Active ingredient: Etanercept
	Remicade and biosimilars Active ingredient: Infliximab
	Symponi and biosimilars Active ingredient: Golimumab
	Cimzia and biosimilars Active ingredient: Certolizumab pegol
Biologic drugs which block CD80/86	Orencia and biosimilars Active ingredient: Abatacept
Biologic drugs which block Interleukin 6	RoActemra and biosimilars Active ingredient: Tocilizumab
	Kevzara and biosimilars Active ingredient: Sarilumab
Biologics which block interleukin 1	Kineret and biosimilars Active ingredient: Anakinra
	Ilarus and biosimilars Active ingredient: Canakinumab
Biologics which block interleukin 17	Cosentyx and biosimilars Active ingredient: Secukinumab
	Taltz and biosimilars Active ingredient: Ixekizumab
	Bimzelx and biosimilars Active ingredient: Bimekizumab
Biologics which block interleukin 23	Tremfya and biosimilars Active ingredient: Guselkumab
	Skyrizi and biosimilars Active ingredient: Risankizumab
Biologics which block interleukin 12/23	Stelara and biosimilars Active ingredient: Ustekinumab

Note on biologics:

- To ensure this is a pragmatic trial, **all current regularly dosed biologics** are be included.
- Women are likely to **know the name of the biologic** they are on.
- A **dropdown list of biologics** will be included on the randomisation webpage

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Biosimilars

- A **biosimilar** is a biological medicine highly similar to another biological medicine already approved in the EU in terms of structure, biological activity and efficacy, safety and immunogenicity profile.
- The already approved biologic is referred to as the **Reference Medicinal Product**.
- Biosimilars approved in the EU are interchangeable.

  Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.
- The biologics listed in the inclusion criteria are **reference medicinal products**

The biologics included in the MAMA Trial includes these reference medicinal products and their biosimilars.

Exclusion criteria

Exclusion criteria

- Prescribed **rituximab** either during pregnancy or in the 6 months prior to conception
- Prescribed **JAK inhibitors**
- Contraindication to cessation of biologics (e.g. 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)

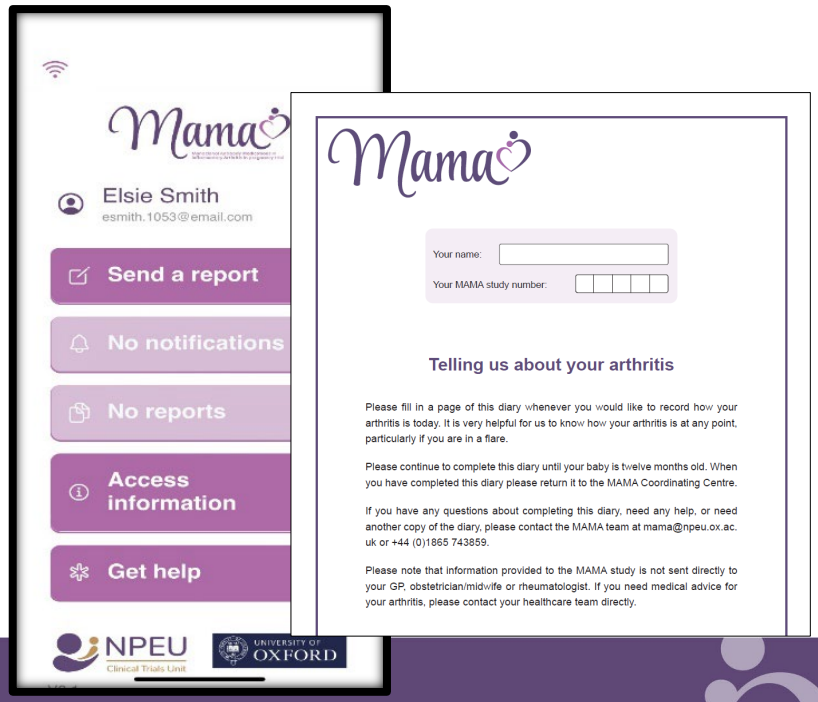
- **Co-recruitment** to other **non-interventional studies** would generally be permitted.
- **Co-recruitment to another CTIMP may be possible** following discussion and agreement between Chief Investigators.

Objectives

- **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 biologics versus those randomised to stopping biologics before the third trimester of pregnancy.

- **Primary outcome measure**: Peak disease activity measured by the **highest RAPID3** total score

Self reported via **MAMA App OR** via **OpenClinica OR** paper diaries



Secondary objectives

- **Secondary objectives – to compare the impact on:**
  - Peak disease activity up to 12 months after the end of pregnancy and other features of disease activity
  - Pregnancy outcomes
  - Neonatal outcomes
  - Infant and child outcomes (up to 24 months)
    - **Including infant immune response for a subset of infants**

	Visit 1	Visit 2	Visit 3
Age	2 months	5 months	13 months
What happens at the visit?			

Written consent Blood test Nasal Fluid sample

  - Health economic evaluation

Study intervention

- MAMA is an open label trial
- Healthcare teams and women will be aware of their allocation following randomisation
- **All women will already be taking biologics in their pregnancy, prescribed by their treating rheumatologist.**
- The biologic will be taken from normal, non-trial stock and the standard NHS labelling for dispensed medicines will apply.

There is no requirement for pharmacy input, no changes to existing prescriptions or dispensing of medication.

We do not require trial accountability logs to be completed.

Data Collection Forms

Form	Where to complete	When to complete
Randomisation form	Baseline	Randomisation website
Contact details form	Baseline	Randomisation website
Trial entry form	Baseline	OpenClinica
Outcomes form	After the end of pregnancy and after the woman has been discharged	OpenClinica
Neonatal outcomes form	Complete for infants if admitted to the neonatal unit, after they have been discharged home	OpenClinica
Wellbeing check	Before contact at 3, 6, 12, and 24 months	Contact details form

Referral pathway

A woman might be being cared for directly by the recruiting site.

A woman might be seen at the recruiting site via maternal medicine network referral pathway.

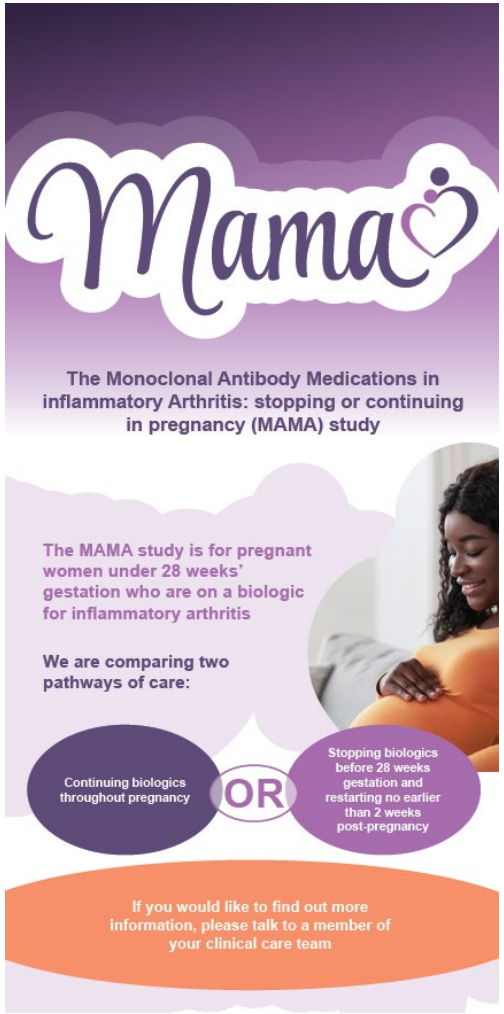
A woman may contact the MAMA Trial Team directly, e.g. where women have heard about the trial via a charity or network.

