Bridging Gaps in Diagnostic, Management, and Global Policy Frameworks for Endometriosis

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Chapter 1: Introduction to endometriosis and global challenges

Thesis abstract

Background

Endometriosis is known to induce a significant socioeconomic burden, which can be felt by the 190 million individuals living with the condition, their peers, their community, their nation, and even globally. Despite its burden, infrastructures for endometriosis care are fragmented, inconsistent across regions, and hindered by systemic barriers that drive global diagnostic delays and concerns with access to standardised care. These challenges are exacerbated by low political prioritisation and the stigma surrounding menstrual disorders. Closing the "women's health gap" requires frameworks for conditions such as endometriosis to be addressed.[1]

Methods

The thesis includes four key projects that address different aspects of the endometriosis healthcare framework. Patient experiences of our current diagnostic framework for endometriosis were explored through a mixed-methods survey, complemented by a Phase 2 novel imaging study (DETECT), conducted to address key concerns, such as the recognised global diagnostic delay. To promote the development of standardised clinical guidelines and to strengthen the evidence within treatment frameworks, a network meta-analysis (NMA) was conducted to rank interventions for endometriosis-associated pain. Finally, a comprehensive scoping review mapped how governments are responding to the challenges of endometriosis globally. Together, the projects within this thesis aim to

evaluate and bridge gaps in diagnostic, treatment, and policy frameworks for endometriosis globally.

Results

The survey, completed by over 1,000 individuals, described the consequences of systemic healthcare gaps. 87% of respondents reported a diagnostic delay, and 72% stated that an earlier diagnosis would have changed their life choices. Laparoscopy, despite being invasive, held higher satisfaction scores compared to US and MRI, as it provided definitive diagnostic answers. The DETECT study aimed to reduce diagnostic delays and limitations in diagnostic imaging by investigating the utility of a novel angiogenic tracer, ^{99m}Tc-maraciclatide. The scan demonstrated a sensitivity of 82% and a specificity of 100% for detecting endometriosis at the participant level, as well as a sensitivity of 75% for detecting superficial peritoneal endometriosis, exceeding the thresholds for a diagnostic triage tool. There was a higher probability of detecting angiogenically 'active' lesions (OR 7.62; 95% CI 1.57–37.05), supporting the biological hypothesis of the study. Acceptability of the scan was high (mean 97.4, SD 5.7 (VAS 0-100), n=13). Treatment and management frameworks were evaluated through an NMA of 95 RCTs assessing the effect of 136 comparisons on 'overall pain'. Ablation ± drainage (SMD 0.96; 95% CI 0.26, 1.67), progestogens (SMD 0.65; 95% 0.44, 0.87), and GnRH agonists (SMD 0.59; 95% CI 0.41, 0.77) ranked among the most effective treatments based on change scores, while acupuncture (SMD 1.45; 95% CI 0.59, 2.31), ranked highest on pain end scores. However, marked heterogeneity in methodology and reporting limited the certainty of comparisons, demonstrating that optimisation of treatment frameworks remains constrained by research limitations. The scoping review

revealed a critical lack of strategic policy responses to the global challenges of endometriosis. Of the 194 countries examined, 98 had no available information on endometriosis policies or prominent advocacy groups for endometriosis. 48 countries had taken initial steps to raise awareness for endometriosis, 36 had set endometriosis on the political agenda, and 12 had adopted national policies for a national endometriosis strategy, but only four of these were found to be implementing their strategies. The review found that globally, policymakers use three frameworks to implement endometriosis policy: stand-alone national action plans, policy integration into other health plans, and stand-alone laws. While Australia and France provide promising models of comprehensive strategies, most countries rely on ad hoc initiatives. The lack of systematic policy infrastructure limits the ability of advances in fields such as diagnostics and treatment to reach patients.

Conclusions

This thesis demonstrates that the challenges of endometriosis cannot be solved through advances in research, clinical practice, or policy in isolation. Patient experiences reveal the cost of fragmented care frameworks; the DETECT study illustrates how diagnostic innovations can help close critical gaps in early detection; the treatment NMA exposes the limitations of current evidence guiding clinical decision-making; and the scoping review further emphasises that without coordinated strategies, innovation and reform cannot reach their full potential. Bridging gaps in endometriosis healthcare frameworks requires strategies spanning across research, clinical care, and policy, built through collaboration among patients, advocates, clinicians, researchers, and policymakers to

create structured, equitable, and responsive frameworks to support our endometriosis population near and far.

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The evolution of endometriosis knowledge

Though descriptions have evolved over time, it is thought that women have endured the consequences of a displaced uterus for over two millennia. 5th and 4th century BC Hippocratic texts proposed that if the womb 'wandered' out of place, it could cause menstrual dysfunctions that, if left untreated, could cause pain, infertility and even extrapelvic symptoms such as breathlessness if the uterus reached the thorax, but it could be cured by pregnancy.[2] This description is strikingly similar to the condition that, in 1860, Carl von Rokitansky provided the first histological evidence of by demonstrating the presence of ectopic endometrial–type tissue (womb-like tissue) outside of the uterus.[3,4] **In 1899, William Wood Russell identified ectopic tissue within the ovary, providing an early description of the first endometriosis subtype, endometriomas** (OE)**.**[5] Subsequently, in the early 1900s, the surgeon Thomas Stephen Cullen began mapping various locations within the pelvis where ectopic endometrial–type tissue could be found. Within his work, Cullen referred to the invagination of endometrial tissue into the myometrium as "adenomyoma" and lesions outside the genitalia, such as the bowel and uterosacral ligaments, as "adenomyosis externa." In 1914, Cullen later described adenomyoma of the rectovagina, stating it was a nodular, fibrotic, deeply infiltrating disease that causes severe dyschezia and dyspareunia. This provided an early description of the second endometriosis subtype we have today, **deep endometriosis (DE).**[5] In 1921, John Sampson analysed perforating haemorrhagic ("chocolate") ovarian cysts and proposed that their lining was ectopic endometrial tissue, which linked them to pelvic "adenomas." In 1922, Sampson proposed the final subtype of endometriosis "intestinal adenomas of endometrial type," describing implants on intestinal and peritoneal surfaces (superficial

peritoneal endometriosis (SPE)), which he believed was a consequence of ruptured ovarian haemorrhagic cysts. However, Sampson revised this theory after performing surgeries timed with menstruation, where he noticed the reflux of menstrual tissue into the pelvic cavity and suggested the theory of retrograde menstruation, which is the most universally accepted aetiology for the condition he then began referring to as endometriosis.[6,7]

Sampson's theory is often criticised for not explaining the presence of extrapelvic endometriosis. However, Sampson had in fact proposed two theories for endometriosis, although the second theory, 'retrograde menstruation', is most often referenced. In 1918, Sampson described questionable experiments where he clamped the cervix to force endometrial tissue out of the uterus, but instead found that the tissue was absorbed into the venous system to 'metastasise' to distant sites.[7,8] He published his findings in a paper in 1927 called 'Metastatic or embolic endometriosis due to the menstrual dissemination of endometrial tissue into the venous circulation'.[7,9]

