



Premature Ovarian Insufficiency: An Investment Case for the 1 in 27

*A White Paper from The POInt,
in Consultation with the Daisy Network*

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01. Executive Summary

Premature Ovarian Insufficiency (POI), the loss of normal ovarian function before the age of 40, affects approximately 3.7% of women globally, or 1 in 27. Despite this prevalence, POI remains one of the most underdiagnosed and underserved conditions in women's health.

The consequences of untreated POI are substantial. Women with the condition face significantly elevated risks of cardiovascular disease, osteoporosis, multimorbidity, depression, anxiety, sexual dysfunction, and premature mortality. Most women with POI cannot conceive spontaneously, and require egg donation to build their families. Yet despite the existence of comprehensive international clinical guidelines and well-established hormone replacement therapy, fewer than one in seven women with POI in high-income healthcare systems are diagnosed and treated. Globally, tens of millions of women with POI are not receiving appropriate care.

This paper makes the case that POI represents one of the most significant, overlooked, yet achievable commercial opportunities in women's health. The treatments required already exist. The regulatory pathway, a Type II Variation application to the EMA, is well established

and has been used successfully in adjacent women's reproductive conditions. What is missing is POI-specific clinical evidence to support a formal indication, and the commercial and policy infrastructure to translate that evidence into widespread patient access.

The case for investment has never been stronger. Updated prevalence data, landmark international clinical guidelines, a transformed regulatory environment following the FDA's February 2026 removal of class-wide HRT warnings, growing patient advocacy infrastructure and the reactivation of the global POI registry have together created an implementation window that did not previously exist. Women's health has been recognised by the World Economic Forum and McKinsey Health Institute as a \$1 trillion annual opportunity by 2040. POI sits within that opportunity, and the first company to invest will define the category.

This paper outlines specific, achievable asks for pharmaceutical companies, policymakers, and clinicians. We invite all three to engage with The POInt directly, to ensure that POI takes its place in every room where decisions about women's health are made.

POI in every room that matters. That's The POInt.

02. Introduction: The Invisible Condition



3.7% or 1 in 27
are living with POI

Premature Ovarian Insufficiency (POI) is a condition in which the ovaries lose normal function before the age of 40 years, resulting in hypoestrogenism and associated symptoms (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; Panay et al., 2025; Panay, 2026). Although it shares some clinical features with natural menopause, POI is a distinct condition with a different aetiology, a younger patient population, and significantly different long-term health implications (Panay et al., 2020; Panay et al., 2025). POI shares the same hormonal mechanism as natural menopause and can, it is believed, be treated with similar hormone therapies (IMS, 2025; ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; Panay et al., 2025). The causes of POI are broad, ranging from autoimmune, genetic, and surgically or medically induced, but most commonly the cause is unknown (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on

POI et al., 2024). POI can occur at any age from puberty onwards and is often diagnosed young, at a stage of life when it is least expected and least recognised (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; Panay et al., 2020), making it one of the most underdiagnosed and underserved conditions in women's health (Butts, 2025).

Historically, it was believed that POI affected approximately 1% of the global female population, with prevalence reducing logarithmically by age (0.01% under age 30, 0.001% under age 20) (Coulam et al., 1986), but this has now been shown to be a substantial underestimate. The most current prevalence data show that 3.7% of women experience POI, or 1 in 27 (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; Golezar et al., 2019; Li et al., 2023; Panay et al., 2020).

That is one in every classroom, office, or GP waiting room.

Despite such a high prevalence, POI remains largely invisible — to the public, to many healthcare professionals, and to the research and commercial communities that have the power to change outcomes for the women living with it. In 2024, new international POI guidelines were released, incorporating the latest epidemiological and genetic research and reflecting the fundamental shift in our understanding of how common POI actually is (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). At the same time, the women's health investment landscape is shifting, with capital beginning to recognise what was always true: that women's health has been systematically underfunded relative to its prevalence and economic cost. The moment to act on POI is now, before another decade passes and another generation of women receives a diagnosis all too late.

This paper was written to make a case for change, drawing on current epidemiological data, clinical guidelines, and the lived experience of women with POI. It is designed to make an argument that is both urgent and commercially compelling. The evidence is already there. What has been missing is the will to act on it.

03. The Patient Reality

Diagnostic delays, dismissals, and deficiencies

Awareness of POI in general practice is thought to be low, with many GPs reporting not being confident in diagnosing the condition (Newson & Lewis, 2018). Awareness is also thought to be low among the general population, meaning that women experiencing symptoms may not be aware that POI could be the cause, although formal awareness data are lacking. This lack of recognition can lead to diagnostic delays, resulting from a failure to fully investigate amenorrhoea, prolonged menstrual irregularity, or vasomotor symptoms (Butts, 2025), particularly in very young women and girls.