MAMA Trial

A woman who has discussed the trial pre-pregnancy may contact a recruiting site directly once she becomes pregnant.

Referral pathways will vary by site.

Pre-pregnancy approach



- Some women will consider whether to stop biologics when planning a pregnancy.
- Allows women to consider the trial in the context of any pre-pregnancy discussions about medication choice during pregnancy.

Engagement of rheumatology services:

- Important for successful recruitment to the trial.

We can provide:

- **Posters**
- **Banners**
- **Preconception Information Leaflets**

MAMA Community Engagement Lead

Screening and eligibility

- Participants may be given information pre-pregnancy but confirmation of eligibility and consent must be taken **after** the woman becomes pregnant.
- **Screening and assessment of eligibility will take place at the recruiting site**
- The MAMA eligibility criteria does not require specific medical evaluation
- **Assessment of eligibility can be performed by staff at the recruiting site who are**:

  - Appropriately trained and experienced doctors, and midwives (as documented on the **MAMA Training Log**)

  AND

  - Delegated by the Principal Investigator to **Confirm Eligibility** (as documented on the **Site Delegation Log**).

Mama Screening Log

- A record of all women screened should be maintained at site on the **MAMA Screening Log**.
- **Include all women screened, even if the woman is not approached or declines participation.**
- Please complete a row on the **MAMA Screening Log** for all pregnant patients who are:

At less than 28 weeks of gestation at first point of contact with your site

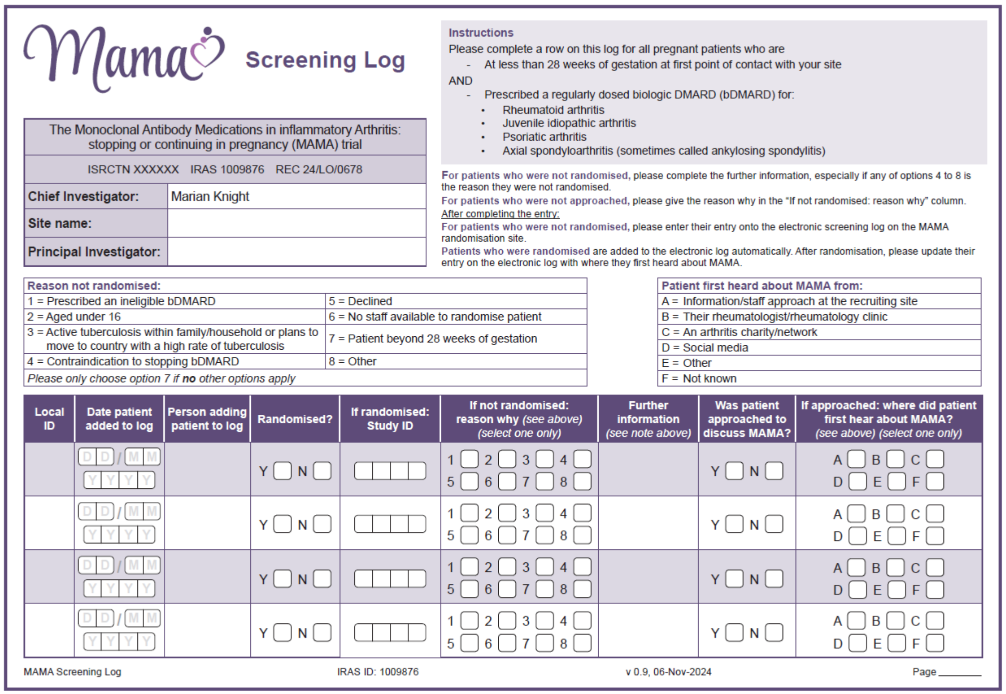
AND

Prescribed a regularly dosed biologic for:

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Psoriatic arthritis
- Axial spondyloarthritis (sometimes called ankylosing spondylitis)

Mama Screening Log

- A paper version of the **MAMA Screening Log** is available in the MAMA Document Box.
- A blank printable electronic copy is included in the **electronic Investigator Site File** (eISF).



Mama Screening Log

Instructions
Please complete a row on this log for all pregnant patients who are
- At less than 28 weeks of gestation at first point of contact with your site

AND
- Prescribed a regularly dosed biologic DMARD (bDMARD) for:
  - Rheumatoid arthritis
  - Juvenile idiopathic arthritis
  - Psoriatic arthritis
  - Axial spondyloarthritis (sometimes called ankylosing spondylitis)

For patients who were not randomised, please complete the further information, especially if any of options 4 to 8 is the reason they were not randomised.
For patients who were not approached, please give the reason why in the "If not randomised: reason why" column.
After completing the entry:
For patients who were not randomised, please enter their entry onto the electronic screening log on the MAMA randomisation site.
Patients who were randomised are added to the electronic log automatically. After randomisation, please update their entry on the electronic log with where they first heard about MAMA.

The Monoclonal Antibody Medications in inflammatory Arthritis: stopping or continuing in pregnancy (MAMA) trial	
ISRCTN XXXXXX IRAS 1009876 REC 24/LO/0678	
Chief Investigator:	Marian Knight
Site name:	
Principal Investigator:	

Reason not randomised:	
1 = Prescribed an ineligible bDMARD	5 = Declined
2 = Aged under 16	6 = No staff available to randomise patient
3 = Active tuberculosis within family/household or plans to move to country with a high rate of tuberculosis	7 = Patient beyond 28 weeks of gestation
4 = Contraindication to stopping bDMARD	8 = Other
*Please only choose option 7 if **no** other options apply*	

Patient first heard about MAMA from:
A = Information/staff approach at the recruiting site
B = Their rheumatologist/rheumatology clinic
C = An arthritis charity/network
D = Social media
E = Other
F = Not known