Between 1900 and 1930, competing etiological theories were also proposed, which persist in contemporary debate. Meyer proposed the theory of coelomic metaplasia, which describes the transformation of peritoneal cells into endometrium-like epithelium during the embryological development of the Müllerian tract, which originates from coelomic epithelium.[10,11] This theory is often used to explain endometriosis in those without a uterus, such as Müllerian agenesis[12] or the rare case reports of endometriosis in men.[13] Halban's theory of lymphatic and hematogenous dissemination helped explain how extra-pelvic endometriosis may occur.[14]

With the adoption of gynaecologic laparoscopy, surgeons could directly visualise peritoneal surfaces. Classically, peritoneal disease was identified by its “powder-burn” (black) appearance. However, in 1986, Jansen & Russell demonstrated that many previously overlooked red and white peritoneal lesions were also associated with endometriosis, broadening the visual spectrum of peritoneal disease.[15] Later studies correlated colour, size and depth with histologic confirmation and activity, and developed the belief that peritoneal lesions progress from red (active), through black, to white (fibrotic).[16]

With advances in science, the initial theories of endometriosis have been expanded and challenged. Experiments in baboons have supported Sampson's theory of retrograde menstruation by demonstrating that retroperitoneal injections of endometrial tissue can induce endometriosis experimentally.[17] However, the expansion of laparoscopy has demonstrated that 90% of women undergo retrograde menstruation, with only a few developing endometriosis.[18] Thus, to develop endometriosis, other mechanisms must occur or not occur to create an environment favourable for endometriosis. For example, it is believed that when refluxed endometrial cells encounter an intact mesothelium, there is a lower propensity to adhere. In contrast, a mesothelium that has undergone mechanical or inflammatory injury will have an exposed basement membrane and extracellular matrix (ECM), making it more adhesive and receptive to refluxed endometrial tissue.[19,20] Moreover, the altered peritoneal microenvironment in women with endometriosis results in significantly higher levels of tissue macrophages that are capable of expressing excess TGF-1 and TGF-β, which promote cell-cell and cell-matrix

adhesion interactions.[21,22] In addition, it is believed that in most cases of retrograde menstruation, the immune system can clear the refluxed endometrial cells. However, individuals with endometriosis have specific immune deficits that allow the disease to persist and progress. For instance, despite women with endometriosis having higher levels of peritoneal macrophages, their cytotoxicity is reduced.[23] Moreover, in baboon studies, there was increased disease progression in the baboons that were intentionally immunosuppressed.[17]

Endometriosis pathophysiology

Attachment and invasion – the role of integrins in endometriosis

Attachment of retrograde menstrual endometrium to the peritoneal surface is orchestrated by endometrial adhesion molecules that regulate cell–matrix and cell–cell contacts, most notably cadherins, integrins, proteoglycans (e.g., syndecans), laminin-binding receptors, immunoglobulin-superfamily adhesion proteins, and CD44.[24]

Integrins are non-covalent α/β heterodimeric transmembrane receptors and are one of five families of transmembrane Cell Adhesion Molecules (CAMs) which play a crucial role in cell-to-cell adhesion and communication. Integrins also uniquely communicate information regarding the ECM intracellularly through interactions with collagen, fibronectin, fibrinogen, and vitronectin.[25] Their importance in human life cannot be understated, starting with their role in the evolution of multicellular organisms, to their role in tissue repair, haemostasis, embryo implantation and human development.

However, they are also implicated in mediating disease states such as cancer and inflammatory diseases. In fact, almost every stage of cancer invasion, from proliferation, migration, invasion, neovascularisation and tumour survival, is regulated by integrins.[26]

Twenty-four distinct αβ combinations are formed in humans. The α subunit largely determines extracellular ligand specificity and influences conformational preference, whereas the β subunit's cytoplasmic tail governs outside-in signalling, assembling focal-adhesion complexes (e.g., FAK/Src/ILK) to regulate proliferation, migration, and differentiation.[27,28] By ligand class, integrins are grouped into leukocyte (β2 family), collagen-binding (α1β1, α2β1, α10β1, α11β1), RGD-binding (notably αvβ3, αvβ5/6/8, α5β1, αIIbβ3, α8β1), and laminin-binding (α3β1, α6β1/β4, α7β1) receptors.[28] The engagement of these receptors with ECM or counter-receptors initiates adhesion, invasion, migration, and proliferation. Importantly, many integrins bind multiple ligands, and each pairing can trigger distinct intracellular responses depending on matrix context and co-receptor crosstalk. Conformational control provides an additional regulatory layer: integrins cycle among bent-closed (inactive), extended-closed (primed, low-affinity), and extended-open (active, high-affinity) states.[27,28] Once a ligand is bound, and the integrin conforms into its active state, its intracellular component initiates a signalling cascade known as 'outside-in-signalling'.[29,30] Thus, integrins allow cells to collect signals from the microenvironment, inducing the necessary localised responses such as cell proliferation, differentiation, apoptosis and angiogenesis. However, signals from inside the cell can also regulate these processes by changing the conformational state of the integrin, therefore enhancing or inhibiting responses from the cell's environment, known as 'inside-out-signalling'.[30]

To develop a better understanding of the roles of integrins in endometriosis, I searched Medline, Embase and PsycINFO using Ovid, Web of Science, and Scopus. I searched the following databases from inception until January 2022 using terms relating to "endometriosis" and "integrins." I identified 20 human studies and 4 animal studies assessing the roles of integrins in various aspects of endometriosis pathogenesis, including adhesion (n=7), invasion (n=4), proliferation (n=2), angiogenesis (n=3), and infertility (n=7), with αvβ3 being the most commonly studied integrin (**Table 1**).

Table 1: Scoping review summary of studies assessing the roles of integrins within endometriosis pathogenesis

Category	Description	Number of studies
Species	Human studies	20
	Animal studies	4
Pathogenesis focus	Adhesion	7
	Invasion	4
	Proliferation	2
	Angiogenesis	3
	Infertility	7
Sectioning method	Frozen	11
	Fixed	8
	Cultured cells	4
Method of analysis	Immunohistochemistry	16
	Western blot	2
	Flow cytometry	3
	Indirect alkaline phosphatase	1
Scoring method	H-SCORE	6
	Semiquantitative analysis	8
	Percentage of vessels with expression	3
	mRNA expression	1
	Image-Pro Plus score/count	1
	Geometric mean flourescent intensity	1
Menstrual phase	Proliferative	10
	Secretory	14
	No information	7
Sample site	Epithelium	14
	Stroma	8
	Glands	10
	Vasculature	2
	Other sites	5
Integrins	αvβ3	9
	β3	6
	β1	5
	α4, αv or α6	4
	α5, α1, α2, α6 or α3	3
	β2, β5, α3β1, α4β1 or α2β	2
	αL, β2, β4, β5, α5β1, α6β4 or β8	1

One notable study identified during my scoping review was conducted within my research department (University of Oxford, Nuffield Department of Women's and Reproductive Health) and demonstrated that the eutopic and ectopic endometrium of

individuals with endometriosis exhibit aberrant expression of integrins, resulting in increased adhesion and proliferative capacity compared to controls. Moreover, integrin expression patterns vary by endometriosis subtype, with significantly higher levels of adhesive integrins and ECM in endometriomas and SPE than in DE. [31] Once endometrial cells are attached, altered expression of matrix metalloproteinases enables endometrial cells to rapidly degrade the underlying peritoneal extracellular matrix, thereby facilitating invasion of the peritoneal surface.[32]