Anecdotally, women recall being told to try different hormonal contraceptives rather than having hormonal investigations. This presents its own problems due to the potential 'masking effect' that hormonal contraception may have on symptoms, and there are currently no formal data exploring how often this masking effect may occur. However, we know that diagnostic delays in general are prevalent. For example, 17% of patients in Hungary waited more than three years from symptom onset to diagnosis, with 5% waiting more than a decade (Csehely et al., 2025). There are currently no average diagnostic delay statistics for POI in the UK, though a recent survey analysis suggests that 17% of patients wait for 4 years or more (Pisana et al., 2026). In the US, a small retrospective case series of 19 patients identified a delay of four years from symptom onset to diagnosis (Minis et al., 2022). The International

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more than 4 years
for a diagnosis

Menopause Society (IMS) 2025 recommendations note that, globally, women with POI report delayed diagnosis, dissatisfaction with care, and substantial variation in the care they receive (IMS, 2025).

The absence of robust diagnostic delay data for POI is itself revealing. We know that around 1 in 27 women experience the condition, but there is currently very little information on how and when it is diagnosed or treated. Initially, it is likely that symptoms may be attributed to stress, anxiety or other conditions not related to ovarian function, but again, no data are available to support or refute this claim. Anecdotally, women speak of being dismissed, gaslit, or diagnosed with something else, before receiving an FSH test. One of the authors experienced dismissal in primary care for approximately ten years, under three different Integrated Care Boards, before receiving hormonal testing. The Daisy Network, the UK's leading POI patient charity, is well placed to collect diagnostic delay data from its members through patient surveys, so financial support for this is critical.

Health consequences of oestrogen deficiency

Women with POI face a prolonged period of oestrogen deficiency during critical years for bone, cardiovascular, and cognitive development. The earlier the onset, the greater the accumulated risk, and delays in diagnosis extend that period of unaddressed deficiency further (Csehely et al., 2025; ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024).

The cardiovascular consequences are significant and well documented. The risk of a composite cardiac event including coronary artery disease, heart failure, atrial fibrillation, ischaemic stroke, and venous thromboembolism was 6.0% in women experiencing premature menopause (including POI), compared with 3.9% in those without (Honigberg et al., 2019). The Canadian Longitudinal Study on Aging found ischaemic heart disease in 5.9% of women with POI, compared with 1.8% in women who experienced menopause at the natural age, representing a 3.3-fold increased risk versus older counterparts (Kirubarajan et al., 2025). Each additional year without oestrogen therapy further increases cardiovascular disease risk by 0.18% to 0.20% (Christ et al., 2018), and a systematic review and meta-analysis of available evidence confirmed a significantly increased risk of cardiovascular and all-cause mortality with early menopause onset, including POI (Muka et al., 2016).



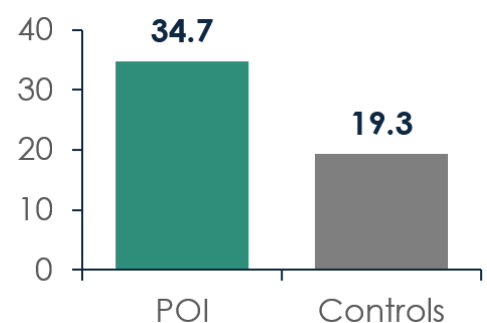
The musculoskeletal burden is equally substantial. Osteoporosis or osteopenia was present in 21.2% of women with POI in a Canadian cohort, compared with just 14.7% of those with average-age menopause (Kirubarajan et al., 2025), and time to diagnosis has been directly correlated with the severity of bone loss; longer diagnostic delays produce more pronounced effects (Csehely et al., 2025). Early initiation of HRT may be the key to mitigating these effects and preserving bone health (Csehely et al., 2025), although more research is needed.

International guidelines link oestrogen deficiency in younger women to potential cognitive decline and an increased risk of dementia (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024), although the evidence base specific to this population remains to be established (Melville et al., 2025).

The multimorbidity burden associated with POI is striking. The Canadian Longitudinal Study found a prevalence of multimorbidity of 64.8% in women with POI, compared with 43.9% in those experiencing menopause at a more usual age (Kirubarajan et al., 2025).

Finally, the mortality implications reframe POI as not only a quality-of-life issue but one of survival. A 30-year Chilean cohort study found that 34.7% of women with POI had died by the end of follow-up, compared with just 19.3% of matched controls, with excess deaths predominantly attributed to cardiovascular causes (Blümel et al., 2022). The benefits of treatment with HRT may go so far as lifesaving.

34.7% of women with POI
had died within 30 years...



