Pregnancy and Rheumatic Diseases 2

Challenges of designing and conducting cohort studies and clinical trials in populations of pregnant people

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Rheumatic and musculoskeletal diseases often affect individuals of childbearing age. The incidence and prevalence of rheumatic and musculoskeletal diseases is rising. More pregnancies in patients with rheumatic and musculoskeletal diseases are anticipated and some rheumatic and musculoskeletal diseases are associated with pregnancy complications (eg, miscarriages, fetal deaths, preterm births, and hypertensive disorders in pregnancy). Despite the need to understand the use of drugs to treat rheumatic and musculoskeletal diseases in pregnancy, clinical trials in pregnancy are rare, therapeutics in pregnancy are understudied, and pregnant individuals are routinely excluded as premarketing trial participants. Data on the effectiveness and safety of disease-modifying antirheumatic drugs are most often based on post-marketing observational data. Observational studies assessing the bidirectional relationship between rheumatic and musculoskeletal diseases and pregnancy, as well as interventional studies of treatments during pregnancy, are scarce. Historical reluctance to perform studies in what was deemed an at-risk group persists in pharmaceutical companies, regulatory bodies, and ethics boards. Additionally, patients must be engaged partners, which requires trust that the research respects the needs and interests of the patient and complies with the rules intended to protect the pregnant person and the fetus from harm. In this Series paper, we share challenges we have encountered in conducting prospective cohort studies and interventional trials of postmarketing approved medications, assessing pregnancy specific outcomes in pregnant women with rheumatic and musculoskeletal diseases in the EU, the UK, and the USA. We discuss the changing landscape around trials in pregnancy and present possible solutions to our challenges.

Introduction

In the journey of pregnancy, every expecting person envisions the joy of cradling a child. Yet, for many, this vision is clouded by an absence of medical knowledge. The US Food and Drug Administration (FDA) noted that nearly 70% of pregnant women take at least one medication (excluding vitamins and supplements) during pregnancy, but the safety and efficacy of these medications during pregnancy are often unknown.[1,2] The scarcity of evidence about medication use in pregnancy puts mothers and babies at potential risk.[3] The exclusion of pregnancy from most clinical trials has left a substantial knowledge gap. Most research funding is used to address diseases that occur more frequently in men, but can affect both men and women, and the majority of recruited study participants are male. With this reality, it is not surprising that clinical trials in pregnancy are rare.[3] Indeed, consider the example of death due to bleeding: there is a wealth of data and research to improve clinical outcomes in traumatic bleeding (the major cause of death of men younger than 40 years),[4] compared with the limited good-quality data on exsanguination from post-partum haemorrhage—the most common cause of death in pregnancy in low-income and middle-income countries.[5]

There are strong arguments to dedicate and prioritise research to improving fetal life, because the intrauterine period effects adult life. The Barker hypothesis, proposed in 1990, argues that difficulties in fetal life, such as intrauterine growth restriction, low birth weight, and premature birth, have a causal relationship with hypertension, coronary heart disease, and maturity-onset diabetes.[6] Therefore, to improve adult life, one needs to optimise fetal conditions. Fortunately, there is growing global recognition that we must advance research in pregnancy and the puerperium. Addressing the gap in knowledge requires effort from regulators, researchers, clinicians, and patients. Strategic initiatives are needed at a global and national level to address the gap and urge regulatory bodies to embrace the entry of pregnant people into clinical trials.[7]

In this Series paper, we reveal challenges encountered by clinical trial teams and provide possible solutions to overcome some of these hurdles. We will also consider a trial design that can include pregnant people. We will focus on barriers and solutions relevant for regulators for clinical trial approvals: the European Medicines Agency (EMA) in the EU, Iceland, Norway, and Liechtenstein; the FDA in the USA; and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. This Series paper is built around the figure, which simplifies this complex topic. Real examples of barriers and potential solutions are provided. Most published work refers to "pregnant women" or "mothers", so we have used these terms throughout this Series when cited studies have. However, we have also used the terms "pregnant people" and "pregnant individuals" where relevant, to reflect that children, transgender men, and gender-diverse people can also be pregnant.

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Current state of prospective cohort studies and clinical trials in pregnant people with rheumatic and musculoskeletal diseases

Rheumatic and musculoskeletal diseases encompass a wide range of conditions that typically affect women of childbearing age[8] who often receive several medications to control their disease. The management of rheumatic and musculoskeletal diseases during pregnancy requires a delicate balance to ensure maternal and fetal wellbeing. Evidence-based management is limited due to the paucity of prospective cohort studies and randomised controlled trials. Prospective observational cohort studies provide a better understanding of the natural history of rheumatic and musculoskeletal diseases during pregnancy, such as the fluctuation of disease activity in rheumatoid arthritis[9] or spondyloarthritis.[10,11] Observational cohort studies also provide valuable insights into the effect of rheumatic and musculoskeletal diseases on maternal and fetal outcomes, and identify related risk factors for adverse pregnancy outcomes, particularly in patients with systemic lupus erythematosus and antiphospholipid syndrome.[12,13] These insights guide the timing and adaptation of therapeutic strategies during pregnancy, such as antithrombotic treatment in antiphospholipid syndrome.[14] Importantly, observational studies have shown an increase in adverse pregnancy outcomes in active disease, when compared to quiescent disease.[15] Despite these data, the safety of many drugs and biologics for the treatment of rheumatic and musculoskeletal diseases during pregnancy is poorly defined.

To advance research, the European Alliance of Associations for Rheumatology (EULAR) has made recommendations for core datasets for pregnancy registries in rheumatology[16] and a European Network of Pregnancy Registries in Rheumatology (EuNeP).[17] Although data are still scarce for less common connective tissue diseases, observational studies have been established in the last 20 years for several of the more common rheumatic diseases: systemic lupus erythematosus,[12,13] antiphospholipid syndrome,[14,18] rheumatoid arthritis,[9] spondyloarthritis,[11] and systemic sclerosis.[19] Non-controlled prospective studies have also evaluated treatments, such as certolizumab pegol, during pregnancy in patients with chronic inflammatory diseases[20] or hydroxychloroquine for the prevention of congenital heart block.[21] A systematic search on public clinical trials registries revealed 11 cohort studies involving pregnant people with any rheumatic or musculoskeletal disease assessing pregnancy-specific outcomes (table 1) and only three active randomised controlled trials.