Angiogenesis and integrins

Implanted lesions enter a hypoxic, pro-inflammatory state, preventing proteasomal degradation of Hypoxia-Inducible Factor-1α (HIF-1α)[33], which in turn upregulates Vascular Endothelial Growth Factor (VEGF)[34] in lesion cells and infiltrating macrophages.[35] VEGF, particularly VEGF-A signalling through VEGF Receptor 2 (VEGFR-2), is a key regulator of endothelial proliferation, migration, and permeability that secures a blood supply to ectopic tissue.[36] Ovarian oestrogen release promotes further VEGF secretion by lesions and macrophages, creating a pro-angiogenic loop within the peritoneal cavity.[37] The peritoneal fluid further enhances angiogenesis by containing various angiogenic cytokines and chemokines such as Tumour Necrosis Factor-α (TNF-α), lipopolysaccharide (LPS), IL-8, −17, as well as VEGF secreted by neutrophils and macrophages and lesions themselves.[35] In fact, there are higher levels of proangiogenic factors within the peritoneal fluid[30,31], blood[32] and eutopic endometrium[33] in those with endometriosis compared to controls, with higher levels, especially VEGF, seen at higher stages of endometriosis severity. VEGF acts in conjunction with neurotrophins, such as

Nerve Growth Factor (NGF), to regulate neuroangiogenesis. This results in new vessel growth accompanied by aberrant innervation, which can lead to hypersensitivity and pain.[38]

Integrins play a crucial role in angiogenesis, including the coordination of endothelial migration and the recruitment of pro-angiogenic macrophages. The αlpha-V subunit heterodimers are typically involved in cancer and inflammatory diseases, with αvβ3 being the most extensively studied integrin in terms of its role in angiogenesis.[39,40] Animal models have demonstrated the role of αvβ3 in the development and maturation of new blood vessels, with a four-fold increase in expression during angiogenesis in the chick chorioallantoic membrane.[39] Antibodies to αvβ3 prevent the development of new blood vessels regulated by basic Fibroblast Growth Factor (bFGF), TNF-α and human melanoma fragments, but do not affect pre-existing vessels, highlighting its functional role in neoangiogenesis, the development of new blood vessels. Through mechanisms such as these, monoclonal antibodies against αvβ3 can halt the development of endometrial lesion growth and reduce the mean vessel density of lesions within mouse models.[41] The endometrium of those with endometriosis express higher levels of αvβ3 compared to controls, suggesting an already higher propensity for angiogenesis before cells are refluxed into the pelvic cavity. [42] This might be explained by the overexpression of HOXD3 found in the ectopic and eutopic endometrium of women with endometriosis, a gene which regulates αvβ3.[43,44]

The role of inflammation and endogenous steroids in endometriosis

Inflammation is central to endometriosis, driving lesion formation, growth, pain and infertility.[45] Persistent immune activation (especially macrophages) and elevated inflammatory mediators (e.g., IL-1β, IL-6, TNF-α) support adhesion, invasion, and angiogenesis. Alterations in immune cells and inflammatory mediators can extend beyond the pelvis and may contribute to associated comorbidities, such as depression, fatigue, central pain sensitisation, and other inflammation-mediated sequelae, such as cardiovascular disease.[46] The inflammatory process is reinforced by a cyclooxygenase-2 → prostaglandin E 2→ aromatase loop that increases local estradiol and prostaglandin production.[45,47] The oestradiol-dominant state promotes lesion survival, invasion, and further angiogenesis and inflammation. Ectopic lesions are relatively progesterone-resistant and poorly respond to progesterone's usual anti-inflammatory effects. This results from loss of Progesterone Receptor (PR) PR-B, epigenetic silencing of progesterone-responsive genes, and a cytokine-rich environment that disrupts PR signalling. Overexpression of ERβ further suppresses PR and promotes survival pathways, leaving lesions oestrogen-driven, invasive, and inflammatory.[48]

The development of endometriosis-associated pain

The oestradiol-dominant, progesterone-resistant state of ectopic lesions amplifies the VEGF/NGF-driven neuroangiogenesis by stimulating the growth of sensory and sympathetic fibres along newly formed vessels, which can ultimately lead to the development of endometriosis-associated pain pathways.

The umbrella term endometriosis-associated pelvic pain encompasses a myriad of more specific symptoms, including but not limited to dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, dyschezia, and chronic pelvic pain.[49–51] The perception of endometriosis-associated pain results from complex interactions between the peripheral and central nervous systems, involving one or more of the pain mechanisms (nociceptive, nociplastic, inflammatory, and neuropathic).[52,53] Peripherally, the immune response induced by the presence of endometriosis lesions can irritate and damage nerve endings and nerve fibres, which can exacerbate the response by the release of pro-inflammatory neuromediators.[54] Pain can be further enhanced through the activation of nociceptive receptors by localised inflammation, leading to sensory nerve sensitisation.[55] Overstimulation of nociceptive inputs is believed to cause central structural and physiological changes, resulting in central sensitisation, increasing one's perception of pain.[54] The development of endometriosis-associated pain symptoms is the most common reason a patient would be investigated for endometriosis.

Diagnosing endometriosis

The current diagnostic pathway for endometriosis

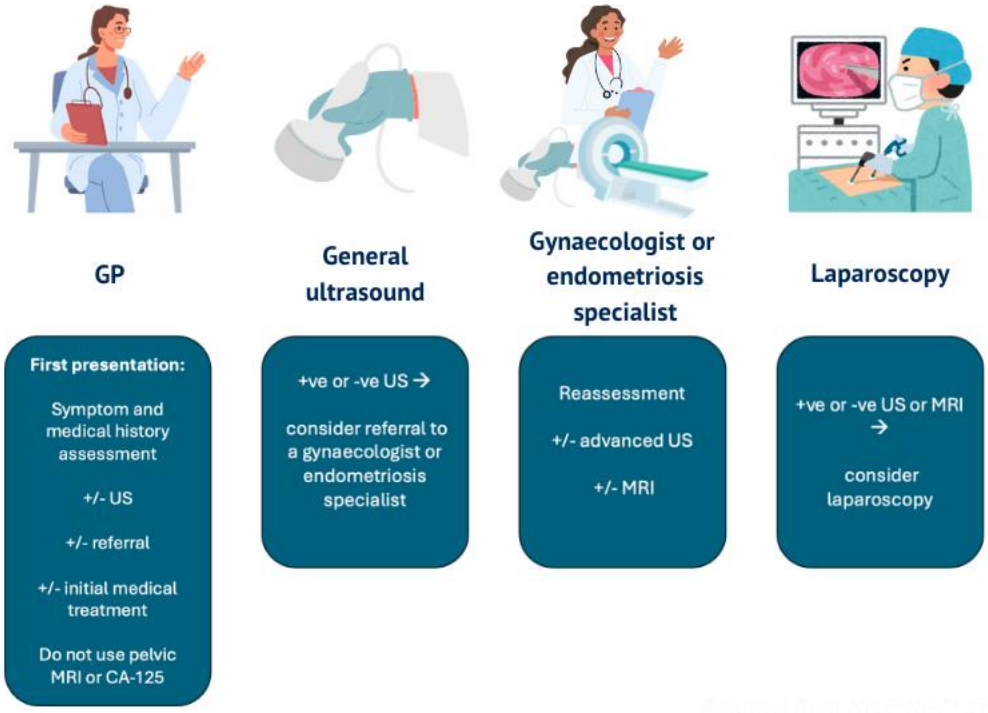


Figure 1: UK endometriosis diagnostic pathway. A summary of NICE guidelines [56]