...compared with just
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The broader burden: psychology, quality-of-life, and fertility

The physical consequences of POI do not occur in isolation. Women with POI are significantly more likely to experience depression, anxiety, and sexual dysfunction than women without the condition. A meta-analysis of seven high-quality studies found that women with POI were more than three times as likely to experience depression, and almost five times as likely to experience anxiety, compared with controls (Xi et al., 2023). A subsequent, larger meta-analysis of 5,820 women confirmed these findings and additionally found that poor quality-of-life was more than twice as likely in women with POI than those without, which the authors suggest may be attributable to the stigma of infertility and the diagnosis itself (Tian et al., 2024). Another systematic review and meta-analysis found that sexual function was markedly lower in women with POI versus controls, as a direct results of hormone deficiency (van Zwol-Janssens C et al., 2024). Psychological support at diagnosis is formally recognised as a core component of POI care in the 2024 ESHRE guidelines, yet the evidence to guide its delivery in this population is insufficient, and specialist support for women with POI is not consistently available (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024).

For many women, the most immediate concern at diagnosis is fertility, likely contributing to the reduced quality-of-life. Spontaneous pregnancy is unlikely for women with POI (Butts, 2025; ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024), and the majority of women who wish to conceive will require oocyte donation (Torrealday et al., 2017) — a pathway that is emotionally, financially and logistically demanding, and not universally accessible. Fertility is, in many cases, the lens through which the diagnosis is first processed, and it shapes the patient's relationship with her condition, and with healthcare, for years afterwards. Specialist fertility counselling at the point of diagnosis is absolutely necessary, but often missed (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024).

The psychological burden, quality-of-life and fertility dimensions represent three areas where the evidence base is thin, patient support infrastructure is inconsistently available, and targeted investment could make a material difference.

5x
anxiety risk

3x
depression risk



04. The Evidence Gap

Mind the gap

The international 2024 guidelines on POI contain 145 recommendations across 40 key questions, representing the most comprehensive clinical guidance on POI ever produced (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). Of those recommendations, 92 are supported by research data (of which 20 are conditional, meaning the evidence is insufficient to make a strong recommendation) and 53 are good practice points based primarily on clinical experience rather than trial evidence. The guidelines also identify research recommendations across ten clinical domains, including optimal HRT regimen, bone and fracture risk, cardiovascular outcomes, cognitive health, and sexual function, where data are simply not adequate to guide clinical practice (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024).

Nowhere is this evidence gap more starkly illustrated than in cognitive health. A systematic review specifically examining the effect of hormone therapy on cognitive outcomes in women with menopause, early menopause, or POI found no eligible studies in POI at all (Melville et al., 2025). International guidelines link oestrogen deficiency in younger women to potential cognitive decline and dementia risk (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024), yet not a single published trial has examined that link prospectively in non-iatrogenic POI.

Cardiovascular and bone health paint a similar picture. The dose of oestrogen that best protects a 28-year-old's cardiovascular system across two decades of treatment, or the formulation most effective for bone preservation in a younger skeleton, or the point at which dose adjustment is appropriate as a woman with POI approaches natural menopause age, have not been answered in POI-specific trial data (Christ et al., 2018; ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; Meczekalski et al., 2023).

Clinical decisions that will shape a woman's long-term health are being made on inference rather than evidence.

The psychological burden of POI is equally well documented and equally understudied in terms of treatment response. Hormone therapy is associated with stability or improvement in quality-of-life scores in women with POI (Gonçalves et al., 2022), and the clinical logic that restoring hormonal balance may also alleviate psychological symptoms is sound. But the specific evidence for HRT's effects on depression and anxiety in this population has not been generated. For women whose mental health has often been the very symptom that led to years of misdiagnosis, that gap is not a minor omission.

Across all of the domains, the guidelines repeatedly note that evidence has been borrowed from women at natural menopause age (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024).

Building on the POI guidelines, the 2025 IMS recommendations explicitly acknowledge a lack of evidence specifically investigating lifestyle interventions on symptoms and long-term health in women with POI, noting that guidance in this area is extrapolated from women at natural menopause age (IMS, 2025). On HRT risks in POI specifically, the IMS 2025 recommendations state that data are, again, predominantly extrapolated from studies of women with usual menopause age. This applies across multiple treatment domains including dose-response, bone protection and cardiovascular outcomes. For women in whom HRT is not preferable, the combined oral contraceptive (COC) pill is sometimes prescribed, but there are currently no data on whether this is a safe and effective alternative (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; IMS, 2025; Panay, 2026). However, the COC may represent a more familiar treatment strategy among young women (Kaldewey & Kiesel, 2021). For women with POI in whom HRT or the COC are contraindicated, there is almost no evidence base at all. The IMS 2025 recommendations note that evidence for non-hormonal pharmacological interventions specific to POI is “lacking” (IMS, 2025).

While the recommendations confirm that women with POI may require higher doses of HRT than women at natural menopause age, they note that few dose-response trials of HRT in POI have been conducted to guide this in practice (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; IMS, 2025). Clinicians are prescribing higher doses without the trial data to support optimal regimens, and women with POI are being managed on the basis of evidence from clinical trials that were never designed to include them.

