AMPt: Autoimmune in Menopause and Pregnancy Transitions
$50 Million Dollar Wellcome Leap Program
Jointly funded by Pivotal

Women represent 4 out of 5 autoimmune disease patients.[1,2] More than 400 million women globally. Autoimmune disease costs each woman affected 4 to 9 healthy, productive years, cumulatively.[3] That's the equivalent of losing 1 or more days a week to pain, fatigue, and joint swelling – for nearly a lifetime. Despite the disproportionate impact of autoimmune disease on women, no existing therapy addresses a woman's unique risk or the biological causes. What accounts for the disproportionate risk experienced by women? What can be done to reduce this risk?

AMPt aims to find out.

Why women? 80% of autoimmune disease patients are women.[1,2] Not by chance, not simply because women live longer.

Three diseases, one clock. A woman's risk for autoimmune diseases rises and falls with her hormone transitions. Excess risk climbs throughout her life: Surging at puberty, after childbirth, before and after menopause. In the 3 months following the birth of her first child, a woman's risk of developing rheumatoid arthritis (RA) rises about 5-fold.[4] If she reaches menopause before age 45, her risk for seronegative RA more than doubles.[5] Multiple sclerosis (MS) quiets in the third trimester of pregnancy, before relapses increase 6-fold during the postpartum window.[6] During the menopausal transition, women with MS show rising markers of nerve-cell injury and declining neurologic function,[7] and disability progression is nearly twice as common after menopause.[8] Lupus tracks a woman's hormonal changes differently, with flares nearly twice as common during pregnancy,[9] disease activity rising again in the late postpartum months[10], and rising again in the final year of peri-menopause.[11]

The timing of autoimmune events across a woman's most important life stages is not a coincidence. The timing *is* the signal. Estrogen dynamically regulates ***self tolerance***, which prevents cells of the immune system from attacking the body's own tissues. As estrogen rises and falls across a woman's life, the immune system's ability to distinguish self from non-self shifts with it.[12-14] Yet autoimmune disease models fail to incorporate immune-endocrine imbalances or distinguish true hormonal states from chronological aging. Interventional trials for preventing autoimmune diseases ignore a woman's specific risk; and no therapy is guided by immune-endocrine transitions.

AMPt aims to change that.

Estrogen and the immune system. Estrogen is both a reproductive hormone and a rheostat for control of the immune system. Immune cells carry estrogen receptors, and through them estrogen shapes how strongly the immune system reacts to foreign pathogens while maintaining the ability to distinguish these pathogens from its own tissues.[15,16]

Self tolerance is set by estrogen-sensitive dials. ***Central tolerance***, set early in life, is how the thymus screens developing T cells (the white blood cells that form a core part of the adaptive immune system) before they enter the bloodstream. This screening eliminates self-reactive T cells that would attack healthy tissues. An increase in estrogen lowers the efficiency of this screening by downregulating a specific thymic protein (AIRE) that drives the presentation of tissue-specific self-antigens to developing T cells.[14] Estrogen initially builds a stronger immune system in women, better at fighting infection and protecting offspring through pregnancy and breastfeeding. This stronger T cell immunity, however, comes at the expense of higher autoimmune risk, which surges as her immune system matures into reproductive age.

Peripheral tolerance is the backup dial, controlling self-reactive T cells that escape the thymus along with other inflammatory cells. Its main effectors are ***regulatory T cells (T_{regs})***, which suppress autoimmune responses. Estrogen, acting through estrogen receptors, expands regulatory T cells and strengthens their suppressive capacity.[13,17,18] In pregnancy the proportion of T_{regs} in blood and placenta rises, peaking in the second-to-third trimester and deepening tolerance to the fetus.[19,20] After delivery, when MS and RA flares cluster, it falls back from that peak,[19] withdrawing pregnancy's heightened tolerance. Estrogen's lasting decline at menopause impairs T_{reg} function[21] and shifts the Th17/T_{reg} balance toward inflammation.[22] Across the menstrual cycle the T_{reg} proportion rises and falls with circulating estrogen,[12] so the dial shifts day-to-day with hormone state.

And the effect of estrogens on autoimmune disease varies across diseases. The direction that estrogen tips the immune system depends on level, context (the local microenvironment), and timing. In some settings, estrogen signaling promotes self-reactive T cells; in others, it favors an immune-suppressive T_{reg} response. At other concentrations, estrogens amplify ***self-reactive B cells*** that produce autoantibodies or up-regulate proteins that promote ***inflammation***. This is why the same hormone may protect in some diseases and provoke in others. RA and MS tend to quiet under high estrogen and flare upon its withdrawal, suggesting that peripheral tolerance dominates in these diseases. Lupus tends to worsen when estrogen is high, suggesting that autoantibodies and inflammation are most important.

One lever, different effects.