Local ID	Date patient added to log	Person adding patient to log	Randomised?	If randomised: Study ID	If not randomised: reason why *(see above)* *(select one only)*	Further information *(see note above)*	Was patient approached to discuss MAMA?	If approached: where did patient first hear about MAMA? *(see above) (select one only)*
	DD/MM YYYY		Y ☐ N ☐	☐☐☐☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐		Y ☐ N ☐	A ☐ B ☐ C ☐ D ☐ E ☐ F ☐
	DD/MM YYYY		Y ☐ N ☐	☐☐☐☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐		Y ☐ N ☐	A ☐ B ☐ C ☐ D ☐ E ☐ F ☐
	DD/MM YYYY		Y ☐ N ☐	☐☐☐☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐		Y ☐ N ☐	A ☐ B ☐ C ☐ D ☐ E ☐ F ☐
	DD/MM YYYY		Y ☐ N ☐	☐☐☐☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐		Y ☐ N ☐	A ☐ B ☐ C ☐ D ☐ E ☐ F ☐

MAMA Screening Log IRAS ID: 1009876 v 0.9, 06-Nov-2024 Page ______

- Completed paper logs can be filed locally in the site folder included in the Document Box.
- **Once a month**, enter summary data for those screened on the **MAMA Randomisation Website** by visiting https://rct.npeu.ox.ac.uk/mama, logging in and choosing the screening log option.

Mama Guidance

For further information see: **Guidance Sheet: Screening and eligibility**

Informed consent

Informed consent can be taken by site staff who are:

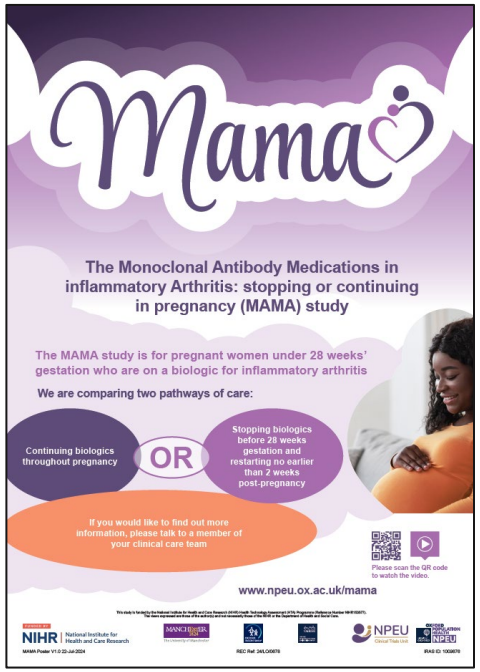
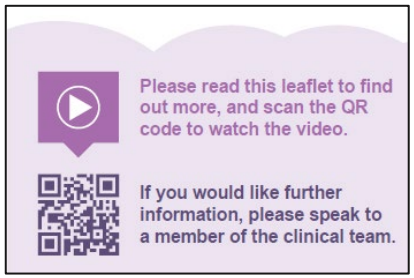
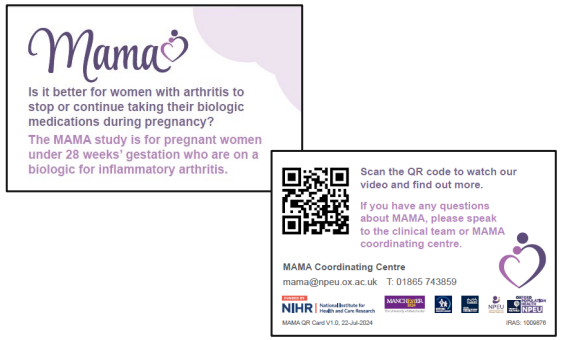
- **Appropriately trained**: Have relevant GCP training and MAMA study training (documented on the **MAMA Training Log**)
- Delegated by the Principal Investigator to '**Obtain informed consent**' (as documented on the **Site Delegation Log**).
- **Please check for any other relevant trust requirements for obtaining consent.**

In order to take part in MAMA, consent must be given before 28 weeks' gestation.

Consent can be obtained **In person** **or** **Remotely**

Informed consent - Materials

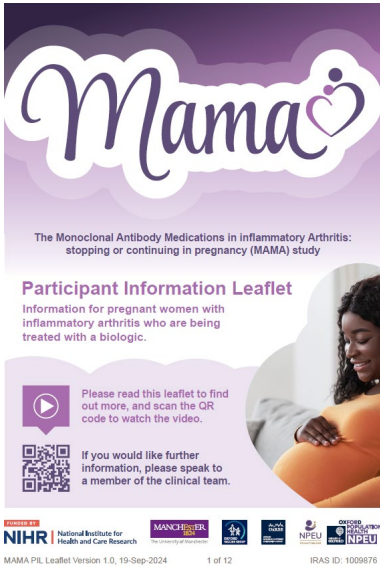
Trial materials for **participants**

Patient Information Leaflet (PIL)	Immune Response PIL	Poster
		
Video	**QR Card**	
		

Informed consent

Provide the woman with:

- A **MAMA PIL** and **Infant Immune Response PIL.**
- The opportunity to **consider the information**, and **ask questions** to decide whether they would like to participate in the trial.



Make women aware that:

- Participation is **voluntary**
- They may **change consent at any time** without giving a reason, and without this affecting the quality of their or their child's care.
- If they choose to discontinue the trial allocation, they will be asked to continue providing data – though they may choose to withdraw from this aspect too.

Infant Immune Response

- Separate, **optional but important** component of the study
- Described in **Infant Immune Response PIL**
- Women to agree to be contacted about this element of the trial in clause 8. on the MAMA Consent Form.

THE FOLLOWING ARE OPTIONAL	PLEASE INITIAL
They relate to measuring infant immune response and whether there are any long term effects of taking biologics during pregnancy	
8. I agree to be contacted by researchers from the MAMA Coordinating Centre about my baby to taking part in the "infant immune response" component of the MAMA study. I understand that agreeing to be contacted does not oblige me or my baby to participate in this part of the study.	_____

- Calls and home visits will be organised by the Oxford Vaccines Group (OVG) part of the MAMA Coordinating Team

	Visit 1	Visit 2	Visit 3
Age	2 months	5 months	13 months
What happens at the visit?			

Written consent  Blood test  Nasal Fluid sample 

Informed consent: In-person

Where in-person consent is possible the **MAMA Consent Form** must be signed and dated by the woman and the healthcare professional taking consent.

Consent form completion

- Complete the consent form in **BLOCK CAPITALS**.
- Women should **initial (not tick)** each box before signing and dating the form (do not complete in advance).
- The dates for the participant and healthcare professional signatures must be the same. Women must not be given a consent form to sign at a later date.

Ensure that:

All boxes are **initialed and completed**.

The writing is clearly **legible**.

Details have transferred through **all copies** of the form.

Informed consent: Remote

Consent may be obtained remotely (via telephone or video call) in order to:

- Facilitate the extended time that might be required for a woman to decide to participate
- Maximise the ease of recruitment for the women who may only visit the maternal medicine service infrequently.
- Facilitate consent for women who may require support for consent, such as language interpretation, or for those with visual impairment.

Remote consent should be of the same standard as in-person consent as outlined above.