The 2020 IMS white paper on POI identified fragmented research and a lack of prospective clinical trials as the defining barrier to progress (Panay et al., 2020). Six years and two sets of landmark international guidelines later, and that verdict remains unchanged.

Closing the gap

Both the international 2024 guidelines and the IMS 2025 recommendations provide a clear and published research agenda (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; IMS, 2025). What is needed now is not further analysis of the problem but the investment to act on it.

At the centre of that agenda sits a straightforward ask: long-term randomised prospective studies determining optimal routes, doses and regimens of HRT in POI populations, with endpoints including quality-of-life, bone density, cardiovascular outcomes and cognitive health. These are not novel or speculative questions. They are documented, endorsed by the leading clinical societies, and answerable with the tools and products that already exist.

The POI registry, developed to facilitate global data collection on diagnosis and management and currently being reactivated under Professor Panay's leadership, represents precisely the kind of infrastructure that sustained investment could bring.

The POISE trial, funded by the National Institute for Health and Care Research, demonstrates that the clinical community has already recognised the unmet need and has taken steps to address it with

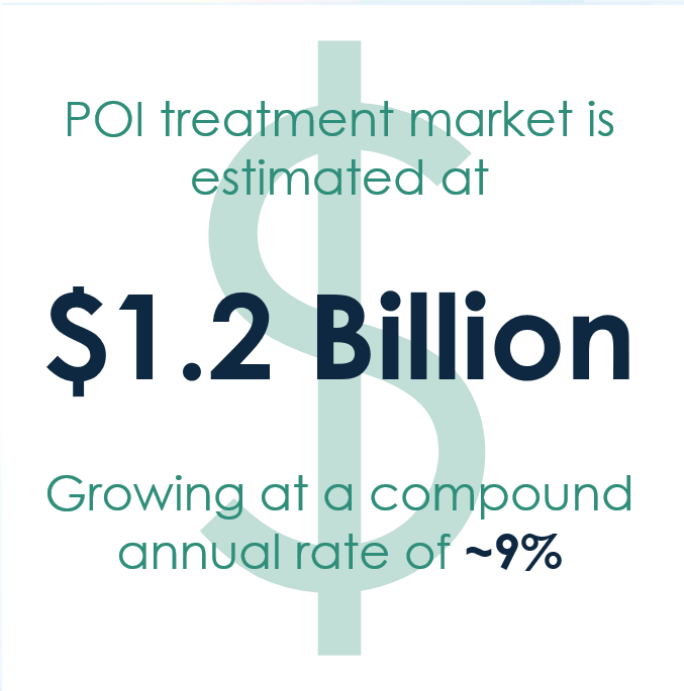
public money. POISE is a landmark, multicentre, randomised controlled trial, powered specifically for a POI population, comparing HRT with the COC pill on bone, cardiovascular, cognitive and quality-of-life outcomes. The clinical community has acted. The question this paper poses to the pharmaceutical industry is a direct one: *why are they absent from a conversation where they are likely to be the primary commercial beneficiary of the results?*

05. The Commercial Case

According to Verified Market Reports, the global POI treatment market is currently estimated at approximately \$1.2 billion and is projected to reach \$2.5 billion by 2033, growing at a compound annual rate of around 9% (Global Primary Ovarian Insufficiency (POI) Market Size, Share, Industry Growth & Forecast 2026–2034, n.d.). This is a market where the products already exist, the clinical need is established, and the growth is already happening without any condition-specific investment to drive it.

Importantly, this figure may substantially underestimate the true commercial potential of POI. The history of women's health demonstrates that market growth is often driven not simply by prevalence, but by recognition. Conditions such as endometriosis and uterine fibroids remained commercially underdeveloped for years despite affecting millions of women, before increased diagnosis, dedicated clinical pathways, and targeted therapeutic development transformed them into major commercial markets. The global endometriosis market alone was estimated at approximately \$2.3 billion in 2023 and is projected to grow substantially over the coming decade (DelveInsight, 2025). The commercial impact of dedicated investment can already be seen at product level. Following the extension of Ryeqo® (relugolix combination therapy) into endometriosis in 2023, Gedeon Richter projected that the new indication would double product sales to at least €30 million in 2024 (Gedeon Richter, 2023), with subsequent investor guidance suggesting peak annual sales of €150–200 million by 2030 (Gedeon Richter, 2025). POI shares many of the same characteristics that historically limited commercial development in these conditions: delayed diagnosis, fragmented care pathways, limited condition-specific evidence, and a patient population that remains largely invisible within existing healthcare systems.

Earlier diagnosis would not create a new patient population; it would reveal and engage one that already exists.