Because of the paucity of interventional trials in pregnant people with rheumatic and musculoskeletal diseases, there is a considerable scarcity of evidence-based guidance to treat the underlying disease during

	Regulators	Ethics boards	Sponsor	Funders	Trial teams	Patients
Barriers	Label content and language	Complexity to obtain multiple approvals (for multicentre trials)	Risk aversion: reluctant to take responsibility for trials including pregnant people	Historic under-prioritisation of women's health	Ethical consideration and feasibility for trial team	Concerns about medication (in interventional studies)
	Trial approval: lack of experience with pregnancy trials	Over cautiousness or reluctance to consider pregnant people			Require extreme dedication and capacity of trial teams (especially for investigator-initiated trials)	Inconvenience of study visits
	GDPR (EU)					Possible barriers and fears from partner or wider network
Solutions	Use of more nuanced language or less restrictive language regarding the inclusion of data from existing guidelines	Central ethics approvals (as for ultra-rare diseases) allowing remote consent	Shift of perception (aligned with regulator and ethics boards)	Prioritisation of funders	Adding pregnancy trials to medical society agenda	Trusting patient–doctor relationships
	Trial approval: use of standing committees of experts	Use of expert advisors	Use of expert advisors	Increase dedicated funding	Protected time for investigators	Combine research visits with routine visits
	Use of (ultra)-rare disease authority frameworks	Shift of perception from protecting patients from research to helping them through research	Define the risk of a pregnancy trial relative to other trials		Potential collaboration with pharmaceutical companies in selected trials	Include third-parties in consultations

Figure: **Barriers and solutions for the conduct of clinical trials and prospective cohort studies in pregnant people with rheumatic and musculoskeletal diseases**
The top half of the figure highlights barriers we have faced at the regulator, ethics board, sponsor, funder, trial team, and patient level when conducting prospective observational and interventional studies assessing pregnancy outcomes in people with rheumatic and musculoskeletal diseases. The bottom half represents considerations for solutions to these barriers. Further detail on these barriers and solutions can be found in panels 1–5. GDPR=General Data Protection Regulation.

pregnancy. How can we optimise treatment for rheumatic and musculoskeletal diseases during pregnancy when pregnant people are excluded from trials? Our review of studies registered on public domains at any time up to and including 2023 showed that most exclude pregnant people, and they require patients who become pregnant during the study to withdraw from the trial. Although the practice of withdrawing trial medication could protect the fetus from potential adverse exposure, it can also cause a flare of the pregnant person's disease in a patient who is responding to the medication—this flare, in turn, could adversely affect the pregnancy. The outcomes of patients in trials who have unintended pregnancies should be reported. There is also an unmet need for treatments for rheumatic and musculoskeletal diseases and specific antibody profiles that have a direct effect on pregnancy outcomes, such as antiphospholipid antibodies and anti-Sjögren's syndrome-related antigen A (SSA). In our experience, these trials are generally well accepted by patients, because patients perceive a benefit to the fetus.

We believe it is essential to conduct research in pregnant individuals. Delaying inclusion until after all testing in non-pregnant populations is completed is problematic as it typically takes years for evidence on their use in pregnancy to accumulate. Furthermore, we cannot wait for or rely on limited, non-incentivised collection of post-hoc observational data. Pregnant and non-pregnant individuals differ in their physiology: metabolism, pharmacokinetics, and efficacy of drugs might not be the same in these two populations.

In this Series paper, we focus on interventional studies of approved drugs used in pregnant people in which rheumatic and musculoskeletal diseases have a direct effect on maternal and fetal pregnancy outcomes. Randomised controlled trials are the gold standard to improve care, but they remain extremely rare in pregnant people. We also focus on the challenges associated with the conduct of prospective cohort studies. Table 1 shows the current registered prospective cohort studies and clinical trials in pregnant women with any rheumatic or musculoskeletal disease that include pregnancy specific outcomes; the table indicates that there are very few randomised controlled trials or open-label studies on public trial registries aiming to improve pregnancy outcomes in people with rheumatic and musculoskeletal diseases.[22–24]

Why are clinical trials in pregnant people with rheumatic diseases so difficult to conduct?

The ethical guidelines governing clinical trials, designed to safeguard participants, often lead to the exclusion of

	Trial design	Location of trial
Australia and New Zealand Clinical Trials Registry (ANZCTR)		
Prospective, randomized, controlled pilot study of aspirin plus nitric oxide donors treatment of recurrent abortion due to primary antiphospholipid syndrome	Randomised controlled trial	Australia
EU Clinical Trials Registry (CTIS)*		
HYPATIA: a prospective randomised controlled trial of hydroxychloroquine to improve pregnancy outcome in women with antiphospholipid antibodies	Randomised controlled trial	Multinational
EU Clinical Trials Registry (EudraCT)		
Evaluation of the benefit of adjuvant treatment with hydroxychloroquine to usual medical care for uncomplicated term pregnancy in patients with primary obstetrical antiphospholipid syndrome (HYDROSAPL)†	Randomised controlled trial (inactive)	France
US Clinical Trials Registry (ClinicalTrials.gov)		
The clinical features and pregnancy outcomes of patients with rheumatoid arthritis	Prospective cohort	China
Apremilast pregnancy exposure registry	Prospective cohort	United States
Stelara and tremfya pregnancy exposure registry OTIS autoimmune diseases in pregnancy project	Prospective cohort	United States
OTIS autoimmune diseases in pregnancy project	Prospective cohort	United States
The lupus pregnancy cohort: an international prospective cohort of lupus pregnancies (LEGACY)	Prospective cohort	Canada
Treatment and clinical outcomes among patients with systemic lupus erythematous in pregnancy	Prospective cohort	China
Maternal autoimmune disease research alliance registry	Prospective cohort	United States
At the heart of the matter—speckle tracking echocardiography in mothers with systemic lupus erythematous and their offspring	Prospective cohort	Canada
Pregnancy and medically assisted conception in rare diseases (EGR2)	Prospective cohort	France
Fetal-hope study: home monitoring of fetal heart rate in anti-Sjögren's syndrome-related antigen A positive pregnant women (FH)	Prospective cohort	Italy
Use of warfarin after the first trimester in pregnant women with antiphospholipid syndrome	Randomised controlled trial	Egypt
IMPACT study: improve pregnancy in antiphospholipid syndrome with certolizumab pegol therapy	Open label trial	United States, Canada
Hydroxychloroquine in primary antiphospholipid syndrome (HYDROSAPL)†	Randomised controlled trial (inactive)	France
Pregnant women with or without primary antiphospholipid antibody syndrome	Prospective case-control	Italy

OTIS=The Organization of Teratology Information Specialists. *New registry in the EU: as of Jan 31, 2023, all EU and European Economic Area initial clinical trial applications must be submitted through CTIS. †HYDROSAPL, which is currently inactive, is registered on both EudraCT and ClinicalTrials.gov.