The diagnostic journey a patient experiences varies greatly between individuals, depending on a multitude of factors, including personal, regional, and institutional influences. Within the United Kingdom, the NICE guidelines[56] for investigating endometriosis can be summarised in four main stages (**Figure 1**). Although not all patients need or reach each stage, the timing of these steps varies greatly. A recent advancement in the diagnosis of endometriosis is the 2022 ESHRE guidelines[57], which promote a shift away from relying on surgery for diagnosis, given the advances in non-invasive imaging.

Clinical diagnosis

There has also been a call to reduce our surgical dependence further and to make a diagnosis more accessible by promoting clinicians to give a clinical diagnosis of endometriosis. This diagnosis can be provided by collecting information on the patient's symptoms (e.g. persistent and/or worsening cyclic or constant pelvic pain), patient history (e.g. dysmenorrhea in adolescence or a positive family history), physical examination findings (e.g. nodules or a retroverted uterus), and finally performing other investigations (e.g. ultrasound) if needed.[58] For instance, the presence of dysmenorrhea, pelvic pain, dyspareunia or infertility can predict a surgical diagnosis of endometriosis with a sensitivity of 76% and specificity of 58%.[59] Although a clinical diagnosis does make a diagnosis more accessible and can reduce the time to diagnosis, there are concerns with its accuracy and that a level of clinical uncertainty will remain, necessitating further investigations.[60]

Ultrasound

Transvaginal ultrasound (TVUS) is the first-line test for suspected endometriosis. Basic pelvic ultrasound scans typically focus on the uterus, ovaries and retrouterine pouch and can therefore detect abnormalities such as OE and concomitant uterine anomalies, including fibroids and adenomyosis. However, advanced pelvic ultrasound has the advantage of being able to identify other pelvic regions affected by endometriosis, such as the bladder, bowel, and rectovaginal septum.[61] The International Deep Endometriosis Analysis (IDEA) group has developed a protocol for performing advanced pelvic

ultrasounds. TVUS accuracy is highly operator dependent, but proficiency can be achieved within a short space of time with dedicated training.[62,63]

In addition to operators, accuracy varies based on the anatomical region and endometriosis subtype. For OE, pooled estimates from a Cochrane review show a sensitivity of 93% and specificity of 96%, which are high enough for TVUS to qualify as a reliable triage test.[64] For DE, accuracy for TVUS detection of rectosigmoid disease shows pooled sensitivity 91% and specificity 97% on meta-analysis, while uterosacral ligament, rectovaginal septum, vaginal, and bladder lesions typically have high specificity (96%–100% but a lower sensitivity (49%–62%).[65,66] The dynamic "sliding sign" adds value for predicting pouch of Douglas obliteration and bowel involvement (pooled sensitivity 88%, specificity 94%).[67] A 2016 Cochrane review found insufficient evidence for the use of TVUS in detecting SPE.[64] More recent studies with advanced TVUS have shown improved accuracy in detecting the pouch of Douglas SPE (specificity 96%, sensitivity 50% and PPV 77%–81%).[68]

MRI

MRI is a valuable adjunct to transvaginal ultrasound for suspected endometriosis, particularly for pre-operative mapping of DE (bowel, uterosacral ligaments, vagina, bladder) and when TVUS is inconclusive. Standardised reporting protocols are now being developed that insist on certain practices, such as reporting by compartment.[69]

MRI shows strong diagnostic accuracy for OE (pooled sensitivity 95% and specificity 91%) and for DE (pooled sensitivity 94% and specificity 77%).[64] Similar to TVUS, diagnostic accuracy varies by region: rectosigmoid (sensitivity 85% and specificity 95%), rectovaginal septum (sensitivity 66% and specificity 97%) and uterosacral ligaments (sensitivity 70% and specificity 93%), but demonstrates a high rule-in value at several locations.[70] Unfortunately, this high accuracy is not replicated for the detection of SPE. Mapping of MRI findings to the #Enzian compartments reported very low sensitivity (14%) and modest specificity (76%) for peritoneal implants.[71] Thus, similar to TVUS, MRI frequently misses SPE, and a negative scan cannot exclude it.

Diagnostic laparoscopy

As discussed, the 2022 ESHRE guidelines[57] have moved away from relying on laparoscopy for a diagnosis. However, it is an important diagnostic tool in those with imaging-negative disease. Despite laparoscopy being considered the gold standard, uncertainties remain surrounding visual and histological diagnoses. Firstly, endometriosis may be missed on visual inspection. Moreover, lesion structure can be destroyed during excision, especially if ablation is used, and lesions can be further damaged during storage, transportation, and processing. One study found that over 1,000 lesions, visual inspection has been shown to have a moderate sensitivity (68%) and specificity (78%). Accuracy was found to be associated with lesion characteristics. Powder-burn lesions were confirmed most often (65.8%), followed by white scarring (51.6%), clear vesicles (45.7%), red flame (39.1%), and peritoneal pockets (28.9%), with differences across types being significant (p=0.003). Notably, 11.3% of samples that

appeared normal still contained histologic endometriosis, indicating that the disease can be occult and easily missed. [72]

Barriers to a diagnosis and the diagnostic delay

Despite the various approaches to diagnosing endometriosis, there are numerous barriers that patients must overcome to obtain a diagnosis. One of the main global challenges facing those with endometriosis and their healthcare providers is the diagnostic delay, with estimates varying between countries, such as up to 12 years in the US[73] and eight years in the UK.[74] The cause of this delay is multifaceted but includes factors such as the presence of non-specific symptoms, normalisation of symptoms, lack of awareness, lack of non-invasive biomarkers and limitations in imaging.[75] Thus, advancing diagnostic imaging in endometriosis has been deemed a global endometriosis research priority.[76]

Novel advances in endometriosis diagnostics

Advances in using patient characteristics for diagnostics

With advancements in menstrual cycle tracking apps and devices, it is becoming a common practice for patients to track various metrics that could be utilised in diagnostics. For example, a patient interview questionnaire designed to identify high-risk patients and streamline referrals for specialist imaging has been both internally and externally validated.[77] Moreover, self-completed questionnaires have also been investigated, such as ENDOPAIN-4D[69,] which is a validated tool for assessing endometriosis pain symptoms. It has been translated and validated in various

languages and has also been shown to hold potential for assisting with early diagnosis (receiver operating characteristic curve of 0.92, 95% confidence interval: 0.87–0.95).[78] Others, such as Bendifallah et al. in 2022 [79], and Goldstein et al. in 2023, have taken a step further by training machine learning (ML) models to predict endometriosis based on self-reported questionnaire data. Goldstein's best-performing model had an AUC of 94%, sensitivity of 93%, and specificity of 95%.[80] Questionnaires have also been adapted specifically for use in adolescents and young adults (16-24).[81]