Informed consent: Remote

Identity check

- The health professional taking remote consent must complete the identity checks and confirm the woman's name and address.
- It must be documented in the woman's medical notes that she consented to the ID checks during the consent process.

Remote consent form completion

- Complete the consent form in **BLOCK CAPITALS**.
- The health care professional must ensure that the parent has verbally agreed to each consent item **by initialling the boxes with their own initials** (not the woman's initials).
- Participant signature not required. Delegated individual signs instead.

A copy of signed form should be sent to the participant electronically or by post.

Informed consent: Filing

After randomisation please add the **participant study ID** to the consent form.

There will be three carbon copies of the completed consent form.

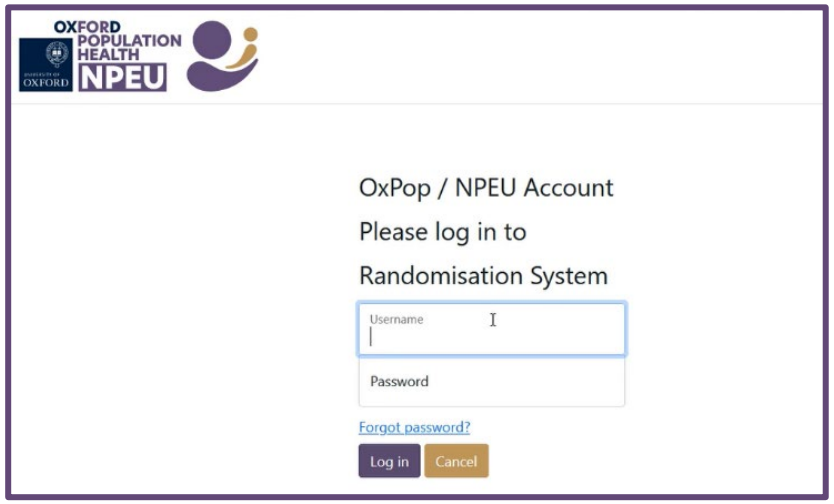
- The original paper copy should be retained in the Site Folder and an electronic copy saved to the electronic Investigator Site File (eISF).
- One copy should be provided to the woman, either as hard copy or electronically via email.
- One copy should be filed in the woman's medical notes.

Once complete, a clear scanned copy of the original should be sent to the MAMA Coordinating Centre via the **NPEU Upload Tool**.

Guidance

For further information see: **Guidance Sheet: Informed consent**

Randomisation



Randomisation will take place via the **Randomisation website** which you can access via our study website.

Login with individual login

To gain access:

1. Watch **Randomisation training video**
2. Delegated to randomise on the delegation log
3. Email MAMA study team

We encourage as many members of staff as possible to have access to the randomisation system. This is to ensure eligible women are not missed due to having nobody available with access to the system to randomise.

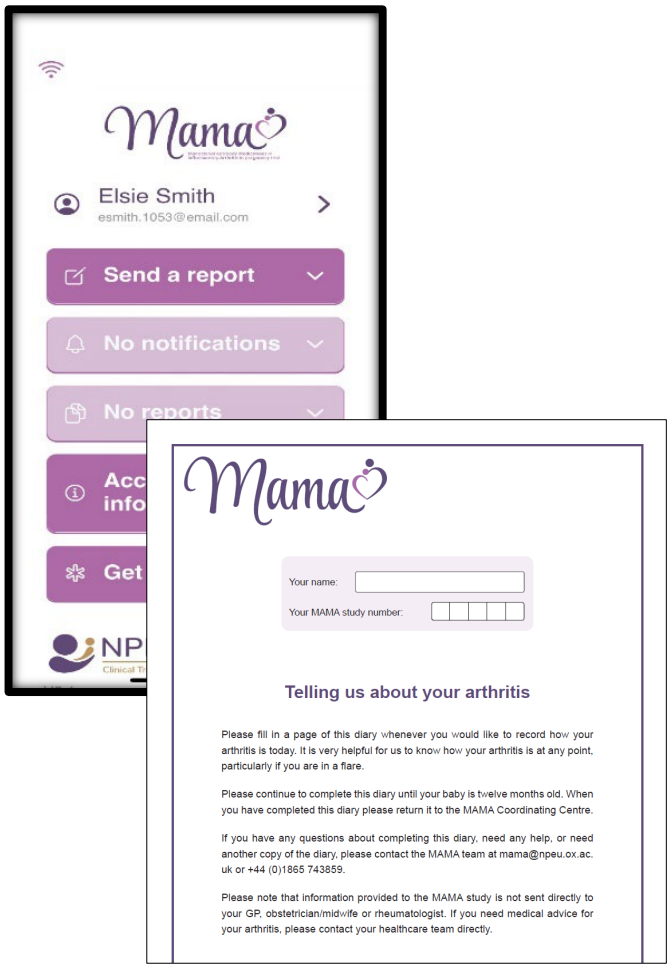
After Randomisation

- Add **MAMA Study ID** to the completed **Consent Form** (4 digit number)
- Add the appropriate **QR Rheumatologist Allocation Card** to the **Welcome Pack** (next slide)
- Complete the **Contact Details** form
  - From the randomisation Menu, click on the '**Recruitment List**' link.
  - On the Recruitment List screen locate the woman's study number, then click '**Edit**', in the '**Edit contact details**' column, adjacent to the required study number

Information from the Contact Details form is essential for the participant to be able to complete the Baseline Questionnaire and use the MAMA App and, for the MAMA Study Team to send the GP Letter, and Rheumatologist Letter.

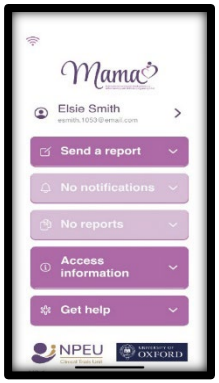
If you are unable to complete the contact details section immediately following randomisation, please return to the website as soon as possible to complete it.