Table 1: **Current registered cohort studies and clinical trials in pregnant women with any rheumatic or musculoskeletal disease examining pregnancy-specific outcomes**

pregnant women and those of reproductive age. This exclusion is, in part, due to historical events in research. Such exclusion, while intended to protect, paradoxically impedes the collection of crucial data necessary for informed treatment decisions in these populations.[25] The unintended consequence of this protectionist ethic is to harm the population that was meant to be protected.

Our experiences with the GR2 study (NCT02450396; a multicentre, French, prospective observational study), the HYPATIA study (EudraCT 2016-002256-25; a multicentre interventional study conducted in the EU, the UK, and Canada) of hydroxychloroquine (approved for rheumatoid arthritis, and discoid or systemic lupus erythematosus) to improve pregnancy outcome, the IMPACT trial (NCT03152058; a multicentre, investigator-initiated, interventional study) of certolizumab pegol (approved for rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, and psoriasis) to improve pregnancy outcomes, and the PROMISSE study (NCT00198068; a multicentre, multinational, prospective observational study), provide insights into this multifaceted issue. In this section we will outline the major barriers we faced as shown in the figure. Potential solutions for each hurdle are addressed later in the paper.

Regulators—content and language of labels for medications

Medicines regulators (EMA, FDA, MHRA, etc) authorise and safeguard the conduct of clinical research. They also oversee labelling of human marketed medications, ensuring that they are safe and effective. National regulatory authorities contribute to the process by safeguarding compliance at the national level. Specifically, for interventional drug trials of marketed drugs, the label design has a crucial influence on indications of medication. The EMA's and MHRA's summary of product characteristics and the FDA's prescription drug labelling (the package insert) are the key safety reference documents and contain information necessary to inform safe and efficacious use of drugs.[26–28]

As pregnant and lactating people have historically been excluded from most clinical trials, there is a scarcity of human data to inform therapeutic decisions about the benefits and risks of medication use during pregnancy and breastfeeding. Therefore, evidence informing the label content on pregnancy use is predominantly based on animal studies. If human data are incorporated, they are primarily derived from post-approval observational research, such as pregnancy registries and database studies.[29]

Regulators base labelling recommendations on a comprehensive review of available data and focus on the quality and clinical relevance of the evidence. The summary of product characteristics and package insert present information on drug use in pregnancy differently. The FDA uses a narrative approach that provides a comprehensive overview compared to the EMA's systematic approach.[29] FDA guidance provides overviews of data in pregnancy, including labour and delivery, breastfeeding, and in reproductive-age individuals, and no longer uses a letter classification to categorise safety.[30] In contrast, EMA summary of product characteristics guidance combines conclusions from animal studies and available human data, and provides recommendations on the use of the medication during different gestation periods.[31] The summary of product characteristics safety information of drug use in pregnancy is based on comparison with a healthy population (ie, the relative risk to the background population), rather than to a population with underlying medical conditions, including rheumatic and musculoskeletal diseases.[26]

For example, the FDA package insert for hydroxychloroquine (used in the HYPATIA study) links to the MotherToBaby registry, which provides the current evidence on medication use in pregnancy and lactation.[32] The package insert includes a section on clinical considerations, which elaborates on disease-associated maternal risk, and risk to the fetus.[32] The FDA's pregnancy labelling includes a summary statement about the risk of untreated disease during pregnancy that allows nuanced discussions between patients and health-care providers regarding the potential risks and benefits of medication use during pregnancy.[33] In contrast, the summary of product characteristics (used in the UK and EU) contains epidemiological data and animal studies, but contains no information on disease-associated risk, nor are there links to a pregnancy registry.[34] Thus, in daily practice, product information in the EU and UK for patients with an underlying rheumatic disease (or any other chronic illness) and health-care professionals, might be difficult to put into perspective taking into account the individual risk of the disease.[35] In the case of certolizumab pegol (used in the IMPACT trial), the FDA included considerations on disease-associated maternal risk, risk to the fetus, and also links directly to the MotherToBaby registry.[36,37]

Safety reference documents and labels inform the sponsor of trial monitoring needs (high risk, risk-based, etc), study insurance cost, and, potentially, also affect patient willingness to enrol in a clinical trial. Product safety documentation and medicine labelling can hinder interventional pregnancy studies. For example, a drug to be studied that is indicated for a rheumatic or musculoskeletal disease could be simpler to trial than one that is used off-label.

Regulators—approval of trials that include pregnant people with rheumatic diseases

Until 2018, the FDA labelled pregnant individuals as vulnerable adults (along with prisoners and those with intellectual disabilities),[38] a category for those who cannot adequately consent to research due to limitations of capacity or circumstance. Pregnant people do not share this limitation by virtue of pregnancy. Although the protectionist ethic emphasised prevention of exposure risk, it disregarded the autonomy of pregnant people and

hindered clinical research. The protectionist ethic might have resulted in harm to pregnant people and fetuses by limiting the capacity to collect data to inform safe and effective use of therapies during pregnancy.[25] Although the vulnerable adult label is no longer applied to pregnant people in the context of clinical trials, remnants of the protectionist ethic are still present within institutional review boards (also known as ethics committees), and regulators.

In June, 2022, the US National Academies of Sciences, Engineering, and Medicine (NASEM) had a workshop to develop a framework to address legal, ethical, regulatory, and policy issues for research specific to pregnant and lactating people. This workshop was part of a consensus study to discuss how institutions and organisations make risk–benefit decisions regarding the inclusion and exclusion of pregnant and lactating persons in clinical research, and considered the role of real and perceived liability, health equity, risk management, and trial insurance. NASEM advocated for abandoning the concept of protecting pregnant people from research because of the absence of evidence of medication safety and efficacy results in increased risk and moving towards fair inclusion of pregnant people in clinical trials.[39]

All clinical trials require a robust protocol detailing the rationale, methods, organisation, and ethical considerations. Scarce data on the safety and efficacy of many drugs in pregnant people forces regulators to be cautious when reviewing trials during pregnancy. Regulators seek to limit exposure to interventions to those who might have a reduced benefit or to those with confounding risk factors, particularly for off-label indications. In the HYPATIA study of hydroxychloroquine and the IMPACT study of certolizumab pegol, both drugs were used for an off-label indication. The IMPACT trial team had cautious regulators, requiring more restrictive inclusion and exclusion criteria (panel 1), which restricted enrolment. The HYPATIA study team faced similar regulatory cautiousness. Hydroxychloroquine is approved for the treatment of systemic lupus erythematosus and rheumatoid arthritis and gained orphan drug designation for the treatment of antiphospholipid syndrome under the EMA in 2017. However, for the purpose of the HYPATIA trial, the use of hydroxychloroquine is off-label and the trial team had to implement several extra visits for trial participants, including eye and ear tests for newborn babies (panel 2).