A woman's immune-endocrine state goes unmeasured in almost all research and clinical care. The trajectory her immune tolerance takes across life, and the biological path that precedes a flare, have never been mapped, nor is it known what might delay or prevent onset. The link between a woman's hormones and autoimmune disease is real, but **we lack the research needed for medicine and treatments that reflect the dynamics of a woman's immune-endocrine state.**

The high burden of autoimmune disease at critical chapters of childbirth and menopause. RA, MS, and lupus affect nearly 20 million women globally. They are among the highest-burden diseases for the women affected, who forfeit more than 6 million healthy life-years each year. All 3 diseases are growing. RA alone is projected to affect more than 30 million people by 2050,[23] roughly 80% higher than in 2020, an estimated 22 million women. RA and MS ease under the high-hormone state of pregnancy while lupus worsens, so together they span opposite ends of the spectrum of how sex hormones act on the immune system. These 3 index cases are important because results across these diseases pin different edges of immune-endocrine system effects. Understanding the dynamics and interplay of the diverse relationships in these diseases should provide insights to autoimmune conditions beyond these 3 and thus help to mitigate the larger female-biased autoimmune burden.

After disease onset, RA costs a woman on average about 1.8 days a week, MS 2.5 days, and lupus 3.3 days. Valuable days are lost to chronic pain, fatigue, joint swelling, muscle weakness, brain fog, insomnia, and failing mental health. Lost days are not spread evenly across her life, they fall disproportionately at the most pivotal chapters.

One chapter is the year after childbirth. More than 500,000 women per year face their sharpest rise in disease activity postpartum: In the 3 months after birth, more than a quarter of women with MS will experience a relapse,[6] and close to 2 in 5 women with RA will experience a flare.[24] Lupus's postpartum rise is more delayed. Disease activity is significantly higher at 6 and 12 months postpartum than in late pregnancy or the first weeks after delivery.[10] For others, the postpartum period brings the onset of disease, with the risk of developing RA roughly 5 times higher than at other times.[4] **An estimated 30,000 new cases of RA each year can be traced to the postpartum window alone**. This time already includes caring for a new infant, and for many women is also coincident with important career advancement. Loss of health at this time is acute for women, their families, and their future choices.

A second chapter is the menopausal transition, a stage when many women are most active at work, in communities, in caring for parents, or all of the above. A woman's risk of developing RA rises by about a third after menopause (Odds Ratio [OR] 1.35), and nearly triples when menopause comes early (OR 2.97).[25] **The menopause transition accounts for an estimated 70,000 new RA cases worldwide each year**. The largest analysis (MSBase, 987 women) found confirmed disability progression in 56% of women after menopause versus 32% before.[8] Serum neurofilament light chain, a biomarker of neuro-axonal damage, rises across the transition,[7]

indicating an association between menopause and MS progression. Whether that progression is hormone-driven or an effect of aging remains unresolved. Estrogen does not simply fade away during the menopause transition, it rises and falls erratically. The instability tracks with disease: In the year before the final menstrual period, when estrogen levels are spiking and crashing, cutaneous lupus flares triple (OR 3.07)[11] and lupus activity is then lower after menopause.[26]

These are not scattered misfortunes but a legible pattern. In women, autoimmune disease tracks with hormone transitions, at the life stages that often matter most to her.

The pattern is both the problem and the way in.

What needs to change? Sex hormones act directly on the immune cells driving autoimmune disease.[16] **Yet measurements of immune-endocrine interactions at hormone transitions are missing in women with autoimmune disease.**

Rheumatology and neurology record immune markers whenever a patient happens to show up, filing hormone transitions and reproductive stages under "background." Endocrinology measures hormones but mostly ignores immune signatures. As separate specialties, **endocrinology and immunology are rarely, if ever, measured together, through a woman's hormone transitions.** Without these measurements, autoimmune disease that is following a hormone-driven clock will be missed. Women are grouped by age rather than by actual hormone levels, and age is a poor substitute for hormone status. The MSBase menopause study did not find a significant effect of menopause on disability in MS, but with hormone data missing in the registry a true null is indistinguishable from a missed signal.[8]

When hormone therapies have been tested as intervention for autoimmune disease, they have been administered without adequate consideration of timing and dose. Estrogen-receptor drugs were tested in RA without accounting for where a woman was in her hormonal cycle or transition. Trial results are often in conflict – one trial shows no benefit;[27] another shifts hormone activity but does nothing for disease.[28]

What if better precision would allow drugs to be more effectively designed and delivered, with fewer long-term side effects? A woman's hormone levels are often already captured in routine care, or can be measured directly. Her immune state can be quantified from a small blood sample. We know the two are linked. We need to track endocrine and immune state together through the life stages when a woman's risk for autoimmune disease shifts. The payoff would be clear: Model precursors of disease to predict onset of disease and act in the window before damage is done. For the women already living with these diseases, those same transition windows are when flares cluster. Anticipating a flare means treating before it strikes as opposed to chasing it afterward, and potentially even new options that avoid suppressing the immune system continuously for life. In this way, if effective, timed treatment could lower cumulative exposure and the infection risk that comes with it.

Program goal

AMPt aims to build immune-endocrine models capable of predicting a woman's risk of autoimmune disease onset or flare with sufficient accuracy to design and deliver effective treatment. The goal is to return the equivalent of 1 healthy day a week to millions of women living with RA, MS, or lupus. This equates to as many as 52 more healthy days a year and 5 years across a lifetime after onset of an autoimmune condition.

Achieving this goal is expected to require flare and new-disease prediction at least 4 weeks before a flare, and for seronegative RA catching it within its ~12-week treatment window. Together, these advances would cut the rate of flares and new disease by at least 33%.