Participant data collection



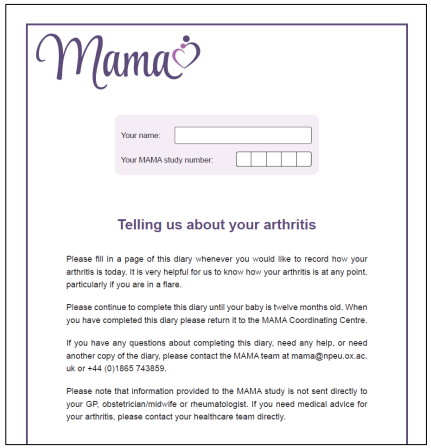
- Primary outcome data is self-reported by participants.
- We recommend that women use the **MAMA app** wherever possible.
- You will be prompted to discuss this with women on the **Contact Details Form**

Participant data collection



For women who wish to use the MAMA app

- Assist women to download and log in to the MAMA app using the **MAMA App User Guide**
- Paper copies of the **User** Guide can be found in your **Document Box** or on the **MAMA Website**

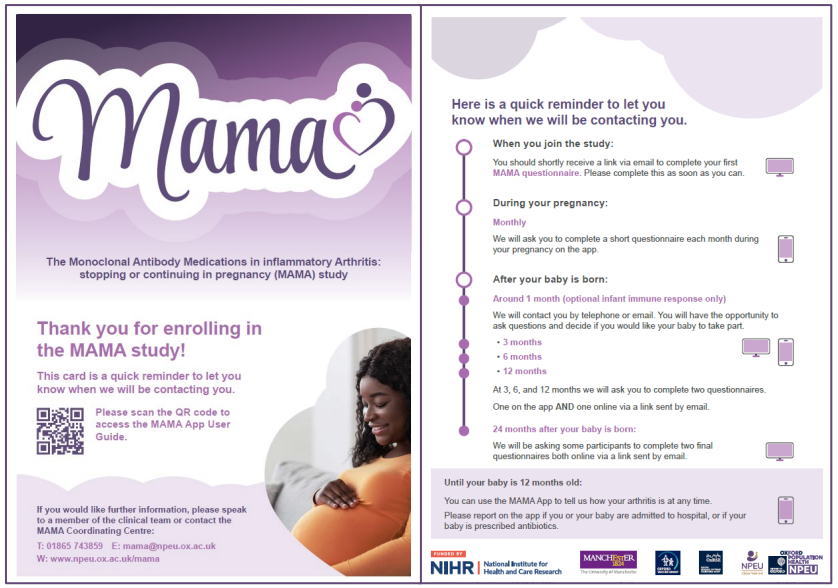


For participants who indicate they would prefer not to use the MAMA App for data collection

- Provide a **Data Collection Pack** containing paper versions of the **Baseline form** and **MAMA Paper Diaries** for recording arthritis activity.

The MAMA Coordinating Centre will send direct links and post paper questionnaires. We will also send reminders and make phone calls to women as required.

Mama Provide Welcome Pack



Welcome card

Rheumatologist QR card

+

MAMA Translation Supplement

Guidance

For further information see: **Guidance Sheet: Randomisation**

Safety Reporting

- 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)**.
- **Only those adverse events or adverse reactions identified as serious (SAEs) and of special interest** will require expedited reporting for the trial.

MAMA SAEs of special interest

- 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

All SAEs of special interest must be reported on the SAE Reporting Form to the MAMA Coordinating Centre immediately and within 24 hours of the site becoming aware of the event.

Safety Reporting

Anyone can report an SAE. No personal identifiers should be included in the report.

There are three ways of reporting the SAE:

- **Complete online**: Complete the **MAMA SAE Form** online on OpenClinica
- **Complete paper/electronic form**: Copies of the paper **MAMA SAE Form** can be found in the Site Document Box and electronic version in the **eISF**.

  Once complete, inform the MAMA study team by email and send using the **NPEU Upload tool**.
- **Report via phone**: Call the MAMA study team in order to report the SAE verbally. Once you have made the team aware of the event, you must still complete a SAE form as detailed above.

A copy of the SAE form along with any follow up information should be filed in the woman's medical notes and also in the electronic Investigator Site File (e-ISF).

Notification of SAEs

Notification of SAEs via the MAMA App

- Women will be able to notify the trial team of infant hospitalisations via the MAMA app.
- When a potential SAE is reported via the app you will be sent an alert. This will also be sent to NPEU CTU .

On receiving an alert you will need to do the following:

- Investigate if admission fits the SAE of special interest criteria:
  - All infant in-patient (>24 hours) hospitalisations that occur after neonatal/postnatal discharge
- If the admission **does** fit these criteria: complete the SAE Reporting Form immediately

Notification of SAEs

Notification of SAEs via Status Check

You will be prompted via an email alert to check existing medical sources at pre-specified intervals to check that the woman and her infant(s) are both alive.

In the event of a death you will need to do the following:

- Confirm whether the event fits the SAE of special interest criteria:
  - Maternal death
  - Stillbirth (fetal loss greater than or equal to 24 weeks' gestation)
  - Neonatal death up to 28 days of life
- If the event **does** fit any of these criteria: complete the SAE Reporting Form immediately

Please complete the relevant section on the Contact Details Form to indicate if the participants or her infants are alive or deceased.

SAE Form Completion

There are completion instructions on the SAE Form.

In MAMA both women and their infants can be affected by SAEs. In **Section 3. Participant detail** please enter the following:

- **Study number**: Woman's study number (even if the SAE relates to the infant)
- **Date of birth**: This may be for an infant, or the woman, depending on who is affected by the SAE
- **Sex**: This may be for an infant, or the woman, depending on who is affected by the SAE
- Where one infant of mutiples is affected please include which infant the SAE relates to in the SAE Narrative box e.g. TWIN 1 or TWIN 2… **Do not include infant names.**

The MAMA Coordinating Centre will call to confirm details if required.

Causality assessments must be undertaken by a delegated medically trained doctor only.

Incident reporting

What is an **incident**?

It can be defined as a deviation from:

- Protocol
- Study specific procedures
- Good Clinical Practice
- Regulatory requirements

Incidents and protocol deviations will be defined as a serious breach if the incident is likely to affect to a significant degree either:

- The safety, physical or mental integrity of the trial participants
- The scientific value of the trial

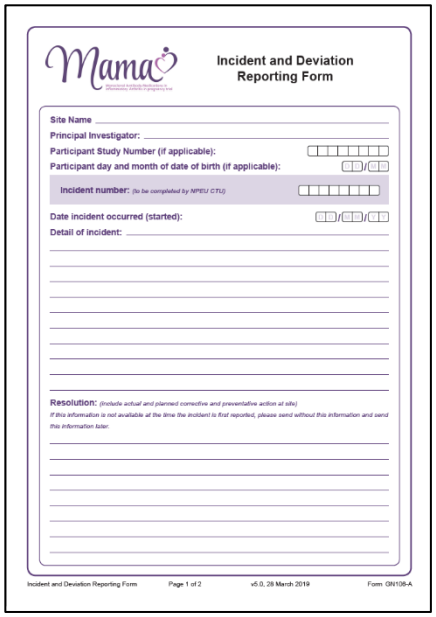
Incident reporting

How to complete?