Another major hurdle for trial teams conducting clinical trials in pregnant people with rheumatic and musculoskeletal diseases is that, in most cases, they require a multicentre design to enrol enough patients. The IMPACT trial team found that the FDA's rare disease study approach, which allows one centre to consent, enrol, and monitor patients remotely, maximised study success (panel 1). The HYPATIA study is also a multicentre study, but central consenting and monitoring does not currently exist in the EU (panel 2).

Regulators—GDPR in the EU

The General Data Protection Regulation (GDPR), initiated in 2016, is a crucial component of EU privacy and human rights law. With the aim of protecting individuals from the data practices of private corporations, these laws have important consequences for the conduct of clinical trials. These practices span four main areas. Data transfer restrictions for personal data going outside the European Economic Area (EEA): in multinational studies, these restrictions can prevent sharing patient data between study sites, particularly those outside the of EEA. Consent specifications mandate explicit and informed consent for data collection and processing: patients must be informed about how their data will be used, which can be challenging when planning multi-phase or long-term studies where exact data usage could evolve over time. Studies in pregnant patients usually require having data on the neonate or child. The collection

Panel 1: Regulator approval process under the US Food and Drug Administration and ethics board approval for off-label drug use—experiences from the IMPACT trial

Off-label interventional study teams can face a regulator (and ethics board) that prioritises precaution over possible benefits in a high-risk population for obstetric morbidity. The IMPACT trial (NCT03152058) serves as an example. This open-label, single-stage, phase 2 study examines the effectiveness of certolizumab pegol (in addition to heparin and low-dose aspirin) during pregnancy in reducing unfavourable outcomes such as fetal death, pre-eclampsia, and placental insufficiency in pregnant people with clinical antiphospholipid syndrome and lupus anticoagulant. Patients from the PROMISSE study, who would have met criteria to participate in the IMPACT trial, serve as untreated controls. Certolizumab pegol is given from 8 to 28 weeks gestation. Researchers obtain medical reports and blood samples monthly and contact patients every 2 weeks.
The IMPACT study team had several challenges, including cautious inclusion and exclusion criteria mandated by regulators (urine protein to creatinine ratio, age, prednisone dose). Babies born to participants in the IMPACT trial must be monitored every 3 months until 12 months of age, requiring continued contact for 1 year after delivery. Despite these challenges, the recruitment is nearly complete.

Lessons learned

- Existing regulation requires a research team with resources to ensure that follow up can happen.
- Rare and ultra-rare disease authority frameworks: these frameworks allowed the team to enrol patients under the rare diseases umbrella using a single site's institutional review board approval and obtain verbal consent over the telephone when enrolling participants, followed by providing written consent electronically. Medical records had to be requested during and after the pregnancy and biological samples had to be shipped overnight from remote locations to the co-ordinating site.

Considerations moving forward

- Consideration of medical society guidelines on drug safety by regulators.
- Standing committee of experts could advise on the risk of the interventional drug trial (advice on risk of drug and feasibility of trial).
- Existing registries (such as the MotherToBaby registry) collect information on medication exposure during pregnancy. The registry infrastructure could be used to record long-term outcomes, rather than adding long-term follow up which adds time and expense to trials.

This panel relates to the Regulators and Ethics Boards elements of the figure.

of such data might require the consent of the coparent, further complicating the process. Data minimisation and purpose limitation emphasises collecting only necessary data and using it solely for the intended purpose. These practices can restrict the breadth of data collection, potentially limiting the comprehensiveness of studies. Finally, GDPR outlines the right to erasure. Patients can request the deletion of their data, including in backup systems. Total erasure might be impossible to completely achieve and can compromise the continuity and completeness of research.

For the study team of the GR2 study, the implementation of GDPR had profound consequences—a reconsent for all participants (>2700) was considered by the sponsor, as was the requirement to obtain consent from both coparents. The complexity of the GDPR process, combined with the need to interpret its guidelines, and the requirement for retrospective application, have led to a delay in decision making on whether reconsent is necessary for all participants, including potential coparents. Panel 3 outlines how the GDPR law affected the activity of the GR2 study.

Panel 2: Regulator approval process under the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) for off-label drug use—experiences from the HYPATIA trial

The HYPATIA study is a randomised controlled study of hydroxychloroquine in women with antiphospholipid antibodies who are planning to become pregnant (EudraCT 2016-002256-25). The HYPATIA study was evaluated under the Voluntary Harmonisation Procedure (VHP) umbrella including three member states (the UK, Denmark, Italy) in 2017–18. Following the VHP application in February, 2017, and divergent VHP outcome from the three member states resulting in rejection, VHP approval was given in November, 2017, with the request to amend the protocol in all member states as patients were classified as vulnerable and high risk. Within the assessment, one VHP member state indicated that given the potential vulnerability and risk level of patients included in the trial, that all participants needed serial blood samples, repeated eye assessments, and a one-off ear and eye test on babies born to the mothers who participated in the HYPATIA study. This practice was not, and is not, standard of care and resulted in several extra visits for trial participants and in a substantial inflation of the excess treatment costs for the study resulting in the loss of recruiting sites in the UK. The timeline from VHP submission (February, 2017) to regulatory approval (November, 2017, in the UK and June, 2019, in Denmark) and ethics approval in two of the three countries took over 2 years. The study team had to change sponsors from the UK to the EU and has received Clinical Trials Information System (CTIS) approval, which took 9 months from application to approval of phase 1 and 2.

Lessons learned

- Existing regulation resulted in extra monitoring of participants and babies.
- Existing regulation resulted in excess treatment costs which resulted in loss of recruitment sites in the UK.

Considerations moving forward

- Standing committee of experts could advise on the risk of the interventional drug trial (advise on risk of drug and feasibility of trial).
- Collaboration between regulator and trial teams: in February, 2023, the EMA published several initiatives to boost clinical trials in paediatric populations. Although one focus under the programme is to support medicines innovation, another defined focus is to align international requirements for paediatric clinical trial authorisation and standards through the European network of paediatric research at EMA.[1] We believe this would also be beneficial for pregnant people with rheumatic and musculoskeletal diseases.

This panel relates to the Regulators element of the figure.