POI treatment market is estimated at

\$1.2 Billion

Growing at a compound annual rate of ~9%

An estimated **32 million** women



not currently receiving
appropriate care

Based on UN population data from 2024 and the updated prevalence figure of 3.7%, approximately 50 million women are living with POI globally at any given time (World Population Data 2024; ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). The proportion of these women currently diagnosed and treated falls dramatically below that figure. Nationwide registry data from Finland, where women diagnosed with POI receive an entitlement to HRT reimbursement, identified 5,221 women diagnosed and treated between 1988 and 2017. That represents a cumulative incidence of approximately 0.5%, against an expected prevalence more than seven times higher (Heinonen et al., 2022). South Korean national health insurance data show a similar pattern, with even lower cumulative diagnosis rates across the reproductive years (Lim et al., 2021). Finland and South Korea both have universal healthcare systems and well-developed clinical

registries, so in lower-resource settings the diagnosis-and-treatment gap is likely larger still. Among the small minority of women who are diagnosed, a large-scale study of more than 255,000 women screened for POI from Saudi Arabia found that only 36% receive adequate hormone therapy, a figure the authors described as 'underuse', in a country that reimburses HRT (Malick et al., 2026). If we applied that number to the global population, knowing the limitations in doing so due to data extrapolation, we can estimate that approximately 32 million women worldwide are not currently receiving appropriate care, assuming that all patients are diagnosed (which of course is not the case). Of course, there are no data to determine the exact number, which is likely to be substantially higher, when undiagnosed patients and those in countries where HRT is not easily available are included. Each percentage point improvement in global diagnosis and treatment rates would represent approximately half a million additional recognised patients.

These additional patients represent a worthwhile commercial investment. They require doses of HRT two to three times higher than the standard menopausal dose (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; Kapoor, 2023), and treatment continuing for up to three decades until the natural age of menopause (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). The lifetime treatment value of a patient with POI is structurally and substantially greater than that of a woman treated for natural menopause, and that value is being lost for every year of diagnostic delay or treatment inadequacy.

The precedent for pharma investment in an underdiagnosed, underserved women's reproductive condition exists. Endometriosis, once routinely dismissed, also underdiagnosed, and undertreated, eventually attracted the kind of investment that changed the clinical landscape. AbbVie's elagolix (Orilissa), approved by the FDA in July 2018, was the first new oral treatment for moderate to severe endometriosis pain in over a decade, supported by the largest Phase 3 endometriosis clinical programme conducted to date (AbbVie, 2018). Pfizer and Myovant Sciences followed in August 2022 with FDA approval for relugolix combination therapy (Myfembree) for the same indication (Myovant Sciences & Pfizer, 2022). Both required substantial first-in-class development investment in entirely

new molecular entities developed specifically for the condition. Ryeqo's extension into endometriosis followed a different and more modest model. Gedeon Richter took an existing product, already approved for uterine fibroids, and pursued a Type II Variation application to add endometriosis as a second indication, approved by the European Commission in November 2023 (Gedeon Richter Plc, 2023). The same molecule, the same manufacturing infrastructure, a single focused clinical programme, and a substantially shorter regulatory pathway delivered a commercially significant new indication.

The investment case for POI sits closer to Ryeqo's endometriosis extension than to Orilissa's first-in-class development. The products already exist, and the regulatory pathway for extending an existing marketing authorisation is substantially less burdensome than developing a new therapy. What POI requires is not invention but evidence, in the form of POI-specific trial data for treatments that are already in clinical use. Women with POI are currently reached by pharma incidentally, within broader menopause prescribing, through the same products, the same channels, and the same clinical conversations, but without a pathway, a communications approach, or a patient identification strategy designed for them. Investment in POI-specific research, diagnosis and communications would make it possible to close that gap.

The cost burden for payers and policymakers

The health consequences of delayed POI diagnosis, documented in Section 3, carry a substantial and quantifiable cost burden for payers and NHS commissioners. Women with POI face significantly elevated rates of ischaemic heart disease, osteoporosis, multimorbidity and premature death. These are the documented consequences of prolonged oestrogen deficiency during decades when it is not being identified, and often not being treated even when it is found (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024; IMS, 2025; Kirubarajan et al., 2025).

To illustrate the scale of the financial burden, fragility fractures alone cost the NHS an estimated £4.7 billion (~\$6.4 billion) annually across the broader population (Gregson et al., 2025).

The downstream arithmetic of untreated POI across a population of working-age women, over two to three decades of unaddressed oestrogen deficiency, does not require a formal health economic model to decipher. Which is just as well, because no published health economic analysis has yet modelled the specific cost burden attributable to POI diagnostic delay or treatment mismanagement. That gap is itself a measure of how far this condition sits outside mainstream policymaker thinking, and commissioning that analysis is among the priorities this paper is calling for. What the available data already make clear is that the cost of appropriate hormone replacement for women with POI is negligible relative to the conditions they are at significantly elevated risk of developing without it. Earlier diagnosis is one of the most straightforward, cost-prevention arguments in women's health, and it is one the NHS has not yet been given the evidence to make.

The strategic direction this paper is calling for is what NHS commissioners would recognise as a 'shift left': moving the point of recognition, diagnosis, and intervention from secondary care and from the downstream complications of untreated POI, back to primary care where the first signals of the condition typically appear. Achieving that shift requires equipping primary care to act on those signals.