- Editable PDF (in eISF)

OR

- Paper form (in Document Box)



Incident and Deviation Reporting Form

Site Name

Principal Investigator:

Participant Study Number (if applicable):

Participant day and month of date of birth (if applicable): /

Incident number: *(to be completed by NPEU CTU)*

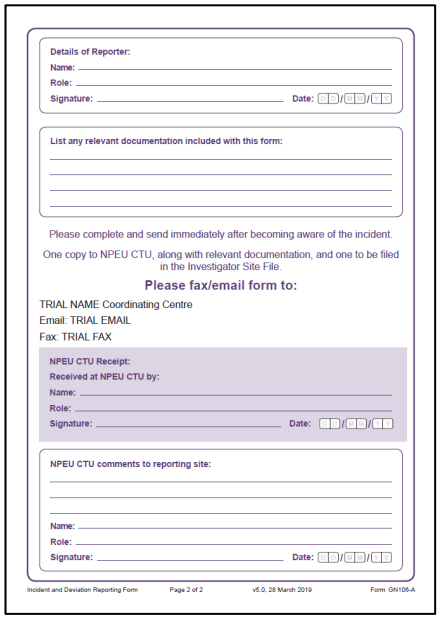
Date incident occurred (started): /

Detail of incident:

Resolution: *(Include actual and planned corrective and preventative action at site)*

If this information is not available at the time the incident is first reported, please send without this information and send this information later.

Incident and Deviation Reporting Form Page 1 of 2 v5.0, 28 March 2019 Form GN106-A



Details of Reporter:

Name:

Role:

Signature: Date: /

List any relevant documentation included with this form:

Please complete and send immediately after becoming aware of the incident.

One copy to NPEU CTU, along with relevant documentation, and one to be filed in the Investigator Site File.

Please fax/email form to:

TRIAL NAME Coordinating Centre

Email: TRIAL EMAIL

Fax: TRIAL FAX

NPEU CTU Receipt:

Received at NPEU CTU by:

Name:

Role:

Signature: Date: /

NPEU CTU comments to reporting site:

Name:

Role:

Signature: Date: /

Incident and Deviation Reporting Form Page 2 of 2 v5.0, 28 March 2019 Form GN106-A

- Once completed, these documents should be uploaded via the NPEU Upload Tool. Further instructions are on the **Incident Forms** themselves.
- NPEU CTU staff will complete an assessment of the incident and, where applicable, complete the relevant corrective and preventative action plan.
- File final signed copies in the eISF.

DO NOT INCLUDE ANY PARTICIPANT IDENTIFIABLE DATA IN AN INCIDENT REPORT

Mama Guidance

For further information see: **Guidance Sheet: Safety and incident reporting**

Mama Associate PI Scheme

The Associate PI scheme is a 6 month training opportunity run by the NIHR, providing practical experience for healthcare professionals starting their research career.

Go to the NIHR Associate PI Scheme Website:
www.NIHR.ac.uk/AssociatePIScheme

Site Initiation Visit (SIV) - Training

Part 2: Study Logistics

Study database

The study database is **OpenClinica**

- Data entry can only be completed by trained and delegated staff
- Online training to be completed
- Log in details will be sent to individuals

Data Collection Forms

Form	Where to complete	When to complete
Randomisation form	Baseline	Randomisation website
Contact details form	Baseline	Randomisation website
Trial entry form	Baseline	OpenClinica
Outcomes form	After the end of pregnancy and after the woman has been discharged	OpenClinica
Neonatal outcomes form	Complete for infants is admitted to the neonatal unit, after they have been discharged home	OpenClinica
Wellbeing check	Before contact at 3, 6, 12, and 24 months	Contact details form

Mama Guidance

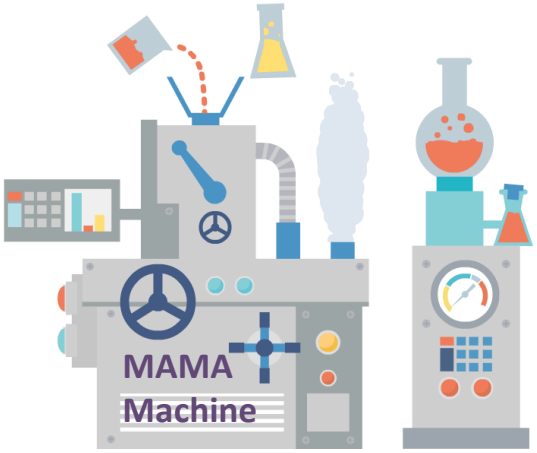
For further information see: **Guidance Sheet: Data collection**

Delivering MAMA

Rheumatology teams
- Pregnancy planning
- Early conversations
- Provide preliminary information

Arthritis networks/charities
- Participant pool is small
- Early communication about trial will be key

Equality, Diversity, and Inclusion networks
- Promotion of EDI in research key component of MAMA



Maternal Medicine Networks
- Different referral pathways
- Participants may not receive care at recruiting site

Forging links

Rheumatology teams
- Pregnancy planning
- Early conversations
- Provide preliminary information

Arthritis networks/charities
- Participant pool is small
- Early communication about trial will be key

Equality, Diversity, and Inclusion groups
- Promotion of EDI in research key component of MAMA

Links with rheumatology teams:	Links with arthritis networks/charities:	Links with Equality, Diversity, and Inclusion groups
- Help identifying contacts - Banners, poster and Information leaflets in rheumatology clinics	- Help developing local links	- Help identifying local groups

Andrea McBride - MAMA Community Engagement Lead

Promoting equality, diversity and inclusion for MAMA

We have trial specific processes in place to ensure maximum inclusivity:

- **MAMA information video** – translated into 5 different languages and available on the study website (can be accessed via **MAMA Information QR cards**)
- **Language Line** set up for follow-up questionnaires. Women with a translation supplement. This asks individuals to contact the trial team for assistance in populating the questionnaire in another language.
- **Remote consent**

Andrea McBride - MAMA Community Engagement Lead

Translation

There is funding for sites to use local translation services.

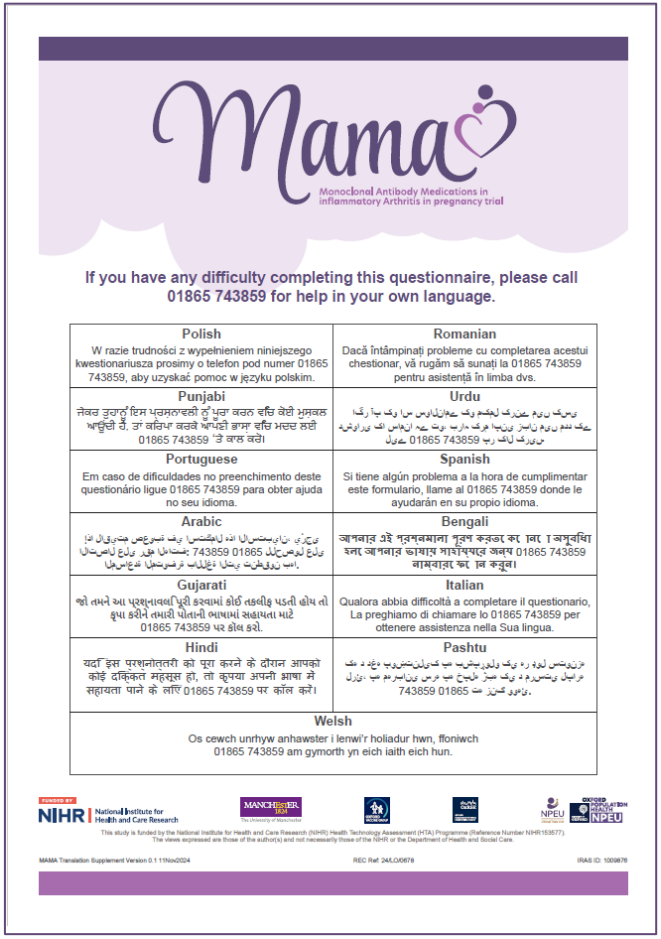
MAMA PILs - – translated into 5 different languages

MAMA will be using Language Line translation service for participant facing follow-up.