The 3 index diseases of AMPt steal healthy days in 3 ways, each concentrated around hormone transitions:

1. **Flares treated only after they occur cause irreversible damage and result in the loss of 5.6 million healthy days a year.** Each year brings roughly 128,000 postpartum flares across RA, MS, and lupus, plus about 390,000 women carrying excess disease activity through the menopause transition. In MS, the burden concentrates in flares around hormone withdrawal. In RA, flares follow the postpartum and menopause transition. In lupus, flares track hormone state most tightly in pregnancy, postpartum, and perimenopause. In each, the day is recovered by predicting flares and intervening before they strike to reduce their intensity or eliminate them altogether.
2. **Disease diagnosed too late to prevent irreversible damage accounts for 3.6 million healthy days lost a year.** Around 140,000 women a year develop seronegative RA around menopause, the form that rises sharply after menopause. This form of RA carries none of the antibodies standard blood tests rely on,[5] and is routinely diagnosed past its ~12-week treatment window. Catching it within that window enables treatment early enough to prevent irreversible damage.
3. **Disease that begins at a hormone transition: 63 million healthy days over the lifetime of each year's new cases.** Roughly 30,000 new RA cases arise after childbirth and 70,000 after early menopause each year. Forecasting who will develop disease at a transition is the first step toward preventing or delaying it.

To reclaim these days, AMPt will work across 3 thrust areas:

1. Demonstration of a computational model that predicts immune-endocrine dynamics indicative of flare and new-onset disease at key hormone transitions.
2. Validation of a biomarker panel that reads a woman's immune-endocrine state from a routine blood draw, including the diagnosis of seronegative RA.
3. Assess the efficacy of interventions dosed and timed to hormone transitions that aim to reduce flares and disability progression by one-third, or more, compared with current

care and that could deliver lactation-safe and hormone-timed protocols ready for later testing.

Success would mean **9.2 million healthy days** returned to women suffering from or at risk of autoimmune disease each year through earlier prediction and flare prevention, including **~3.6 million** from diagnosing seronegative RA sooner, and roughly **63 million healthy days** over a lifetime for each year of new cases prevented.

Thrust Area 1. Measure & model. Build a dynamic immune–endocrine model that forecasts flare and new-onset disease with ≥80% sensitivity and specificity at the postpartum and menopausal transitions, and resolves the immune tolerogenic–provocative mechanism per disease.

Success in Thrust 1 is a computational model that: (1) forecasts flare ≥4 weeks ahead and postpartum new-onset disease ≥12 weeks ahead at ≥80% sensitivity and specificity, calibrated, and better than the clinical baseline of prior disease activity plus age (≥80% power, α=0.05), replicated in ≥2 independent cohorts. (2) Assigns the immune–endocrine state as a reproducible continuous index (ICC ≥0.8). (3) Resolves, per disease, whether higher or lower estrogen is tolerogenic (Th17/Treg axis) or provocative (interferon/B-cell axis), shown by a significant indirect effect ($p<0.05$) replicated across ≥2 cohorts, with a meaningful share of the hormone⟶disease effect mediated through that axis (proportion mediated ≥30%; above 50% identifies it as the dominant mediator). (4) Stratifies risk ≥50% more accurately than chronological age (AUC). These are each described in more detail below.

The computational model should be trained on densely sampled longitudinal cohorts spanning the hormone transitions of menstruation, pregnancy, and menopause. Using a woman's hormone and immune measurements, the model returns her risk for an autoimmune flare or onset as a continuous score, her position on the immune tolerogenic–provocative axis, and the immune pathways associated with it.

The model should score autoimmune risk from measured hormone values and immune measurements already on record, prospectively sampled or assayed from banked plasma across hormone transitions. Prospective and retrospective designs each report an appropriate discrimination or association measure (e.g. a time-updated hazard ratio with a C-statistic, or an odds ratio), with risk quantified from hormone-staged exposures rather than age. The model should produce a single, reliable score for a woman's immune–endocrine state (ICC ≥0.8) that traces how hormone changes influence autoimmune risk.

Thrust 1A develops the computational model; Thrust 1B generates the cohorts and measurements the model is trained on. No single team needs to cover all of Thrust 1. All work will use common data and protocol aligned assay standards, and the single shared immune–

endocrine model is to be assembled at the program integration layer from multiple team contributions.

Sub-thrust 1A. A dynamic immune–endocrine computational model using healthy and autoimmune hormone transition trajectories.

The model is trained on existing records and Thrust 1B cohorts, together spanning pregnancy, menstrual cycle, and menopause transitions, with the following outputs:

1. **A current immune–endocrine score**: A continuous index that is reproducible (ICC ≥0.8) and stratifies downstream disease at least 50% more accurately than chronological age by AUC, placing her on the tolerogenic–provocative axis at a given timepoint.
2. **A forward prediction of autoimmune deviation:** The model must flag, as a deviation from the healthy reference, an impending flare at least 4 weeks ahead and new-onset disease at least 12 weeks ahead in the postpartum window (where new RA clusters), at ≥80% sensitivity and specificity, calibrated, and significantly better than a clinical baseline of prior disease activity plus age (≥80% power, α=0.05), replicated in ≥2 independent cohorts.
3. **The driving path, the mediating route:** Which hormone change, through which immune axis, produces the predicted deviation, reported per disease and established by mediation analysis replicated across ≥2 cohorts, with ≥30% of the hormone→disease effect mediated through the axis (proportion mediated) and a significant indirect effect ($p<0.05$).
4. **A forward prediction of immune state:** Given a held-out woman's measurements to a prespecified decision point (late pregnancy for the postpartum window; rolling at menopause) and her hormone trajectory thereafter, predict her immune-axis trajectory. Scored as mean absolute error by prediction horizon, against an identically specified model given the population-average hormone trajectory for her transition stage in place of her own.