Ethics boards

Institutional review boards or research ethics committees provide core protection for human research participants through advance and periodic independent review of the ethical acceptability of proposals. Ethics committees must balance the potential benefits of an interventional trial or observational study with the risks. They can request additional safety measures, changes in inclusion and exclusion criteria, or additional examinations of patients and their babies (panels 1 and 4).

When exposing pregnant people to an intervention, research teams also need to access outcome data from the newborn. In the EU, some ethics boards require consent from one or both parents to align with ethical standards of consent, respecting the autonomy and involvement of both parents in decisions affecting the child. It also ensures that both parents are informed about the trial and its potential effects on the child, leading to a more comprehensive understanding of the trial's risks and benefits. Though recognised as essential, these mandates lead to logistical challenges with potential delays or limitations to participation in research. The GR2 study team had major difficulties when the reconsent of more than 2700 previously enrolled individuals (including coparents) was required to comply with GDPR (panel 3). The WHO Council for International Organisations of Medical Sciences ethics document does not recommend requiring paternal consent.[40]

Sponsors

A sponsor is the organisation or person that accepts the overall responsibility for the trial: arranging, setting up, managing its implementation, and reporting the results. The sponsor is responsible for ensuring that a clinical trial complies with the legislation and good clinical practice. For interventional drug studies, a sponsor is legally required for trials.

Sponsors generally seek low-risk, high-reward investments. Trials to prevent pregnancy complications in patients with rheumatic diseases or to assess safety in pregnancy of medications used to treat rheumatic diseases are complex and such patients are uncommon. They often will require multicentre, multinational setups at great expense to potential sponsors, with little financial upside. Efforts to communicate the scientific importance and potential clinical impact are crucial and require broad advocacy. The HYPATIA study team found that moving from one institutional sponsor to an expert sponsor (a named expert as sponsor representative) lightened bureaucratic burden for the trial team. Panel 5

is an example of sponsorship challenge and how it was overcome by having an expert clinical trials sponsor representative.

Funders

Research in women's health has been underfunded for decades[3,41] leading to a scarcity of robust clinical data regarding the management of several areas within the field of women's health. Rheumatic and musculoskeletal diseases are particularly relevant, as these chronic conditions often affect women of childbearing age. Their incidence and prevalence are rising,[8] and as the obstetric population is growing older and the use of assisted reproduction techniques are evolving, we anticipate more pregnancies in patients with rheumatic and musculoskeletal diseases in the future.

Prioritisation of this area by funders is crucial to reshape the landscape of clinical trials in the field of rheumatic and musculoskeletal diseases and pregnancy. As the main public funder in the UK, the National Institutes for Health and Care Research has called for a greater focus on women's health and is actively promoting research during pregnancy.[42] The main public funder in the USA, the National Institutes of Health, has established Maternal Health Research Centers of Excellence, which focus on advancing and promoting maternal health equity. The National Institutes of Health also strongly encourages including pregnant people in clinical research whenever it is scientifically valid and ethically appropriate. In the EU, the EMA Regulatory Science to 2025 Strategic Reflection advocates inclusion of neglected populations such as pregnant people, older people, and those of diverse ethnicities in clinical trials.[43] Accordingly, the EMA will support "initiatives in maternal–fetal health with other regulators and international stakeholders, to advance access through better understanding and communication of benefits, risks, and uncertainties of medicines use in pregnancy and breastfeeding".[43]

Trial teams

In addition to the feasibility barrier discussed previously, an obstacle for researchers considering a trial in pregnant patients involves ethical considerations that arise from potential risks to maternal and fetal health. Data on the safety and teratogenicity of drugs in pregnancy are limited, as pregnant people are often excluded from preclinical and early phase studies even if the drugs under investigation are considered safe in pregnancy.[44] The thalidomide tragedy shall never be repeated, and many seem to forget that regulators such as the FDA protected the USA from the tragedy, and medication regulation as we know it today in the EU did not exist at the time.[25] The protectionist ethic that resulted from the thalidomide tragedy has led to the exclusion of people who are pregnant or of childbearing age from most trials. This exclusion was evident in the COVID-19 treatment trials, where 80% of 155 treatment trials of non-biological drugs and 74% of 176 non-teratogenic treatment trials specifically excluded pregnant people.[45] The exclusion was not well justified, as many of the treatments evaluated had no or low safety concerns during pregnancy.[45] Of note, randomised controlled trials that excluded pregnant people were more likely to have industry sponsorship than those that did not.[44] As is the case for all clinical trials, the risks should not be used to prevent inclusion of a large

Panel 3: **How General Data Protection Regulation (GDPR) affected trial activity of the GR2 study**

The French GR2 study is a prospective observational study that evaluates pregnancies in women affected by rare diseases, rheumatic diseases, or both, including systemic lupus erythematosus, antiphospholipid syndrome, and other autoimmune conditions. The study aims to predict pregnancy complications by assessing factors like lupus anticoagulant presence, disease damage, and remission. The study focuses on maternal health and potential pregnancy complications.

The GR2 study was initiated before the GDPR came into effect in 2018. Upon implementation of the GDPR, the study team was asked by the sponsor to stop the study. After several discussions with the sponsor and among the different teams of the sponsor (that are changing regularly), the study team was asked to have each mother and coparent sign a new consent form, including those who had been recruited retrospectively (>2700 participants). This led to several discussions due to the complexity of the GDPR and the fact that its application is subject to interpretation. Currently, this is still under discussion and evaluation. Also, the sharing of data with colleagues has become extremely complicated, especially outside of the EU. Indeed, data from a patient with a rare disease and a rare outcome (for instance a catastrophic antiphospholipid syndrome postpartum), in which the child's year of birth and birthweight need registration, could be considered as pseudoanonymised by the sponsor. This precludes the simple sharing of data.

Lessons learned

- The strict interpretation of EU regulations can lead to major difficulties when considering international academic collaboration. In particular, anonymisation of data, a prerequisite for data sharing, could be considered impossible for patients with rare and ultra-rare diseases.

Considerations moving forward

- Establish a secure, centralised data repository within the EU. Data from non-European Economic Area countries can be anonymised before being uploaded, ensuring GDPR compliance while still allowing for multinational collaboration. The sharing of anonymised data with colleagues must be simplified.
- Dynamic consent models can be implemented, which allow patients to give tiered or modular consent, offering them flexibility and transparency while also accommodating the evolving nature of research. Patients could consent to have data shared for academic research, for research with pharmaceutical companies, or other, and consent for their data to be shared inside or outside of the EU. Data on the children are needed as an outcome of the pregnancies. If these data can be obtained verbally (and do not require extra visits for the child), this should be possible without the consent of the co-parent.
- Collaborative agreements could be implemented. This could include agreements with partner institutions outlining standardised GDPR-compliant data collection and processing procedures.