Translation Supplement will be provided as part of the MAMA Welcome Pack.

Asks individuals to contact the trial team for assistance in populating the questionnaires in another language.

Translation Supplement



Mama

Monoclonal Antibody Medications in inflammatory Arthritis in pregnancy trial

If you have any difficulty completing this questionnaire, please call 01865 743859 for help in your own language.

Polish W razie trudności z wypełnieniem niniejszego kwestionariusza prosimy o telefon pod numer 01865 743859, aby uzyskać pomoc w języku polskim.	**Romanian** Dacă întâmpinați probleme cu completarea acestui chestionar, vă rugăm să sunați la 01865 743859 pentru asistență în limba dvs.
Punjabi ਜੇਕਰ ਤੁਹਾਨੂੰ ਇਸ ਪ੍ਰਸ਼ਨਨਾਵਲੀ ਨੂੰ ਪੂਰਾ ਕਰਨ ਵਿੱਚ ਕੋਈ ਮੁਸ਼ਕਲ ਆਉਂਦੀ ਹੈ, ਤਾਂ ਕਿਰਪਾ ਕਰਕੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਮਦਦ ਲਈ 01865 743859 'ਤੇ ਕਾਲ ਕਰੋ।	**Urdu** اگر آپ کو اس سوالنامے کو مکمل کرنے میں کوئی دشواری ہو تو براہ کرم اپنی زبان میں مدد کے لیے 01865 743859 پر کال کریں۔
Portuguese Em caso de dificuldades no preenchimento deste questionário ligue 01865 743859 para obter ajuda no seu idioma.	**Spanish** Si tiene algún problema a la hora de cumplimentar este formulario, llame al 01865 743859 donde le ayudarán en su propio idioma.
Arabic إذا واجهت صعوبة في استكمال هذا الاستبيان، يرجى الاتصال بالرقم 01865 743859 للحصول على المساعدة بلغتك.	**Bengali** আপনার এই প্রশ্নমালা পূরণ করতে কোনো অসুবিধা হলে আপনার ভাষায় সাহায্যের জন্য 01865 743859 নাম্বারে কল করুন।
Gujarati જો તમને આ પ્રશ્નાવલિ પૂરી કરવામાં કોઈ તકલીફ પડતી હોય તો કૃપા કરીને તમારી પોતાની ભાષામાં સહાયતા માટે 01865 743859 પર કૉલ કરો.	**Italian** Qualora abbia difficoltà a completare il questionario, La preghiamo di chiamare lo 01865 743859 per ottenere assistenza nella Sua lingua.
Hindi यदि इस प्रश्नोत्तरी को पूरा करने के दौरान आपको कोई दिक्कत महसूस हो, तो कृपया अपनी भाषा में सहायता पाने के लिए 01865 743859 पर कॉल करें।	**Pashtu** که تاسو د دې پوښتنلیک د بشپړولو په وخت کې له ستونزې سره مخ یاست، مهرباني وکړئ خپلې ژبې کې د مرستې لپاره 01865 743859 باندې زنګ ووهئ.
Welsh Os cewch unrhyw anhawster i lenwi'r holiadur hwn, ffoniwch 01865 743859 am gymorth yn eich iaith eich hun.	

NIHR | National Institute for Health and Care Research

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Reference Number NIHR163577). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

MAMA Translation Supplement Version 0.1 11Nov2024 REC Ref: 24/LO/0678 IRAS ID: 1009878

Document box & eISF

Document Box:

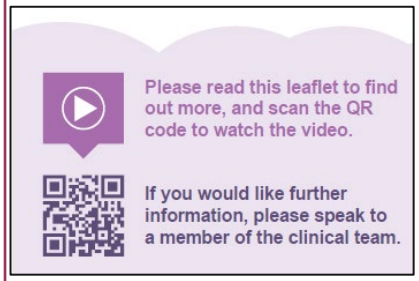
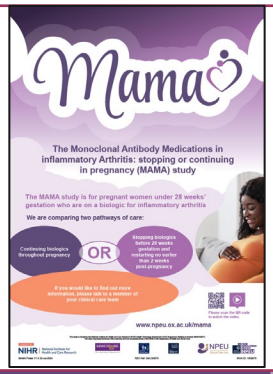
- Trial materials
- Data collection packs
- Guidance sheets

Electronic Investigator Site File (eISF):

- A downloadable electronic site file will be sent to sites; all electronic documents should be kept here
- It should be stored securely and maintained on a backed up and appropriately restricted location

Trial Materials - Women

Trial materials for **women:**

Preconception Information Leaflet	Participant Information Leaflet	Infant Immune Response Information Leaflet	QR Information Card
			
Video	**Welcome card**	**QR Rheumatologists Allocation Card**	**Poster/Banner**
			

Ordering Supplies

Email mama@npeu.ox.ac.uk when you need more documents and trial materials

Mama Guidance

For further information see: **Guidance Sheet: Document box and ISF**

Delegation Log

- Please complete and maintain delegation log throughout duration of the study
- All staff members carrying out study related activities must be on the log and signed off by the PI
- Ensure all columns on the log are correct and complete paying particular attention to the **responsibility codes.**
- **Do not strike through** an entry on the log. If there is an error or you need to update an entry, complete a new line for that individual in the log.
- Enter '**end dates'** for any staff who leaves.

Try and get as many staff members of the Delegation Log as possible.

Mama Delegation Log

NPEU Clinical Trials Unit

PM107-B
Site Delegation Log
MAMA Trial

Study Name:	**MAMA Trial** **IRAS ID: 1009876**	**Title:**	The Monoclonal Antibody Medications in inflammatory Arthritis: stopping or continuing in pregnancy (MAMA) trial	**Page _____ of _____**
Hospital:		**Principal Investigator:**		

Legend

Use this legend to complete the "Responsibilities" column on the next page. For each individual listed in the "Full Name" column, enter the letter(s) (e.g. A, C, E) from the legend below that correspond to their study-related responsibilities. If there are significant protocol related responsibilities that are not already included in the legend, add them in the empty spaces provided below.