The model must resolve change over time, not a single snapshot, with the key changes concentrated in 2 windows: The weeks after delivery, when estrogen falls steeply and RA and MS risk rebounds while lupus settles, and the perimenopausal transition, when estrogen becomes erratic and then low over months to years. The signal is hypothesized to be the rate and direction of hormone change through these windows, not the absolute level at any one visit, so the model must handle unevenly spaced longitudinal samples and track each woman against her baseline.

The age comparison (output 1) is a key secondary that adjudicates discrepancies between studies that lack explicit hormone measurements, such as the MSBase menopause study[8], which could not separate the effect of hormone state from that of age on MS progression.

Sub-thrust 1B. Prospective and retrospective cohorts spanning hormone transitions.

Thrust 1B generates the additional cohorts and measurements to train and validate the Thrust 1A model, spanning pregnancy→postpartum and menopause, with the menstrual cycle as a high-frequency reference. Teams may propose one or more cohorts, built to a common standard so data can be pooled: A shared hormone and immune panel meeting the precision targets in Appendix Table 1, a common sampling schedule, and shared definitions of flare, onset, and disease-activity endpoints.

- **Healthy pregnancy→postpartum**: The reference trajectory for how a hormone transition reshapes immune pathways, against which disease deviations are compared.
- **Healthy menstrual cycle:** High-frequency hormone-oscillation dynamics, ~12 cycles a year per woman, the primary, event-free test bed for the forward immune-state prediction (Thrust 1A, output 4).
- **RA, MS, lupus pregnancy→postpartum**: The disease trajectory and supervised flare signal, concentrated in the postpartum window. ~28% of women with MS relapse in the first 3 months after delivery,[6] 46.7% of RA pregnancies flare postpartum,[29] and even among women with stable lupus ~23% flare 2 to 6 months postpartum.[30]
- **Menopause and perimenopause:** Extends the model to a transition where estrogen becomes erratic before settling low, rather than crashing sharply as it does postpartum, and the instability window tied to perimenopausal lupus flares.

Hormone and immune measurements. At each timepoint a *hormone panel* is intended to locate a woman on her menstrual, pregnancy, or menopause trajectory, together with an *immune panel* to assess the tolerogenic and provocative pathways that set her risk. The testable **hypothesis** is that autoimmune risk at each transition is set by the balance between immune tolerance and provocation as described earlier – namely, RA and MS may flare as the tolerogenic T_{reg} pathway withdraws when estrogen falls after delivery, while lupus may flare as the provocative interferon pathway is driven when estrogen is high in pregnancy or unstable in perimenopause.

Hormones. Estrogen's immune effect is biphasic and species-specific, so the panel should span the physiological estrogens that dominate different windows (estradiol in the cycle, estriol and estetrol in pregnancy, estrone after menopause), with progesterone and testosterone to separate estrogen's effect from the sex steroids that move with it, prolactin because it rises with lactation and is pro-inflammatory in RA, FSH, and AMH to stage menopause, and SHBG because immune cells respond to the free fraction.

Immune pathways. Features read tolerance and provocation: The type I interferon signature (lupus's central driver and the clearest readout of estrogen's provocative arm); the Th17/T_{reg} balance; the pro-inflammatory effector cytokines TNF-α, IL-6 and the IL-12/IL-23 axis (RA/MS drivers and drug targets); autoantibody and B-cell compartments (the shared effector output,

and the only route to a signal in seronegative RA); complement C3/C4 (an established lupus-activity marker); and EBV, the leading environmental trigger of MS,[31] implicated in lupus,[32] and reactivating in pregnancy.[33]

The core panel, assay methods and precision level are specified in Appendix Table 1. Performers may propose an alternative assay, platform, or target with justification. Teams are encouraged to add unbiased or discovery-scale immune readouts.

Precision, pooling and biobanking. Every assay must hold the composite immune–endocrine index at ICC ≥0.8 and preserve cross-site comparability. All sites measure against shared reference samples and calibrators and must agree within ±15% (or the analyte-specific bound) for data to be pooled. Viable cells and plasma are to be biobanked for Thrust 2. Required covariates, each a modifier of both trajectories: Lactation, resumption of menses, exogenous hormone use, and the timing of any therapy interruption and restart. Proposals should describe data sharing approaches, privacy-preserving integration, and sample sharing across the program, including any foreseen limitations, under a governance framework meeting local and international standards for health data. Participants' informed consent should cover biobanking and sharing within the program, and participants should be able to withdraw. Proposals drawing on cohorts in lower-resource settings should describe equity in scientific leadership, benefit-sharing, and data and sample sovereignty.