This panel relates to the Regulators element of the figure.

Panel 4: Ethics boards in the PROMISSE study and the IMPACT trial

The PROMISSE study (NCT00198068) was a prospective, multicentre, observational study to identify markers that predict poor pregnancy outcomes in patients with persistent antiphospholipid antibodies, systemic lupus erythematosus, or both. The PROMISSE study, funded by the National Institutes of Health from 2003–13, enrolled 496 pregnant patients with antiphospholipid antibodies, systemic lupus erythematosus, or both, and 210 pregnant healthy controls. Patients were enrolled before 12 weeks gestation at eight sites in the USA and one site in Canada. Participants were followed monthly with examinations, obstetric ultrasounds, laboratory-required and research blood collection. Prospectively collected longitudinal clinical, laboratory, and biomarker data from the PROMISSE study have enabled the creation of risk stratification models and biomarker predictors of adverse pregnancy outcomes—discoveries that have influenced the counselling and care of patients and provided the basis for an interventional trial to prevent adverse placental insufficiency in pregnant women with antiphospholipid syndrome. Studies that enrol pregnant people are often perceived as high risk by regulators and the institutional review board, mostly due to historical reluctance.

Lessons learned

- Logistics of a multicentre study with multiple institutional review boards are complex.
- Patients with systemic lupus erythematous, antiphospholipid antibodies, or both, want to be in studies and to learn about and help others with their diseases—few patients declined participation (<1%).
- Patients are engaged and part of the team—very few people were lost to follow up (<2%).
- Relationship between patient and study co-ordinator: accessibility and approachability; patients were happy to have another support person to see monthly.
- No difficulty enrolling patients from ethnic minorities, in part due to site selection to maximise diversity.

Considerations moving forward

- Enrolment of healthy controls (less engaged), less willing to make the extra visits (approximately 40% declined participation).
- Institutional review boards approve studies in pregnant people when the risk–benefit balance is clear; PROMISSE had eight sites, each with its own institutional review board. Starting in 2018, National Institutes of Health-sponsored studies require a single institutional review board for most studies involving multiple sites with the purpose of enhancing and streamlining the institutional review board review process so that research can proceed as effectively and expeditiously as possible.

This panel relates to the Ethics Boards element of the figure.

section of the population but rather need to be balanced against the potential benefits. In the case of rheumatic and musculoskeletal diseases, the benefits include the positive effects on the pregnant person, fetus, and child, that come with treating the underlying condition during pregnancy and the puerperium.

Patients

Patient concern about potential harm to their unborn child can lead to reluctance to take part in clinical trials. With the current information gap on drug safety in pregnancy, patients might not be able to gauge the risk of taking the drug relative to not taking treatment for their condition. Fears of family members can also influence decisions to participate in a clinical study (non-interventional or interventional trial). Frequent visits or additional monitoring could also be a deterrent, especially if the individual already attends multiple clinics to manage both their disease and their pregnancy. Clinical research teams must be flexible and adapt to the patients' needs (panel 1).

For example, the PROMISSE study enrolled over 700 patients and followed them monthly through pregnancy (panel 4). To minimise inconvenience to patients, a study team member met each patient at their monthly obstetric visit and collected blood samples and clinical data. Patients were true partners in the PROMISSE study with 208 (3·8%) of 5473 of those offered enrolment declining— the majority of these refusals were people being recruited as healthy controls. Seven (0·9%) of 758 of the enrolled patients who were pregnant were lost to follow up. Contrary to what was expected, patients wanted to be part of this observational study to define predictors of adverse pregnancy outcomes in systemic lupus erythematosus and antiphospholipid syndrome, knowing that there was no direct personal benefit (but also no risks).

Suggestions for solution—how to make pregnancy trials easier to conduct?

Regulators—content and language of labels for medications

The HYPATIA trial of hydroxychloroquine shows how drug safety information affects clinical trials and their participants. An unprecedented global response followed the EMA background information update on hydroxychloroquine that suggested an increased risk of teratogenicity.[46] Experts in the field of pregnancy and patient representatives voiced united concerns and advocated for a more systematic approach to present available safety evidence.[47] They called for closer communication between regulators and clinicians to prevent direct and indirect harm to pregnant patients with rheumatic and musculoskeletal diseases who require treatment with hydroxychloroquine during pregnancy.[46,47] At present, almost all medications used in pregnant people with rheumatic and musculoskeletal diseases are used off-label. The IMPACT trial shows how the labelling of a medication affects the conduct of interventional studies. Certolizumab pegol, a tumour necrosis factor inhibitor, was the proposed experimental treatment to prevent placental insufficiency and pre-eclampsia in patients with antiphospholipid syndrome. Certolizumab pegol does not cross the placenta and has been shown to be safe in registry data of pregnant people.[48–50]

The data on pregnancies in people with rheumatic and musculoskeletal diseases exposed to certolizumab pegol were systematically reviewed by all major rheumatology societies including the American College of Rheumatology (ACR), EULAR, and the British Society for Rheumatology (BSR), and their guidelines agree on its compatibility during the periconception period and during pregnancy.[48–50] Regulators should consider these evidence-based and expert-based guidelines and include clinicians from the guideline panels in their

pharmacovigilance teams. The BSR guidelines consider risk of drug use in pregnancy in people with rheumatic and musculoskeletal diseases relative to not treated disease controls and to the general population. Such data should be displayed on medication labels.[48,51] According to the systematic literature reviews informing the EULAR, ACR, and BSR guidelines, certolizumab pegol and hydroxychloroquine are compatible with pregnancy and breastfeeding.[48–50] Moreover, links to ongoing pregnancy registries, such as MotherToBaby, are useful for those reading the summary of product characteristics.[37]

Standing committees composed of expert clinicians who treat pregnant people with rheumatic diseases in pregnancy, and those with experience developing guidelines, can address the nuances regarding risk benefit assessment of medication use in pregnant people with these diseases. These expert clinicians are also well placed to provide information on how subtle differences in wording can influence patient perceptions of medication safety. Standardised approaches to labelling medications that refer to pregnancy outcomes in untreated rheumatic disease support shared decision making between patients and their health-care professionals, many of whom only deal with this situation infrequently.