GP confidence in diagnosing POI is currently low (Butts, 2025; Newson & Lewis, 2018), and the absence of UK-specific diagnostic delay data is itself a symptom of how rarely the condition is recognised in primary care settings. A coordinated investment in primary care education, diagnostic protocols, and referral pathways for POI is the operational mechanism by which the cost-prevention argument set out above can be realised. For example, mandatory pathways for any young woman with 4+ months of unexplained amenorrhoea, including referral to a specialist.

A practical example of this approach can already be seen in the Bristol, North Somerset and South Gloucestershire (BNSSG) Integrated Care Board (ICB) POI pathway, which provides primary care clinicians with clear guidance on investigation, diagnosis, treatment, and referral through their Remedy clinical referral system. While aspects of the pathway will require updating to reflect evolving evidence and the 2024 international guidelines, it demonstrates what 'good' can look like in practice: a structured pathway that gives primary care clinicians the confidence to recognise, refer, and manage POI appropriately. Future best-practice models should go further, by providing clearer guidance on when POI should be suspected, including common presenting symptoms and risk factors, alongside streamlined diagnostic pathways, evidence-based treatment recommendations and clear referral criteria. The goal is not to turn every GP into a POI specialist, but to ensure that women with possible POI are recognised earlier and can access appropriate investigation and treatment without preventable delay.

06. Why Existing HRT is (Mostly) the Answer

No existing HRT product currently holds a POI-specific indication, representing both a regulatory gap and a commercial opportunity. The first company that invests in the clinical programme to support that application would define the category.

The investment case for POI does not require Pharma to develop a new drug. Most of the products that would treat this population already exist, are already licensed, and are already being prescribed to women with POI. Oestradiol, progesterone, and testosterone are mature, well-characterised treatments with decades of safety and efficacy data in the broader menopausal population. The clinical community is waiting for the evidence infrastructure to catch up with what it is already doing in practice.

What is missing is not the medicine; it is the data. The 2024 international guidelines identified research recommendations across ten clinical domains where POI-specific evidence is absent because the trials required to generate POI-specific data have not been conducted, despite the treatments being widely available (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). Women with POI are currently managed on evidence extrapolated from older menopausal populations, with dose adjustments made on clinical judgement rather than trial data. The 2025 IMS recommendations note



that few dose-response trials of hormone therapy in POI have been conducted, despite the clear physiological rationale for higher doses in this population (IMS, 2025). Clinical practice is ahead of the evidence base. Formalising that evidence base is the investment this paper is calling for.

POISE demonstrates that POI-specific trial design is feasible, that the clinical community has the will and the infrastructure to conduct it, and that the evidence gap is closable. What it cannot provide is the condition-specific, product-level data that would support a formal POI indication for an existing licensed medicine. That requires industry investment.

The regulatory pathway for that investment is well established. In the European Union, extending the therapeutic indication of an existing licensed medicine to include a defined patient population requires a Type II Variation application to the EMA — a post-authorisation procedure distinct from, and substantially less burdensome than, a full new marketing authorisation application.

Under current EMA guidance, a Type II Variation for extension of indication has a standard assessment timeline of 90 days (European Medicines Agency, 2024). Pharma companies selling HRT products in the EU already hold the marketing authorisations to which a POI-specific indication could be added. The legal right to make that application sits with them alone.

What the clinical evidence would need to demonstrate is safety and efficacy in a POI population specifically. The established safety profile of HRT in the broader menopausal population forms a substantial part of that package, but POI-specific data, particularly for the higher doses this younger population requires, and across the longer treatment duration involved, would need to be generated. This is precisely the kind of data that POISE is designed to produce, and that future industry-funded trials could generate. The trial programme required would be focused and finite: bone mineral density, cardiovascular markers, vasomotor symptom control, and quality-of-life outcomes in an adequately powered POI population.

In February 2026, the FDA approved labelling changes to several menopausal hormone therapy products, removing risk statements related to cardiovascular disease, breast cancer and probable dementia from their boxed warnings (FDA, 2026). This is the most significant regulatory development in HRT in over two decades, but its relevance to POI extends beyond the headline. The Women's Health Initiative (WHI) studies that generated those warnings were conducted in women with an average age of 63, more than a decade past the average age of natural menopause, using a hormone formulation no longer in common use. The warnings that followed were applied class-wide, across all HRT products and all patient populations, including women with POI who were decades younger and for whom untreated oestrogen deficiency carried its own well-documented risks. The regulatory environment now reflects what has long been understood by the clinical community: that the WHI findings were never generalisable to younger women with POI, and that the risk calculus for hormonal treatment in this population is fundamentally different.