Thrust Area 2. Predict flare and new-onset disease across a hormone transition at ≥80% sensitivity and ≥80% specificity, with enough lead time to start disease-modifying and/or hormone-timed therapy at least 4 weeks before flares and 12 weeks for new-onset RA.

Disability is the bulk of the autoimmune disease burden, and it occurs through relapses and the onset of new cases. Care is reactive after a flare or new diagnosis. Yet windows are identifiable in advance. A biomarker that forecasts the event in time to act turns a hormone transition into a window to pre-empt disease: Start a disease-modifying drug before the flare strikes (e.g. a DMARD or biologic in RA, a disease-modifying therapy in MS, hydroxychloroquine or an immunosuppressant in lupus), and/or the hormone therapy examined in Thrust 3. The biomarker must outperform a clinical baseline of prior disease activity plus age by at least 0.05 in AUC ($\Delta AUC \geq 0.05$) and significantly ($p<0.05$), with calibration reported alongside discrimination, and should express continuous near-term risk rather than a binary threshold.

Thrust 2 runs in tandem with Thrust 1B. Discovery begins on the earliest-accrued cohort samples and existing biobanks; the locked panel is then validated retrospectively on independent resources.

Sub-thrust 2A. A predictive biomarker that works across one or more hormone transitions. The biomarker must retain ≥80% sensitivity and specificity when measured under clinical-lab conditions from a routine blood draw, and return results in time to start a disease-modifying drug before autoimmune flare or onset.

Using a densely-sampled pre- and postpartum cohort, apply broad multi-omic measurement to collected samples, test each candidate against observed events, and reduce to the minimal set of markers that forecasts the event ahead of time. The panel must be measurable from a routine blood draw rather than monthly specialist assays, so it is usable in the postpartum year and perimenopause, when women are least likely to be in rheumatology or neurology follow-up.

Two endpoints; teams may address either or both, each with its own success bar:

- **Flare in established RA, MS, or lupus**: Predict a flare against a validated disease-activity measure (e.g. DAS28 in RA, SLEDAI in lupus, confirmed relapse in MS), at ≥80% sensitivity and specificity and at least 4 weeks ahead, enough lead time to pre-empt it.
- **New onset RA in at-risk women** (autoantibody-positive but asymptomatic, first-degree relatives, the postpartum population): Predict incident disease, confirmed by clinical diagnosis, at ≥80% sensitivity and specificity and at least 12 weeks ahead in the postpartum window.

Validate the locked panel in independent resources. Apply the biomarker to independent, diverse cohorts and biobanks not used in its development, and confirm it retains ≥80% sensitivity and specificity, calibrated, above the clinical baseline. Retrospective validation on banked samples fits a panel built to read from a single routine blood draw. A panel that needs serial measurements requires biobanks with matching serial samples, or prospective validation. Replication across ≥2 independent resources is required.

Sub-thrust 2B. A diagnostic biomarker that identifies seronegative RA across the menopause transition, where antibody tests fail.

Seronegative RA, carrying neither rheumatoid factor nor anti-CCP, is routinely missed or diagnosed late in women, and its incidence rises after menopause (adjusted HR ~2.1).[5] Standard serology reads normal while disease is active, so women accrue irreversible joint damage before treatment begins. This sub-thrust will deliver a biomarker that classifies symptomatic peri- and postmenopausal women as seronegative RA at the point of presentation, informed by hormone state, which helps separate seronegative RA from menopausal joint pain (arthralgia).

The intent is to deliver a validated diagnostic biomarker or panel, that separates true seronegative RA from osteoarthritis, menopausal arthralgia, and other inflammatory arthritides. The biomarker must reach ≥80% sensitivity and ≥80% specificity against a clinical reference standard (2010 ACR/EULAR classification with expert adjudication and imaging where available), and reproduce at $\kappa \geq 0.8$. It must also shorten time-to-diagnosis against a standard-of-care baseline in at least 1 independent cohort. The work draws on the Thrust 1B biobank and existing seronegative-RA cohorts, with no new recruitment required.

Thrust Area 3. Intervene at measured hormone transitions to reduce postpartum flares and slow menopause-associated progression, delivering lactation-safe, hormone-timed protocols.

The hormone transitions of postpartum estrogen withdrawal and perimenopausal decline are measurable windows of elevated autoimmune activity. Thrust 3 uses measured hormone trajectories (Appendix Table 1) to identify who is entering a risk window and when, and to intervene before disease worsens rather than after.

Prior hormone trials tested maintaining hormone levels rather than managing the decline, and dosed without verifying the serum level actually reached. POPARTMUS, a fixed-dose estradiol–progestin regimen, did not reduce postpartum MS relapse.[34] The estriol-in-MS trial added estriol to glatiramer acetate, a disease-modifying therapy for relapsing-remitting MS, and lowered the relapse rate by roughly a third versus glatiramer acetate alone. Among women on the same dose of hormone therapy, those who reached the highest serum estriol had better cognitive and brain-atrophy outcomes, an exposure–response pointing to achieved serum level, not nominal dose, as the key variable.[35] Neither trial tested controlling the *rate* of hormone decline.