Regulators—approval of trials that include pregnant people with rheumatic diseases

Given that pregnancies in patients with rheumatic diseases (systemic lupus erythematosus, antiphospholipid syndrome, vasculitis, systemic sclerosis, etc) fall into the category of rare diseases, enrolment in clinical trials for these individuals is challenging. The IMPACT study enrolled patients under the rare diseases umbrella using a single site's institutional review board approval and obtained written consent following remote contact with patients by telephone. This approach was crucial for the success of the trial which enrolled 50 patients throughout the USA and Canada over 5 years. A solution to facilitate such rare disease studies in the EU and UK could be the establishment of a single regulatory approval via a centralised ethics review process.

The IMPACT study also highlighted the potential benefit of a standing committee of experts within the area of relevance for individual clinical trial in pregnancy. The data safety and monitoring board, responsible for oversight of patient safety, was composed of a rheumatologist, a maternal–fetal medicine doctor, a neonatologist, an ethicist, and a statistician.

Likewise, a solution for the future could be a standing committee of experts within the area of relevance for individual clinical trials in pregnancy under the EMA and MHRA. Such a committee would allow regulators and researchers to have collaborative dialogue and would foster mutual understanding, facilitating tailored guidelines while maintaining safety standards.

***Panel 5:* Sponsorship approval from the HYPATIA trial**

The HYPATIA study team was successful in receiving full National Institute for Health and Care Research (NIHR) under the Research for Patient Benefit Programme in November, 2015. The study team was based in the UK and the HYPATIA study was designed as a multinational European study. From a sponsor perspective, the study was perceived as high risk, being classified as a study type B under the Medicines and Healthcare products Regulatory Agency (MHRA) at the time.* The high-risk study classification and the political effects of Brexit were factors that delayed study sponsorship approval in the UK until January, 2017. Due to several other factors, the HYPATIA study had to move sponsorship during the study to Denmark. In Denmark, the study team now operates with a sponsor representative, who is a clinical expert within the field of antiphospholipid syndrome. Having an expert as a sponsor representative, who can assess the risk of the trial relative to other trials, means that the trial team can navigate more easily and quickly as decision-making processes are managed upfront with the sponsor representative.

Lessons learned

- Expert sponsor representative with knowledge about clinical trials conduct on pregnancy is crucial.

Considerations for solutions

- Supporting sponsor with expert advisors if needed will allow sponsors to define the risk of a specific trial relative to other trials.
- Shift of perception away from protecting patients from research to helping them through research (aligned with regulator and ethics boards).

This panel relates to the Sponsors element of the figure. *Type A trials are no higher risk than standard medical care versus Type B trials, which are somewhat higher risk than standard medical care. This includes dosage modifications or combinations with other medical products where an interaction might be suspected.

Regulators—GDPR in the EU

There are opportunities to limit the negative effects of GDPR on clinical studies. A centralised, secure data repository can be established within the EU. Data from non-EEA countries could then be anonymised before being uploaded, ensuring GDPR compliance while still allowing for multinational collaboration. Dynamic consent models can be implemented to allow patients to give tiered or modular consent, offering them flexibility and transparency, including the opportunity to agree to have anonymised data shared outside of the EU, while also accommodating the evolving nature of research. Collaborative agreements can be implemented, including agreements with partner institutions outlining standardised, GDPR-compliant data collection, and processing procedures. In summary, although GDPR introduces challenges for clinical research, especially in rare diseases, strategic planning and adherence to transparent, patient-centred practices can help in successfully navigating these challenges (panel 3). An obstacle in studies of pregnancy outcomes, which include data on children as these are defined as an outcome, is the requirement to obtain consent of both the birthing parent and coparent. If outcome data do not require any extra study visits, but just information reported by the parent, trial teams should be allowed to access the data of the child based on the initial consent of the trial participant or the coparent.

Ethics boards

A shift from the perception of protecting pregnant people with rheumatic and musculoskeletal diseases from research to helping them participate in clinical research is fundamental to improve outcomes. Expert advisors could be helpful in this setting. Centralised institutional review board approval was fundamental for the success of the IMPACT trial (panel 1), as it enabled enrolment of patients using a single institutional review board and remote consenting. Future studies in pregnant patients with rheumatic and musculoskeletal diseases could use such a rare disease framework. To the best of our knowledge, this concept does not exist in the UK or the EU. In the EU, this approach could be hindered by individual countries, but a centralised ethics approval considering individual EU country requirements might still be an option, if an upfront ethics board approval review could be available at Clinical Trials Information System approval level.

Sponsor

A supportive sponsor is crucial for the successful completion of any clinical study. Support from expert advisors to define the risks of a clinical trial or observational study in pregnant people with rheumatic and musculoskeletal diseases will allow sponsors to gain insight as to the risk, feasibility, and likelihood of trial completion.

A named expert as sponsor representative is an alternative solution. The HYPATIA study team had a fundamental shift of sponsor support when an expert sponsor representative assisted on behalf of the sponsor institution (panel 5). Although this might not be a universal solution, as this option depends upon institutions' individual requirements, supporting sponsors with expert advisors could provide a way forward.

Funders

Within the last 5 years focus has shifted, with recognition of the importance of research in women's health, including the need for pregnancy trials. Support from public funders for investigator-initiated clinical trials and observational studies of pregnant people with rheumatic and musculoskeletal diseases is essential.

Such studies are slow to enrol and require multiyear investment and support. In addition, clinical research in pregnant people with rheumatic diseases is often multinational and can take longer than research conducted in single centres. The opportunity to access more patients comes with more complex logistics and regulatory issues associated with the enrolment of patients from different countries. Funders must understand the complexity of conducting such studies, and we encourage the continuous support from public funders to prioritise these areas of research.

Trial teams

Established clinical research networks and teams that study pregnancy have the important responsibility of sharing their experience and best practices. To advance the field for patients, investigators should be inclusive towards other research teams and champion research in pregnant people with rheumatic and musculoskeletal diseases to medical societies and the public. To facilitate networking of research teams interested in pregnancy, EULAR has established a study group for reproductive health care and family planning.[52] Clinical researchers must continue to call for protected research time. Collaborations with pharmaceutical companies should be encouraged, as they can be key partners in interventional drug trials.

Patients

Success of observational and interventional studies requires a partnership between patients, researchers, and health-care providers. Both the IMPACT and HYPATIA trial teams, which sought to determine if specific medications could improve pregnancy outcomes in patients with antiphospholipid antibodies or antiphospholipid syndrome, found remarkable enthusiasm and willingness from patients to participate. In the IMPACT study, 6 (8%) of 78 patients of patients declined participation in a trial of an immunosuppressant that continued enrolment during the COVID-19 pandemic (panel 1). The experience of the HYPATIA study team was similar, in that they had direct queries about enrolment from patients and colleagues at non-participating hospitals. Such willingness to participate could be because this patient population has had adverse pregnancy outcomes in the past, and they see participation as a chance to increase their pregnancy success rate. A trusting patient–doctor relationship and the possibility to make trial visits coincide where possible with routine outpatient follow-up appointments are crucial to patient enrolment in research studies. Providing patients as well as patient organisations with feedback on the progress of the trial and results is helpful to build trust and partnership. In this regard, patient organisations might play an important role in supporting researchers by informing patients and answering questions about clinical studies that patients might not bring up in front of health-care providers.