Biomarker development

It is believed that 70% of clinical decision-making is based on *in vitro* diagnostics.[46] However, endometriosis is one such condition where *in vitro* diagnostics currently holds little value. That said, there is no shortage of biomarker research. A 2024 systematic review identified that at least 1107 biomarkers have been studied in 9 biological compartments, with peripheral blood being the most common.[82] As part of my initial research into understanding the landscape of non-invasive diagnostics, I conducted a literature review that was published in Fertility and Sterility[46] on blood biomarkers for endometriosis. I found that many blood biomarkers show promise across various categories, including immune cell populations, acute-phase proteins (e.g., C-reactive protein), glycoproteins (e.g., Cancer Antigen 125), endothelial markers, microRNA, and extracellular vesicles. Despite these biomarkers showing promise within the discovery phase, due to the lack of standardised and robust methodologies, they rarely progress to the development stages (**Figure 2**).

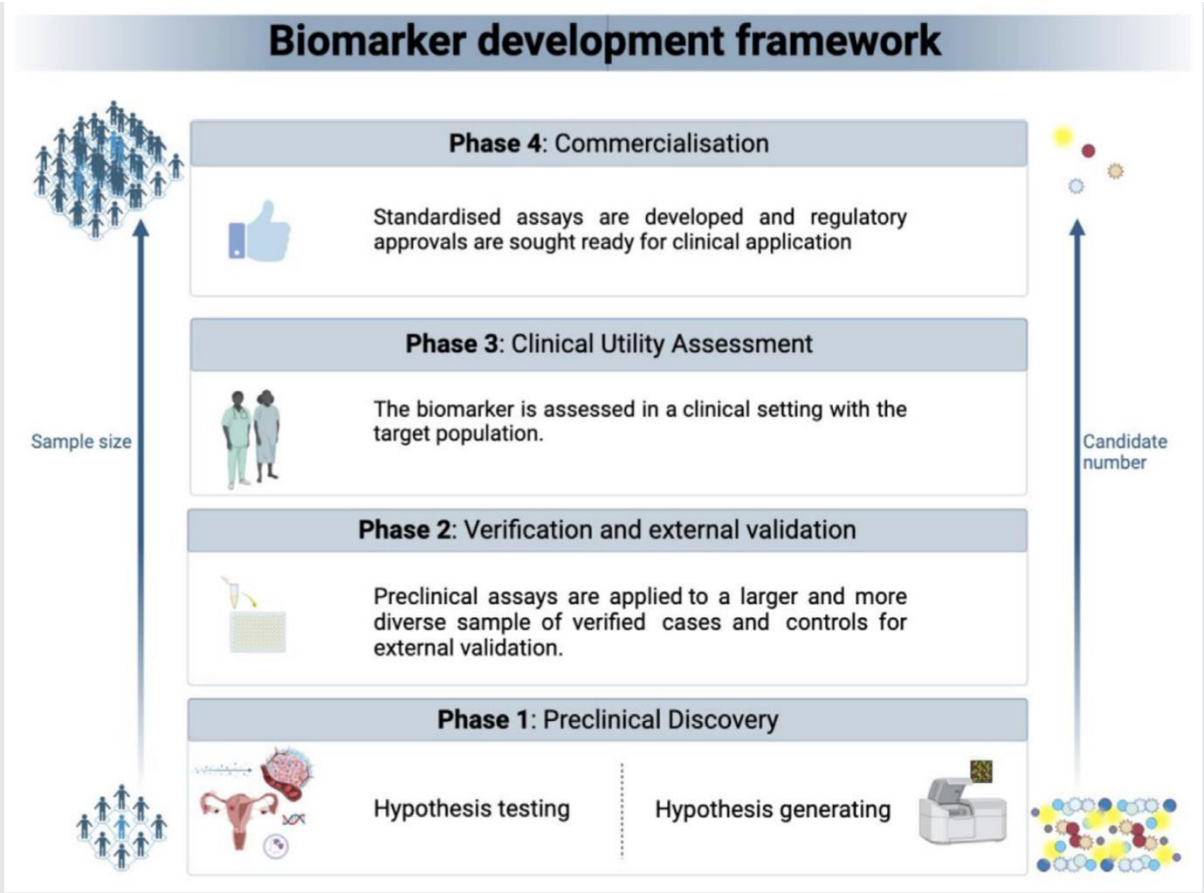


Figure 2: Recognised phases of biomarker development.[46]

Phase 1: Preclinical Discovery: In this initial phase, two approaches can be taken: hypothesis testing (identifying potential biomarkers based on the evolving comprehension of endometriosis pathophysiology) or hypothesis-generating (involving omics profiling of biological samples to identify differential expressions, e.g., using microarrays). Investigators will often then internally validate their biomarkers with a larger, independent group. Phase 2: Validation and verification - external validation in independent, larger, and more diverse case-control sets. Often, phase 2 is divided further: (A) external validation in an independent data set, defined in the same way as the discovery phase; (B) external validation in an independent data set with more diverse samples of cases and controls from different source populations in different laboratories. Once a biomarker is highlighted, preclinical assays are applied to a larger and more diverse sample. Often, the biomarker is compared with the gold standard, and dependent and independent variables are considered. The detection of the biomarker must be reproducible and reliable. Phase 3: Clinical utility assessment: the biomarker is assessed in a clinical setting with the target population. Often, randomised controlled trials are conducted to determine the clinical consequences (both positive and negative) of the test. Additional factors are reviewed, including cost, ease of measurement, and a high-throughput analysis. Phase 4: Commercialisation: standardised assays and reference ranges are developed, ready for clinical application. Regulatory approvals will also be sought. Created on Biorender. Adapted from Fassbender et al.[83], Davis et al.[84] , and D.F.O. et al.[85] .

I found that there is a growing trend among researchers to use combinations of blood biomarkers, such as miRNA expression profiles, to improve diagnostic accuracy. However, the combination of biomarkers with clinical characteristics[86] or imaging[87] was

uncommon. The review highlighted fields such as Genome-wide association studies (GWAS), which are expanding, and so is the hope for utilising combined panels of SNPs in generating Polygenic Risk Scores (PRSs) for endometriosis risk prediction. Although no PRSs have been found to be currently accurate enough, they hold promise for the future as GWAS studies increase in size and can detect more significant risk loci. Moreover, combining genetic PRS with clinical symptomatology and family history is likely to yield better results.