If risk tracks the rate and direction of hormone change and not the absolute level alone, it suggests 2 potentially new interventions. A serum-guided hormone taper would smooth the abrupt postpartum crash and the erratic perimenopausal fall creating a descent the immune system can more readily adapt to. Such an intervention would be dosed to a measured serum target rather than a fixed amount, and might use pregnancy estrogens such as estriol. A hormone-timed disease-modifying therapy would track the hormone trajectory to pinpoint the risk window and start or intensify existing therapy ahead of the expected flare. Lupus follows the same trajectory logic in the opposite direction: It is thought to flare as estrogen rises or becomes unstable, so it could be newly addressed by timing therapy to the estrogen rise rather than by a taper.

Which intervention applies depends on disease and lactation status:

	Hormone taper	Hormone-timed DMT
RA / MS, not breastfeeding	Yes	Yes (alone or combined)
RA / MS, breastfeeding	No — see 3A pumping sub-study	Yes, lactation-safe agents
Lupus	No — estrogen carries flare and thrombosis risk	Yes

The comparator throughout is the current standard of care: Guideline-based management carried through the transition, with treatment adjusted only after the patient worsens. For the disease-modifying arm this makes timing the key variable, the same drug class given ahead of the flare versus escalated reactively after it, not the drug itself.

Thrust 3 operates independently of the other thrusts. Performers should describe how they would incorporate the Thrust 1 model and Thrust 2 biomarker panel once these mature.

Thrust 3 aims to deliver

- **An efficacy estimate at each window.** A 33% reduction in postpartum flare (Risk Ratio [RR] ≤0.67), and a ≥0.5 SD protective shift in a menopause progression marker, each prespecified, powered at ≥80%, α=0.05, and reported with a confidence interval.
- **A hormone-timed DMT protocol.** A schedule specifying whom to treat, at what hormone level, and when, relative to the measured hormone transition.
- **A lactation-safe hormone protocol.** A serum-guided taper whose effect on milk supply and whose hormone transfer into milk are measured directly in the Thrust 3A pumping sub-study described below. Thrust 3A aims to establish whether and how a taper alone or in combination with DMT could later serve breastfeeding women effectively and safely.
- **Characterized hormone-state dynamics.** How the intervention shifts the hormone trajectory and disease activity, measured against the untreated transition.

Sub-thrust 3A. Prevent postpartum flare, and define new lactation-safe treatment options.

This sub-thrust proposes a randomized patient study in established RA, MS or lupus, enrolled before delivery and followed through the postpartum hormone transition. The postpartum drop in estrogen and progesterone is abrupt, and flare follows closely. Within 12 weeks of delivery, 46.7% of women with RA flare[29] and 28% of women with MS relapse.[6] Lupus flares later, with activity rising at 6 to 12 months as estrogen recovers.[10] Thrust 3A asks whether smoothing or supplementing estrogen blunts postpartum flare in RA and MS, and whether timing therapy to the estrogen recovery blunts it in lupus.

The goal is a 33% reduction in postpartum flare (RR ≤0.67) versus standard of care on a validated activity measure, within 12 weeks for RA (DAS28) and MS (confirmed relapse), and across the first postpartum year for lupus (SLEDAI), powered at ≥80%, α=0.05. Women are enrolled at elevated flare risk, scored at the outset from disease-appropriate clinical risk factors: Prior postpartum or pregnancy flare, disease activity around conception, and, where relevant, autoantibody status.

Pumping sub-study. Unless otherwise justified, the hormone taper should be restricted to women who are not breastfeeding, because exogenous estrogen can suppress milk supply and may expose the infant.[36] Rather than treat that as a limit on reach, Thrust 3A efforts should plan to use the non-breastfeeding taper cohort to define the conditions under which a hormone taper could be made lactation-safe. Women randomized to the taper may consent to a pumping sub-study, expressing milk throughout. This measures, at the Appendix Table 1 precision standard, how the taper affects milk production and how much hormone passes into milk judged against a prespecified lactation-safe limit set from the literature or estimated within the study. The goal is a lactation-safe taper protocol ready for follow-on safety testing.

Sub-thrust 3B. Slow menopause progression of autoimmune disease as indicated by a validated progression biomarker of disease.

Clinical outcomes accrue too slowly at menopause to read inside a trial, so proposed interventions should be judged on a biomarker endpoint. A randomized intervention across the menopausal transition would thus measure the shift in an established progression marker toward the premenopausal reference of NfL for MS, the MBDA/Vectra score for RA, complement and anti-dsDNA for lupus, targeting a prespecified ≥0.5 SD protective shift versus standard of care, powered at ≥80%, α=0.05, with the intervention timed to measured hormone state. The goal is an effect estimate and a proposed hormone-timed menopause protocol for follow on testing.

Safety and reporting. Both sub-thrusts are intended to enroll by measured hormone state and time interventions to it. Hormone dosing, where used, should be set to a serum target and verified by assay. Measures of hormone in milk must meet the Appendix Table 1 precision standard. Safety is reported alongside every effect estimate: Postpartum venous thromboembolism in hormone taper studies, breast, and endometrial safety where menopausal estrogen is used, and milk hormone concentration against the lactation-safe limit in the pumping sub-study. Breastfeeding participants are expected to enroll only in the hormone-timed disease modifying therapy arm, on lactation-safe agents with infant exposure monitored. Breastfeeding status should be recorded and used as a stratifier.