Remove/insert additional responsibilities as required

A	Screen patients	F	Provide study-related Training	K	
B	Confirm Eligibility (appropriately trained and experienced doctors, nurses, and midwives)	G	Data collection / resolution of data queries (OpenClinica)	L	
C	Obtain Informed Consent	H	SAE clinical review/causality assessment & sign off*	M	
D	Randomisation	I	Sign off other members of staff on delegation log (PI/Co-PI)**	N	
E	Maintain Investigator Site File (ISF)	J	All of the responsibilities(A-I (PI/Co-PI)**	O	

Note: *This can only be delegated to medically trained doctors. If a research nurse/midwife is the site PI, you will still need medically trained doctors for this task.
** Responsibilities I and J cannot be undertaken by Associate PIs.

The Principal Investigator should sign below during the **Site Close-Out Visit.**

I have reviewed the information on this log and have found it to be accurate. All delegated duties were performed with my authorisation.

Principal Investigator Signature: _____ **Site Close-Out Visit Date:** _____

Delegation Log

Study Name:	**MAMA Trial** IRAS ID: 1009876	**Title:**	The Monoclonal Antibody Medications in inflammatory Arthritis: stopping or continuing in pregnancy (MAMA) trial
Hospital:		**Principal Investigator:**	

This log should include all relevant study staff and other clinical staff who routinely carry out study procedures or who have specific data collection/interpretation responsibilities.

Add new or replacement staff as appropriate. Please send updated copies to the MAMA Co-ordinating Centre.

Note: Please complete the log and obtain the PI's approval before starting study-related responsibilities.

							Delegated Individual		**Principal investigator**	
Full Name *(Please print)*	**Role**	**Responsibilities** *(Use codes listed above)*	**Dates of responsibilities**		**Email address**	**Appropriate GCP?** ✓	**Usual Initials**	**Signature**	**PI's Signature**	**Date**
			From	**End**						

Training and Training Logs

Complete training log for all those trained on the study

MAMA Training includes:

- SIV (attend SIV or read through slides)
- OpenClinica Training (video)
- Randomisation Training (video)

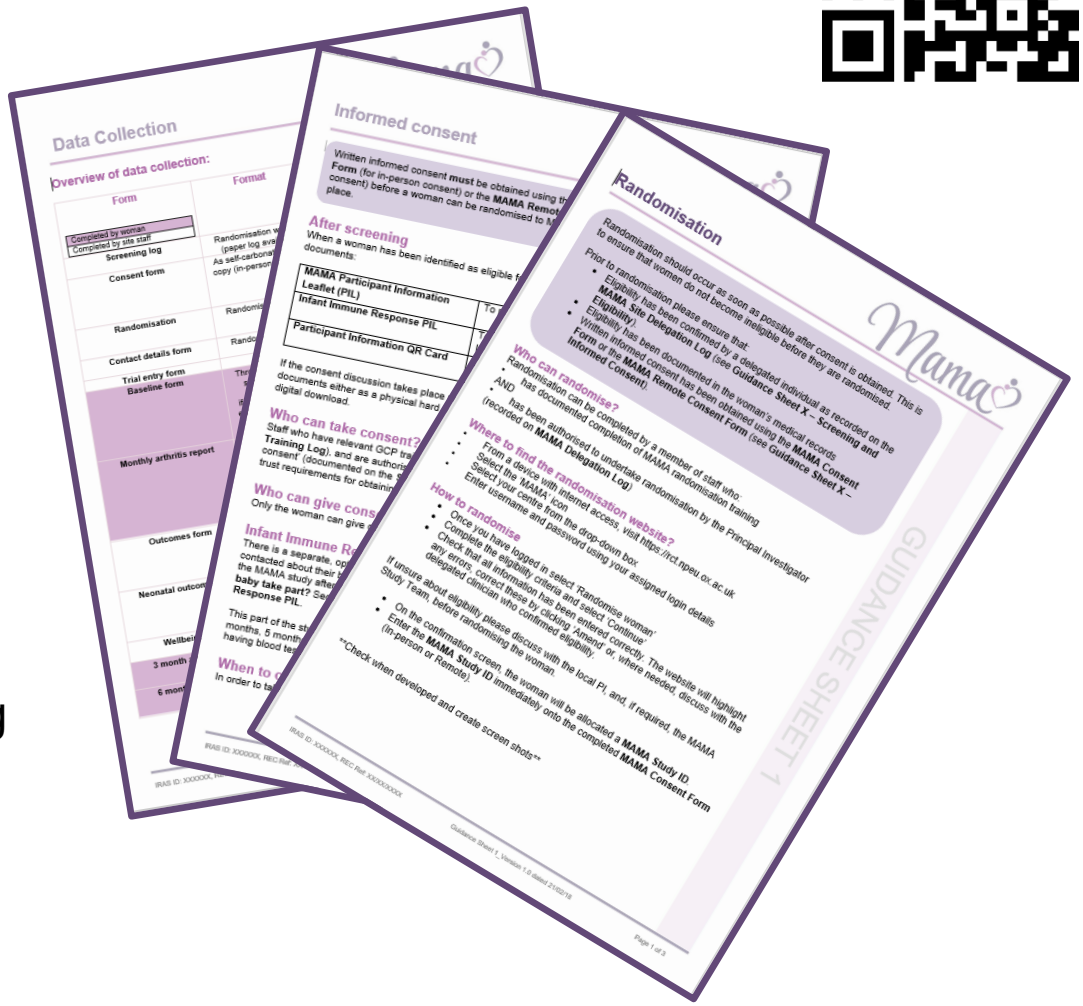
GCP training is essential for the PI and Lead RN.

It is the responsibility of the PI and Lead Research Midwife to:

- **Maintain their training records in the ISF**
  AND
- **Ensure and maintain appropriate training and documentation for their team. For example, completing Training Logs, filing CVs, and GCP certificates.**

Guidance sheets

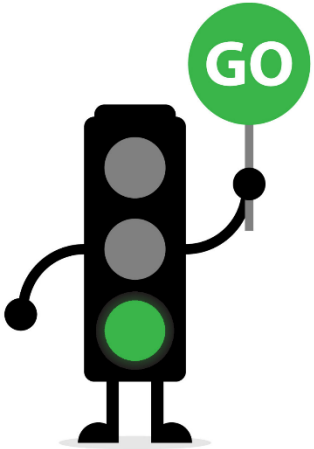
- Trial pathway infographic
- ISF and document box
- Screening & eligibility
- Informed consent
- Randomisation
- Study intervention
- MAMA App
- Data collection
- Safety and Incident Reporting
- Emergency queries
- Change of consent



Site activation

Before we can issue greenlight, the following actions must be completed:

- Receive CV and GCP for PI and lead RM
- Complete delegation log
- At least PI and lead RN trained on and has log in for OpenClinica
- At least PI and lead RN trained on and has log in for Randomisation website
- Complete SIV report
- PI complete protocol sign off sheet
- Download eISF
- Confirm receipt of Document Box
- R&D approvals (fully signed mNCA and C&C from R&D department)



Mama

Thank you for listening!

What can we do to help launch MAMA at your site?