Of course, HRT is not an option for all women with POI. Women who have had oestrogen receptor-positive breast cancer, have certain clotting disorders, or have other contraindications cannot safely take hormonal treatment (NICE, 2024). For these women, the situation is starker still: the evidence base for non-hormonal pharmacological interventions specifically in POI is described by the 2025 IMS recommendations as “lacking” (IMS, 2025), and the 2024 ESHRE guidelines identify non-hormonal management as a named research priority (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). Non-hormonal options that have shown efficacy in natural menopause, including NK receptor antagonists now licensed for vasomotor symptoms, have not been studied in POI populations (Astellas Pharma Inc., 2023). A woman in her twenties who cannot take HRT has, currently, almost nothing evidence-based to turn to for symptom relief. Yet another research failure that targeted investment could relatively easily address.

The evidence gap in POI is not only a function of too few standalone trials, but also the result of a trial design convention that has, for decades, routinely excluded younger women. Age eligibility criteria in menopausal hormone therapy (MHT) trials typically set a lower limit that excludes most women with POI, meaning that even trials generating data on the products these women are being prescribed produce no data applicable to them. A systematic review of 33 MHT randomised controlled trials, involving 44,639 postmenopausal women, found mean participant ages ranging from 48 to 72 years; a range within which women with POI, by definition diagnosed before the age of 40, simply do not appear (Gu et al., 2024).

Including a dedicated POI cohort within existing or planned trials, whether for HRT, non-hormonal therapies or other interventions, would not require a new study from scratch, but a design decision made early enough in the protocol to be built in rather than bolted on. The incremental cost is modest, but the data generated would be disproportionately valuable, providing the condition-specific evidence that POI currently lacks across multiple treatment domains simultaneously. The ask to the pharmaceutical industry is specific and achievable: *when designing trials for menopausal indications, include POI as a defined subpopulation.*

07. Why Now?

The case for POI investment is not new, but the convergence of the following factors makes inaction significantly more costly than it was a decade ago:

- **The prevalence of POI has shifted.** Long cited at approximately 1%, a figure that shaped clinical training, research prioritisation and commercial thinking for a generation, the global prevalence of POI has now been revised to 3.7% by two large meta-analyses (Golezar et al., 2019; Li et al., 2023). This is not a marginal correction. It means that POI is not a rare condition, the patient population is nearly four times larger than the field assumed, and every commercial model built on the old figure underestimates the opportunity by a corresponding margin.
- **The clinical guidance has followed.** The 2024 ESHRE guideline, co-developed with ASRM, CREWHIRL and IMS, is the most comprehensive international consensus on POI

management ever produced, spanning diagnosis, hormone therapy, fertility, bone health, cardiovascular risk, psychological support and quality-of-life (ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI et al., 2024). Its publication signals that the clinical community has reached a level of maturity on POI that creates an implementation window. Guidelines of this scale create clinical momentum; that momentum requires a commercial infrastructure to sustain it. The 2025 IMS recommendations reinforced the same message, explicitly noting the absence of POI-specific trial data and the need for dose-response research in this population (IMS, 2025).

- **The regulatory environment has shifted in favour of hormonal treatment.**

In February 2026, the FDA removed cardiovascular disease, breast cancer and probable dementia risk statements from the boxed warnings for several HRT products (FDA, 2026); the regulatory environment is now more receptive to the investment case for hormonal treatment than it has been at any point since 2002.



- **Women's health has moved from a niche interest to a recognised investment priority.**

The World Economic Forum, in collaboration with the McKinsey Health Institute, has estimated that closing the women's health gap represents a \$1 trillion opportunity for the global economy annually by 2040 (World Economic Forum & McKinsey Health Institute, 2024). In the UK, the renewed Women's Health Strategy for England, released in April 2026, placed hormonal health, menopause and reproductive conditions explicitly within the NHS improvement agenda.

- **The reactivation of the POI**

registry signals renewed clinical infrastructure ambition. A functioning global registry will accelerate the research agenda the 2024 guideline calls for, and represents an immediate opportunity for pharma investment in data collection infrastructure.

- **The patient and advocacy infrastructure around POI is growing.** The Daisy Network has an active clinical advisory board, a new patient advocacy working group and established relationships with the clinical community. World POI Day, launched on 25 October 2025, marks the first dedicated international awareness moment for the condition. Patient voice in POI is becoming organised, evidence-informed and visible in ways that create the conditions for productive industry engagement.

The question for pharma is not whether POI will become a recognised treatment priority. The clinical evidence, the regulatory environment and the patient infrastructure are already moving in that

direction. The question is when the companies best placed to benefit from that shift will invest in it, or whether they will wait for others to define the category first.

08. From Evidence to Action

There is, of course, a moral imperative to address the evidence gap in POI. But the arguments in this paper are not designed solely to encourage investment from a moral patient perspective. There are real, commercial arguments for investing in this underserved population, and the infrastructure to do so is relatively achievable. The pathway is clear.