References

1. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol. 2008;173(3):600-609. PMID: 18688037.
2. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol. 1997;84(3):223-243. PMID: 9281381.
3. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133-2161. PMID: 38642570.
4. Silman A, Kay A, Brennan P. Timing of pregnancy in relation to the onset of rheumatoid arthritis. Arthritis Rheum. 1992;35(2):152-155. PMID: 1734904.
5. Bengtsson C, Malspeis S, Orellana C, Sparks JA, Costenbader KH, Karlson EW. Association between menopausal factors and the risk of seronegative and seropositive rheumatoid arthritis: results from the Nurses' Health Studies. Arthritis Care Res (Hoboken). 2017;69(11):1676-1684. PMID: 28085997.
6. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T; Pregnancy in Multiple Sclerosis Group. Rate of pregnancy-related relapse in multiple sclerosis. N Engl J Med. 1998;339(5):285-291. PMID: 9682040.
7. Silverman HE, Bostrom A, Nylander AN, Akula A, Lazar AA, Gomez R, et al. Association of menopause with functional outcomes and disease biomarkers in women with multiple sclerosis. Neurology. 2025;104(2):e210228. PMID: 39715474.
8. Bridge FM, Sanfilippo PG, Zhu C, Skibina OG, Nguyen AL, Kalincik T, et al. Menopause impact on multiple sclerosis disability progression. JAMA Neurol. 2025;82(12):1219-1226. PMID: 41021242.
9. Ruiz-Irastorza G, Lima F, Alves J, Khamashta MA, Simpson J, Hughes GR, et al. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. Br J Rheumatol. 1996;35(2):133-138. PMID: 8612024.
10. Götestam Skorpen C, Lydersen S, Gilboe IM, Skomsvoll JF, Salvesen KÅ, Palm Ø, et al. Disease activity during pregnancy and the first year postpartum in women with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2017;69(8):1201-1208. PMID: 27696790.
11. Allibert Q, Teboul A, Sonigo G, Louchez A, Barbaud A, Fareau J, et al. Increased risk of cutaneous lupus erythematosus flare during the late menopausal transition: a retrospective study of 64 women. JAAD Int. 2026;27:112-114. PMID: 42436872.

12. Arruvito L, Sanz M, Banham AH, Fainboim L. Expansion of CD4+CD25+ and FOXP3+ regulatory T cells during the follicular phase of the menstrual cycle: implications for human reproduction. J Immunol. 2007;178(4):2572-2578. PMID: 17277167.

13. Polanczyk MJ, Carson BD, Subramanian S, Afentoulis M, Vandenbark AA, Ziegler SF, et al. Cutting edge: estrogen drives expansion of the CD4+CD25+ regulatory T cell compartment. J Immunol. 2004;173(4):2227-2230. PMID: 15294932.

14. Dragin N, Bismuth J, Cizeron-Clairac G, Biferi MG, Berthault C, Serraf A, et al. Estrogen-mediated downregulation of AIRE influences sexual dimorphism in autoimmune diseases. J Clin Invest. 2016;126(4):1525-1537. PMID: 26999605.

15. Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007;28(5):521-574. PMID: 17640948.

16. Sharma S, Gibbons A, Ollmann Saphire E. Sex differences in tissue-specific immunity and immunology. Science. 2025;389(6760):599-603. PMID: 40773572.

17. Polanczyk MJ, Hopke C, Huan J, Vandenbark AA, Offner H. Enhanced FoxP3 expression and Treg cell function in pregnant and estrogen-treated mice. J Neuroimmunol. 2005;170(1-2):85-92. PMID: 16253347.

18. Adurthi S, Kumar MM, Vinodkumar HS, Mukherjee G, Krishnamurthy H, Acharya KK, et al. Oestrogen receptor-α binds the FOXP3 promoter and modulates regulatory T-cell function in human cervical cancer. Sci Rep. 2017;7(1):17289. PMID: 29229929.

19. Somerset DA, Zheng YM, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. Immunology. 2004;112(1):38-43. PMID: 15096182.

20. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol. 2004;5(3):266-271. PMID: 14758358.

21. Motta F, Di Simone N, Selmi C. The impact of menopause on autoimmune and rheumatic diseases. Clin Rev Allergy Immunol. 2025;68:32. PMID: 40117049.

22. Bhadricha H, Patel V, Singh AK, Savardekar L, Patil A, Surve S, et al. Increased frequency of Th17 cells and IL-17 levels are associated with low bone mineral density in postmenopausal women. Sci Rep. 2021;11(1):16155. PMID: 34373550.

23. GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023;5(10):e594-e610. PMID: 37795020.

24. de Man YA, Dolhain RJEM, van de Geijn FE, Willemsen SP, Hazes JMW. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241-1248. PMID: 18759316.

25. Namavari N, Jokar M, Ghodsian A, Kargar Jahromi H, Rahmanian V. Menopausal state and rheumatoid arthritis: a systematic review and meta-analysis. BMC Rheumatol. 2024;8(1):48. PMID: 39350181.

26. Urowitz MB, Ibañez D, Jerome D, Gladman DD. The effect of menopause on disease activity in systemic lupus erythematosus. J Rheumatol. 2006;33(11):2192-2198. PMID: 16981295.