Combined multimodal imaging

Research into combined multimodal imaging is expanding, especially for the detection of DE.[88] AI is now being utilised to integrate skills from one imaging modality into another, for example, improving the accuracy of MRI in detecting an obliterated POD by integrating TVUS findings.[89] In fact, combining physical examination, US, and MRI findings has been shown to improve the sensitivity of MRI compared to MRI alone.[90]

Nuclear imaging

Nuclear medicine (NM) is a field that is rarely used within gynaecology, but as our understanding of various diseases expands and more radiolabels become available, it may become evident that NM can improve the detection of endometriosis. So far, most endometriosis NM studies have been limited to single case studies or case series, most often utilising PET-CT and fluorodeoxyglucose (18F-FDG).[91] However, novel tracers for PET imaging have also been investigated, such as 16α-[18F] fluoro-17β-estradiol[92], Gallium-68-labelled somatostatin analogue[93] and Technetium-99m-labelled red blood

cells.[94] Similarly, novel radiotracers for SPECT-CT imaging that may show a future benefit have been investigated in animal models. For example, [111In]In-FnBPA5, the binding of relaxed fibronectin was shown to represent a potential target for imaging endometriosis.[95] The introduction of NM is an exciting approach, and will be explored further in **Chapter 2**, where an exploratory imaging study will be discussed.

Endometriosis treatments

As there is no cure for endometriosis, the mainstay of treatment is a medical and surgical approach to treat endometriosis-associated pain. Medical management consists of agents such as hormonal contraceptives, progestins, and gonadotropin-releasing hormone agonists (GnRHa) or antagonists. It is thought that oestrogen-progestin hormones promote decidualisation and eventually atrophy of endometriosis implants with ongoing use, interfering with the growth of endometriosis.[96] GnRH analogues are long-acting and downregulate gonadotroph cells in the pituitary, resulting in a reversible decrease in gonadotropins and a subsequent hypoestrogenic state mimicking menopause with continued use.[97] Non-hormonal analgesic medications are also commonly used (e.g. NSAIDs). Surgical treatment includes excision and/or ablation of endometriosis to normalise anatomy and remove/destroy active endometrial-like implants and their surrounding fibrosis.[98] The approach to these techniques is generally through a minimally invasive approach (i.e. laparoscopic or robotic surgery for pelvic/abdominal endometriosis) as laparotomy is now rarely utilised. There is debate

over the longevity of outcomes following surgery due to the possibility of recurrence of endometriosis.[99]

Due to the complex nature of endometriosis and its symptoms, standard pharmaceutical therapies cannot address all aspects of endometriosis for instance central sensitisation.[100] Moreover, there is a growing desire of patients to manage symptoms more "naturally" or holistically. As such many patients regularly seek and utilise adjunctive therapies such as acupuncture, exercise, dietary changes, and various forms of psychotherapy.

The global burden of endometriosis

Global burden estimates are likely underestimated due to the sparsity of epidemiological data, particularly in many low- and middle-income countries, where access to diagnosis and specialised services, as well as epidemiological studies, is limited.[101]

Shen et al.[101] examined the Global Burden of Disease 2019 estimates across 204 countries from 1990 to 2019 and found that, although there have been gradual reductions in the rate-based endometriosis burden, there is still a substantial worldwide impact. The authors found that the burden is socio-demographically dependent, with Daily Adjusted Life Years (DALY) being highest in low-sociodemographic index (SDI) settings and lowest in high-SDI settings. Country-level extremes in 2019 included higher DALY rates in New Zealand, Afghanistan, and the Solomon Islands, and lower rates in Iceland, the United States, and Denmark. Age–period–cohort analyses indicate a peak prevalence at ages

25–29, with a persistently high burden through ages 30–39, consistent with a concentrated burden within the reproductive years.

The implications of endometriosis extend beyond the affected individual and can be felt by those around them, their peers, the community, the nation, and globally (

Figure 3).

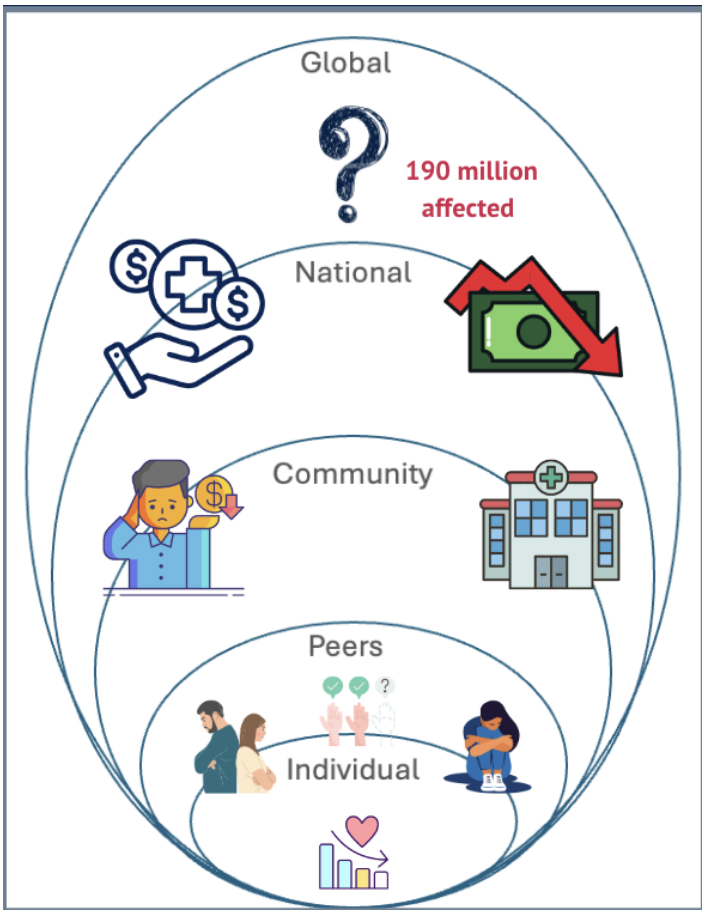


Figure 3: The burden of endometriosis, using the socioeconomic model.

The burden of disease is felt at various socioeconomic levels, starting with the individual and expanding outward. The individual may experience, among other effects, a reduced quality of life. Their peers may experience a strain on their relationships, as well as the effects of the individual's absence from school and work. The community and the nation experience the direct and indirect economic burden of increased healthcare costs and reduced productivity. However, the global implications of 190 million people living with endometriosis are still unknown. Created on Canva.

Endometriosis presents an economic burden in terms of direct and indirect costs. Direct costs refer to the healthcare expenses incurred for investigating, treating, and monitoring individuals with endometriosis. Indirect costs refer to productivity losses. In 2012, it was estimated that the economic burden of endometriosis in the UK was 9.9 billion per year.[102] International studies by Simoens et al.[102] and Grundström et al.[103] attributed the largest direct costs to hospitalisation, surgery, and clinician appointments. Notably, younger patients showed higher direct healthcare costs due to repeated emergency department visits. Surrey et al.[104] found that in the US, the time to diagnosis can also affect healthcare costs, as those experiencing a long delay (3-5 years) have higher healthcare costs than those with a short delay (<1 year), $34,460 and $21,489 per patient per annum, respectively. In terms of indirect costs, Grundström et al.[103] found that 32% of the 431 patients who completed the study's questionnaire reported absences from work due to endometriosis, and 36% reported needing to reduce their working hours as a result of the condition. These are both key examples of the productivity loss that can occur with endometriosis. These figures are exacerbated when one considers that the majority of endometriosis symptoms begin in adolescents. The effects of endometriosis on the community and peers can also be felt with school absenteeism[105], reduced social engagement and negative impact on relationships.