For pharma

- **Commission health economic analyses** of POI diagnostic delay and the cost burden of inadequate treatment. Pharma is uniquely placed to fund the analysis that makes the payer and policymaker case, and in doing so to shape the evidence base that drives diagnosis rates, treatment uptake and long-term commercial returns.
- **Develop POI-specific communications and patient identification infrastructure.** Women with POI are currently reached incidentally. A condition-specific approach to diagnosis support, clinician education and patient awareness would expand the treated population in ways that passive prescribing cannot.
- **Commission POI-specific trial programmes,** using existing HRT products that are already on the market and being used in this population. This is not a first-in-class development challenge. The clinical infrastructure already exists. A focused, specific clinical investment is both achievable and commercially logical.
- **Invest in non-hormonal treatment options** for women with POI who cannot access HRT. This population currently has almost no evidence-based pharmacological alternatives, representing both an unmet clinical need and an untapped commercial opportunity.
- **Include a dedicated POI cohort as standard,** where new trials are in development for menopausal indications. The incremental cost of doing so is modest relative to the value of the data generated, and would accelerate the evidence base for a population that is currently excluded from almost all trial design by default.
- **Collaborate directly with institutions such as ESHRE, ASRM, Monash, and IMS, and with advocacy groups such as the Daisy Network,** to address the fragmentation that currently characterises the POI landscape. Despite growing recognition of POI, activity remains dispersed across clinical practice, research, patient advocacy, and industry. Convening these stakeholders around shared priorities will accelerate progress, reduce duplication of effort and create a more coherent pathway from evidence generation to clinical implementation.

For policymakers

- **Include POI-specific diagnosis targets** within the next iteration of the Women's Health Strategy for England, and equivalent frameworks in devolved nations and internationally. A condition affecting 3.7% of women, with documented consequences for long-term health and premature mortality, warrants explicit inclusion in women's health policy, not subsumption within broader menopause guidance.
- **Commission a health economic analysis** of the cost burden of POI diagnostic delay to the NHS. The components of that burden are individually well documented. Their aggregate cost, attributable specifically to delayed or absent diagnosis in women with POI, has not yet been modelled. That analysis would provide the evidence base for a cost-prevention argument that is currently unavailable to NHS commissioners and health economists.
- **Include POI-specific psychological support programmes**, validated quality-of-life tools designed for this population, and expanded access to fertility treatment pathways in women's health strategy and commissioning frameworks.
- **Fund a coordinated primary care education and mandatory pathway development programme for POI.** The cost-prevention argument set out in this paper is realisable only if primary care has the awareness, training and diagnostic confidence to identify women with POI earlier and refer appropriately. This is a 'shift-left' intervention with clear precedent in NHS commissioning thinking, applied to a condition that has so far been left out of it.
- **Recognise POI as a distinct women's health priority requiring coordinated action** across clinical, research and policy domains. POI currently occupies an ambiguous position between reproductive medicine and menopause care, contributing to gaps in diagnosis, research investment and service provision. Policymakers have a critical role in creating the structures, partnerships and accountability mechanisms needed to ensure that POI is addressed as a coherent health challenge rather than a series of disconnected clinical issues.

For clinicians

- **Apply the 2024 ESHRE guideline in practice.** Its implementation requires clinical champions in gynaecology, endocrinology, general practice and related specialities, willing to carry its recommendations into training, referral pathways and service design.
- **Participate in research.** The POISE trial demonstrates that POI-specific trial infrastructure exists and is viable. Future research programmes will require patient recruitment, clinical collaboration and the institutional support that only practising clinicians can provide.
- **Collaborate with professional societies, patient advocacy groups, policymakers and industry** to build a more coordinated approach to POI. Clinicians are uniquely positioned to connect research, policy and lived experience, helping to ensure that future priorities are informed by both scientific evidence and the needs of women living with the condition.

What Collaboration Can Achieve

The conditions for meaningful progress on POI have never been more favourable. Updated prevalence data, landmark clinical guidance, a shifting regulatory environment and growing patient advocacy infrastructure have created a window that has not previously existed. What has been missing is a coordinating function — an organisation that holds the commercial argument, the patient voice and the clinical evidence in the same frame, and that can convene the right conversations at the right level.

That is what The POInt exists to do. This paper is the beginning of that conversation. We invite Pharma, policymakers, and clinicians who recognise the opportunity it describes to engage with us directly.

The data, the guidelines and the regulatory environment have all shifted. The commercial and policy infrastructure around this patient population has not, and closing that gap is what this paper is calling on Pharma, policymakers, and clinicians to do.

POI in every room that matters. That's The POInt.

09. Acknowledgements

The authors would like to thank Amy Bennie and Corinna Bordoli of the Daisy Network for their input into this paper, and for their ongoing commitment to ensuring the patient voice remains central to clinical, research, and policy thinking on POI. The Daisy Network is the UK's leading patient advocacy organisation for women with POI and provides peer support, advocacy and information to women affected by the condition.

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