27. Roman-Blas JA, Castañeda S, Cutolo M, Herrero-Beaumont G. Efficacy and safety of a selective estrogen receptor β agonist, ERB-041, in patients with rheumatoid arthritis: a 12-week, randomized, placebo-controlled, phase II study. Arthritis Care Res (Hoboken). 2010;62(11):1588-1593. PMID: 20556817.

28. van Vollenhoven RF, et al. The selective estrogen receptor α agonist Org 37663 induces estrogenic effects but lacks antirheumatic activity: a phase IIa trial investigating Org 37663 in postmenopausal female rheumatoid arthritis patients. Arthritis Rheum. 2010;62(2):351-358. PMID: 20112368.

29. Jethwa H, Lam S, Smith C, Giles I. Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis. J Rheumatol. 2019;46(3):245-250. PMID: 30385703.

30. Davis-Porada J, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Low frequency of flares during pregnancy and post-partum in stable lupus patients. Arthritis Res Ther. 2020;22(1):52. PMID: 32188491.

31. Bjornevik K, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296-301. PMID: 35025605.

32. Moon UY, Park SJ, Oh ST, Kim WU, Park SH, Lee SH, et al. Patients with systemic lupus erythematosus have abnormally elevated Epstein-Barr virus load in blood. Arthritis Res Ther. 2004;6(4):R295-R302. PMID: 15225364.

33. Haeri S, et al. Prevalence of Epstein-Barr virus reactivation in pregnancy. Am J Perinatol. 2010;27(9):715-720. PMID: 20387188.

34. Vukusic S, et al. Oral nomegestrol acetate and transdermal 17-β-estradiol for preventing post-partum relapses in multiple sclerosis: the POPARTMUS study. Mult Scler. 2021. PMID: 33269975.

35. Voskuhl RR, Wang H, Wu TC, Sicotte NL, Nakamura K, Kurth F, et al. Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(1):35-46. PMID: 26621682.

36. Lopez LM, Grey TW, Stuebe AM, Chen M, Truitt ST, Gallo MF. Combined hormonal versus nonhormonal versus progestin-only contraception in lactation. Cochrane Database Syst Rev. 2015;2015(3):CD003988. PMID: 25793657.

Appendix Table 1

Analyte	Method	Precision / sensitivity	Why set here
Estradiol (E2)	LC-MS/MS	CV ≤10%; LLOQ ≤5 pg/mL	Immunoassays are unreliable at the low postmenopausal range that defines the menopause window
Estrone (E1)	LC-MS/MS	CV ≤10%; LLOQ ≤10 pg/mL	Becomes the dominant estrogen after menopause, when E2 is near the floor
Estriol (E3)	LC-MS/MS	CV ≤10%; wide dynamic range	Pregnancy's dominant estrogen, spanning ~1,000-fold from non-pregnant to term
Estetrol (E4)	LC-MS/MS	CV ≤15%; low LLOQ	Fetal/pregnancy-specific estrogen, near-absent otherwise; no validated immunoassay
Progesterone	LC-MS/MS	CV ≤10%	Defines luteal phase and pregnancy; immunoassays cross-react with related steroids
Testosterone	LC-MS/MS	CV ≤10%; LLOQ ≤2 ng/dL	Immunoassays are inaccurate at female concentrations
AMH	Automated immunoassay	CV ≤10%; cross-platform calibrated	Ovarian-reserve / menopause-timing marker; historically platform-variable
FSH	Immunoassay, WHO IS–calibrated	CV ≤8%	Core menopause-staging hormone (STRAW); must be comparable across sites
SHBG	Immunoassay	CV ≤10%	Converts total to free hormone; its error propagates into free-E2/testosterone estimates

Analyte	Method	Precision / sensitivity	Why set here
Prolactin	Immunoassay	CV ≤10%	Lactation-driven and pro-inflammatory in RA; a second hormonal axis to resolve from estrogen
Type I interferon signature	ISG score (qPCR/ NanoString)	CV ≤15%; shared reference RNA	Central lupus driver; a multi-gene score must be comparable across platforms
Th17/Treg balance	Standardized flow cytometry	CV ≤15%; central gating + shared control	The tolerogenic–provocative axis; flow is operator/instrument-sensitive
Effector cytokines (TNF-α, IL-6, IL-12/23)	Multiplex immunoassay	CV ≤15%; shared calibrators	Central RA/MS inflammatory drivers and drug targets; IL-6 also drives Th17 differentiation
Autoantibody & B-cell compartments	Multiplex autoantibody + flow	CV ≤15%; common calibrators	Titres and subset frequencies must be calibrated to shared standards to pool
Complement (C3/C4)	Nephelometry/ turbidimetry	CV ≤8%	Established lupus-activity marker; routine but must be cross-site comparable
EBV activity	Serology + plasma EBV DNA qPCR	CV ≤15%; viral load to WHO IS	Latent and lytic read separately; DNA load needs the WHO International Standard

CV targets apply at clinically relevant concentrations, with CV up to 20% accepted near the LLOQ; the LLOQ column is the sensitivity floor, not where the CV target must hold. Proposals must state the current precision of each assay from the literature, how they will reach and hold these targets across the cohort and across sites, and the justification for any deviation from the default method or target.