A 2024 report by the World Economic Forum[1] stated that endometriosis was one of the nine conditions that could generate an annual trillion-dollar saving if the "Women's Health Gap" were closed, meaning if global disparities in diagnosis, treatment, data, and research were addressed. Given the prevalence of endometriosis and the wide-ranging burdens it causes, there has been a call for policy leaders to prioritise and address the

challenges we and our endometriosis population face.[106] How far countries are, in fact, prioritising endometriosis will be discussed in **Chapter 4**.

Endometriosis healthcare framework gaps and thesis aims

The aim of this thesis is to address key systemic gaps that limit the infrastructure supporting individuals with endometriosis. The World Health Organisation (WHO) Health System's Six Core Building Blocks[107] is an analytical framework used to describe Healthcare systems. **Figure 4** outlines the WHO Healthcare System Building Blocks within the context of endometriosis.

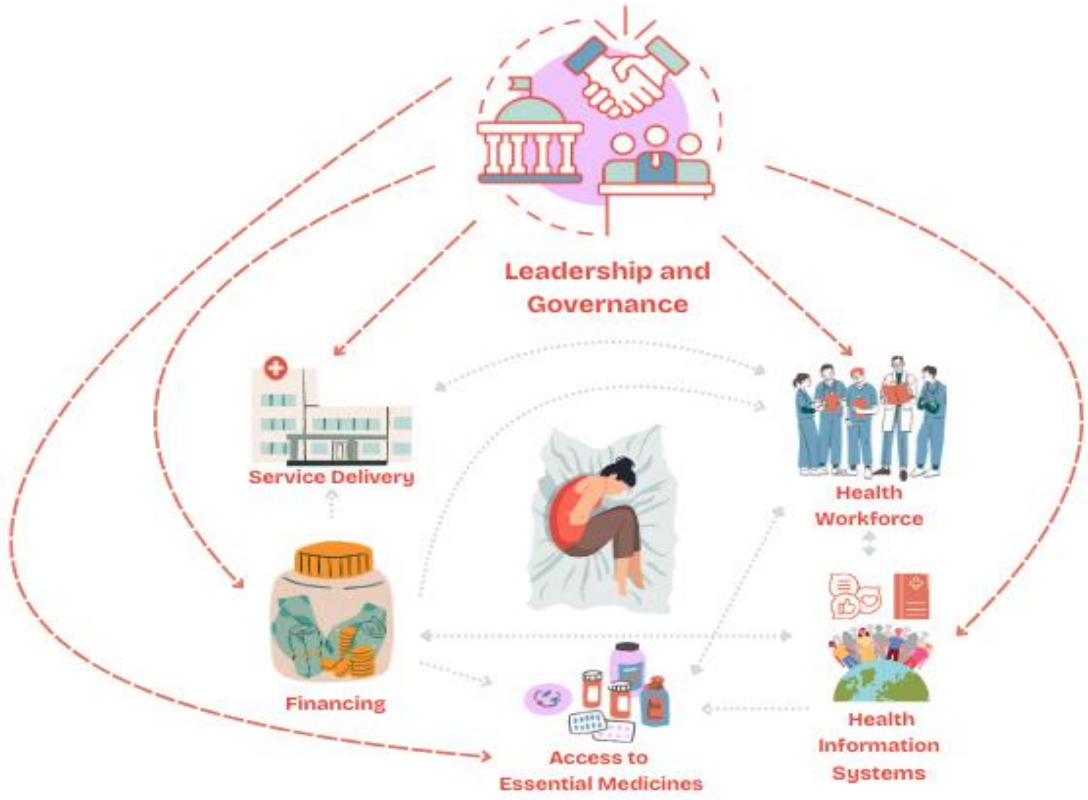


Figure 4: WHO Building Blocks mapped to the endometriosis infrastructure of care

Governance and leadership: This building block describes the strategic planning and oversight of health systems to ensure policies are implemented effectively and are accountable through monitoring practices. It is an integral building block interwoven into all the remaining building blocks. **Service delivery:** This building block describes a health system comprising primary, secondary, and tertiary care, providing timely access to high-quality services, including specialised centres. **Health workforce:** This building block ensures that patients with endometriosis, when they seek support, are met with a well-trained, informed, and adequately distributed workforce. **Health information systems:** This building block builds a well-informed population, patient group and clinicians. This means patients are empowered with enough information to make autonomous decisions, and that endometriosis receives societal acceptance and understanding. **Access to essential medicines:** This building block encompasses the infrastructure necessary to develop a care system that ensures timely access to high-quality treatments for endometriosis. **Financing:** This building block provides financial support and protection for the health challenges that people with endometriosis face. Health systems should support their population's ability to receive the care they need without financial hardship. Created on Canva.

As outlined within this introduction, those with endometriosis typically suffer from a diagnostic delay. The cause of the delay is multifaceted, resulting from gaps in governance and leadership, service delivery, the health workforce, and financing. Within healthcare systems, there are recognised limitations in our non-invasive diagnostics, which contribute to this diagnostic delay. **Chapter 2** aims to address this by discussing a

patient survey of over 1000 respondents on the experiences of those undergoing investigation for endometriosis. This examines the complex factors that contribute to diagnostic delays and their resulting socioeconomic implications. The chapter then attempts to address the diagnostic delay and limitations of the healthcare system by describing an exploratory Phase 2 imaging study.

Once a patient is diagnosed with endometriosis, as there is no cure, clinical uncertainty often surrounds which interventions are most efficient at treating endometriosis-associated pain, which is the most common endometriosis symptom experienced. This is primarily due to gaps within our Service Delivery and Health Information Systems, as well as the Financing of endometriosis research, which prevents the development of standardised endometriosis guidance. Thus, **Chapter 3** reviews the findings of a scoping review on the global availability of endometriosis guidance and discusses a network meta-analysis which aimed to address limitations in Service Delivery and Health Information Systems by providing evidence of the most effective treatments for pain, with the aim of reducing clinical uncertainty, supporting guideline development and resource allocation.

Governance and leadership are integral components of every nation's healthcare system, and only through collaborative efforts between stakeholders can the challenges of endometriosis be addressed. **Chapter 4** describes a comprehensive scoping review that maps the availability of policies, initiatives and delivery systems supporting endometriosis infrastructures across the globe. The review aimed to provide key political stakeholders with details of existing policy frameworks to support advocacy efforts and

enhance the presence of national endometriosis strategies and global endometriosis reform.

Chapter 2: Bridging Gaps in Diagnostic Frameworks for Endometriosis

Introduction

As discussed in **Chapter 1**, despite the various current and novel approaches to diagnosing endometriosis, our ability to detect endometriosis non-invasively remains limited. This is a contributing factor to the diagnostic delays experienced in most countries worldwide. Based on a 2016 Cochrane review[64] that demonstrated the ability of MRI and US to detect OE and DE, the ESHRE guidelines[57] were amended in 2022 to remove the need for surgery to detect OE and DE. However, the review and the guidelines highlighted that imaging can't exclude SPE.[57,64] Moreover, many of the research advances have led to improvements in detecting moderate to advanced stage endometriosis as opposed to mild stages and SPE. For example, the presence of endometriomas is believed to be a determining factor in the accuracy of many biomarker tests[46] and genetic signatures[108].