Trial design

Clinical trials in pregnant people with rheumatic diseases are complex and difficult to conduct. The prevalence of rheumatic diseases differ, and distributions among demographic groups vary. Rheumatoid arthritis, the most common inflammatory disease, is estimated to affect 0·46% of the global population,[54] but ankylosing spondylitis affects between 1 and 3·2 people per 100 000,[55] systemic lupus erythematosus around 43 per 100 000,[56] and antiphospholipid syndrome around 5 per 100 000.[57] As pregnancy lasts for only a short period of reproductive life, a pregnant person with any rheumatic disease might be classified as rare or ultra-rare, depending on the

definition used.[58,59] As a consequence, prospective observational studies and randomised trials require multicentre and often multinational designs to meet target sample sizes. Thoughtful planning and design of clinical trials and the implementation of innovative strategies, such as the establishment of trial platforms designed to assess multiple interventions, the adoption of automated data capture systems, the use of factorial trial designs to assess two or more interventions simultaneously, could help to overcome obstacles in gathering evidence regarding the safety and efficacy of interventions for pregnant people with rheumatic diseases. By creating trial platforms incorporating automated data collection, fewer resources are required to run the trial and reach the sample size, and the data quality is enhanced. The factorial trial design enables patients to participate concurrently or sequentially in multiple trials evaluating different interventions. These innovative approaches promote a more rational and efficient allocation of resources and patient involvement (table 2).

In the last 5 years, several trials have used the adaptive platform trial design, especially for treatments of COVID-19. Such a design involves assessing multiple interventions against a shared control group; use of an adaptive design to drop less promising interventions early; and allowing new interventional groups to be added into the trial as it progresses. Adaptive platform trials have several appealing benefits, including the fact that they allow more research questions to be answered with a limited pool of participants. Nevertheless, they are large trials and could be difficult to run in rare diseases. Adaptive platform trials also make blinding difficult if the intervention groups represent distinct treatments with different routes of administration (although partial blinding, where each intervention group has its own placebo control group that is then merged in the analysis, could mitigate this difficulty).

In some cases, there is already substantial randomised efficacy data from trials in diseases that exclude pregnant participants. These data could justify using approaches that reduce the required sample size in the new study through borrowing of information[53] or creation of synthetic control groups.[54] However, doing this will make strong assumptions and lead to potential for biases that would not be present in a typical randomised controlled trial.

The adoption of innovative trial designs is promising to help evaluate the safety and efficacy of more drugs in pregnant patients with rheumatic diseases. However, their use should be justified and the effect on the quality of evidence produced should be assessed at the design stage and in discussion with regulators.

Paediatric trials are encouraged through paediatric investigation plans that provide incentives for industry sponsors. These incentives include additional patent life for a drug together with permitting innovative trial design approaches. We suggest regulators adopt similar measures to encourage more clinical trials for pregnant patients with rheumatic diseases.

Conclusion

Conducting clinical trials and cohort studies in pregnant people with rheumatic and musculoskeletal diseases requires a delicate balance of scientific rigor, ethical considerations, compliance with legal norms, and collaboration with various stakeholders. Challenges to investigators include adapting to regulatory changes, managing privacy laws, and securing sponsors and funders.

	Description	Considerations
Adaptive design	Allows patient outcome data in the trial to make changes to the design in a statistically robust way.	Allows a variety of useful changes such as dropping less promising treatment groups, changing dose, changing the sample size target; introduces more operational complexity and could require unblinding.
Borrowing of information	Allows use of relevant information external to the trial, usually with a Bayesian approach. Examples could be borrowing information on the treatment effect from a rheumatic disease trial that excluded pregnant patients in the analysis.	Can substantially reduce the sample size needed and potentially eliminate need for a control group; if external information is systematically different (eg, treatment effect differs in pregnant and non-pregnant patients with a rheumatic disease) then will give misleading answers.
Factorial trial	Assesses multiple interventions that can be given in combination; each participant randomised separately for each intervention to receive it or not.	Very efficient way to evaluate multiple interventions if safe to give them in combination; assumes no or low statistical interaction between arms (ie, treatment effect of one intervention is not influenced by whether another intervention is received).
Platform trial	An ongoing trial that assesses multiple intervention groups against a shared control group, has an adaptive design to allow dropping less promising treatment groups, and allows new treatment groups to be added in.	Highly efficient way to evaluate ongoing pipeline of new drugs; makes blinding difficult; complex trial to deliver.
Synthetic control methods	Uses external data from trials or patient registries to create an untreated control group to replace or supplement the contemporary trial's control group.	Can substantially reduce the sample size needed and potentially eliminate need for control group; requires good quality information on outcomes and patient-level variables to ensure patients in the trial and control groups are comparable.

Table 2: **Overview of innovative trial design types including descriptions and considerations for each approach**

Search strategy and selection criteria

For the Series paper we used search terms such as "pregnancy", "clinical trials", "prospective cohort studies" on public databases such as PubMed, regulator and funders webpages, publicly available information from the National Academy of Sciences, and clinical trials registries. The intial search took place in August, 2023, was updated in February, 2024, and included the most recent publically available regulator documents.

Continued engagement with regulators, clear understanding of privacy laws, creative strategies for sponsorship, innovative trial designs, and committed funding are essential to advancing this important area of clinical research. The PROMISSE, IMPACT, GR2, and HYPATIA studies offer valuable lessons that could inform future trials and contribute to improved care and outcomes for pregnant people with rheumatic and musculoskeletal diseases. To advance this essential area of medicine, policies and research should acknowledge and address the challenges discussed within this Series paper.

Contributors

KS and JES developed the overall layout. CG designed the tables. KS, BJH, NC-C, MMG, CG, and JES provided their experience of conducting research in these populations. JMSW wrote the trial design section. SA provided input from the patient's point of view. All authors contributed to all sections of the manuscript and have approved the final version.

Declaration of interests

KS reports advisory board participation for UCB (not related to pregnancy study) and is trial manager for the HYPATIA study. NC-C reports grants from UCB and Roche. JES reports grants and consultancy fees from UCB. All other authors declare no competing interests.

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