Detecting SPE presents a crucial diagnostic challenge, as many with negative imaging cannot be reassured that they do not have endometriosis. This is particularly important as SPE is the most common disease subtype[109] especially in younger patients.[110] Therefore, if we are to improve the diagnostic delay and reduce the years of clinical uncertainty and socioeconomic burden, diagnosing early-stage endometriosis is crucial.

An international cross-sectional online survey[111] of 743 women with endometriosis found that the majority had experienced a significant diagnostic delay, with 42% waiting over 10 years from symptom onset to diagnosis. Participants reported that endometriosis had affected various domains of their lives. For example, 74% had missed work because of the condition, 45% were unable to work full-time, 83% reported negative effects on intimate relationships, and 81% felt they had lost time in life due to their symptoms. Additionally, 75% believed endometriosis had prevented them from reaching their full potential. These findings underscore the extensive diagnostic delays and the broad, long-term consequences of endometriosis on patients' personal and professional lives.

It is clear that the diagnostic accuracy of SPE limits our current diagnostic framework, leading to many individuals experiencing diagnostic delays, which have significant socioeconomic implications. To address these gaps, I investigated whether a novel imaging marker, ^{99m}Tc-maraciclatide, could be used to non-invasively diagnose endometriosis, aiming to improve the current diagnostic pathway and reduce diagnostic delays. However, before embarking on the study to better understand the current experiences of individuals undergoing an investigation for suspected endometriosis within our diagnostic framework, I released a mixed-methods questionnaire. It assessed patients' satisfaction with current diagnostic methods, identified their primary concerns, evaluated the impact of diagnostic delays on their lives, and assessed their acceptance of novel diagnostic methods currently being researched. This chapter begins by exploring the results of the diagnostic questionnaire, which delves deeper into the healthcare gaps within the diagnostic framework. This is followed by a discussion of a novel imaging study aimed at addressing crucial concerns raised in the questionnaire.

^{99m}Tc-maraciclatide is an intravenous radioisotope marker which contains the RGD component found on ligands to certain angiogenic integrins, particularly αvβ3, which were discussed in **Chapter 1**. ^{99m}Tc-maraciclatide has been used in 5 clinical trials in over 200 people to date to detect various inflammatory conditions, as shown in **Table 2.**

Table 2: Maraciclatide studies

Author (Year)	**Indication**	**Study Design**	**Participants**	**Key Results**
Gibbons et al. (2024)[112]	Healthy volunteer biodistribution and dosimetry	Phase I, randomized, dose-escalation study	30 healthy adults	Well tolerated; GI uptake ~20%, liver ~15%, lungs ~9%; elimination half-life ~1 h; effective dose ~7.8 µSv/MBq
O'Connor et al. (2017)[113]	Breast cancer imaging	Prospective diagnostic comparison	39 evaluable women with suspected breast cancer	Detection rate: maraciclatide 90% vs sestamibi 86% (p=1.0); AUC: 0.87 vs 0.83; LBR: 1.79±0.66 vs 1.71±0.59
Cook et al. (2018)[114]	Prostate cancer bone metastases	Observational imaging study	17 men (11 with follow-up at 12 weeks)	Tracer uptake correlated with low-density, osteoclast-rich lesions; change in CT density vs T:M ratio: r=−0.59, p=0.006
Attipoe et al. (2020)[115]	Imaging neoangiogenesis in rheumatoid arthritis	Prospective observational imaging study	39 RA patients with active wrist/hand synovitis	Whole-body ^{99m}Tc-maraciclatide SPECT uptake was **highly correlated** with power Doppler ultrasound (PD-US) scores. r = 0.80 for total synovial uptake vs. PD score ($p < 0.0001$). r = 0.78 for joint-level uptake vs. grey-scale synovitis ($p < 0.0001$). Tracer uptake localised to inflamed joints with excellent anatomical resolution.

Cobb et al. (2023)[116]	Rheumatoid arthritis imaging	AI segmentation of SPECT images	48 patients, 192 scans	nnU-Net Dice scores: 0.94 (normal), 0.51 (low), 0.76 (high inflammation); significantly outperformed thresholding

Summary of studies investigating the use of 99mTc-maraciclatide for diagnostic imaging across various clinical indications. All studies demonstrated the tracer's favourable safety profile and promising diagnostic or predictive utility. Abbreviations: AI – Artificial Intelligence, AUC – Area Under the Curve, CT – Computed Tomography, GI – Gastrointestinal, LBR – Lesion-to-Background Ratio, RA – Rheumatoid Arthritis, SPECT – Single Photon Emission Computed Tomography, T:M – Target-to-Muscle ratio and nnU-Net – Neural Network U-Net (deep learning model for image segmentation).

Previous studies using ^{99m}Tc-maraciclatide have demonstrated its ability to image inflammation in various parts of the body, both centrally, such as the bowel, and peripherally, such as joints affected by rheumatoid arthritis. This is of particular interest in endometriosis, which is thought to be a disease that can affect any part of the body, and it has been reported that 12% of endometriosis patients have extra-pelvic endometriosis. However, this figure is potentially larger considering the prevalence of multi-site pain and current limitations in diagnosing extra-pelvic endometriosis. Thus, SPECT-CT imaging of ^{99m}Tc-maraciclatide may be beneficial not only for pelvic endometriosis but also for extrapelvic endometriosis.

Hypothesis

Diagnostic survey

Low satisfaction is reported in the current diagnostic journey for those being investigated for endometriosis, with a diagnostic delay being identified as a contributing factor, which also affects the way patients choose to live their lives, underscoring the need and likely acceptability of novel diagnostic tests.

DETECT imaging study

By detecting angiogenic integrins within ectopic pelvic and extrapelvic lesions, ^{99m}Tc-maraciclatide will demonstrate its potential as an safe, acceptable, non-invasive diagnostic test for endometriosis.

Methods

Research objectives

Diagnostic survey

1. To understand the experiences of those undergoing a diagnosis of endometriosis
2. To understand the implications of a diagnostic delay, including its impact on life choices
3. To understand the acceptability of novel diagnostic methods, including CT

DETECT imaging study

1. To understand how the biodistribution and safety of ^{99m}Tc-maraciclatide may impact its use as a novel imaging marker for endometriosis
2. To design and initiate an exploratory study to assess whether endometriosis can be detected by identifying angiogenic integrins in endometriosis
3. To develop an imaging protocol to optimise the detection of endometriosis
4. To understand the potential of ^{99m}Tc-maraciclatide in the detection of pelvic and extrapelvic endometriosis
5. To understand the acceptability and tolerability of ^{99m}Tc-maraciclatide as a non-invasive test for endometriosis

Diagnostic survey

I designed an online survey to understand how gaps in the healthcare framework are impacting patients and to identify areas for systemic improvement. The questions were divided into categories to identify gaps before and after patients seek medical attention, whether novel diagnostic tests could help address these gaps, how these identified gaps contribute to diagnostic delays, and what that means for patients' experiences and life choices.

Including respondents' views on novel diagnostic tests aligned with the World Endometriosis Societies' and World Endometriosis Research Foundation's Research priority[76] to seek patients' views on research developments. I chose to focus on life choices because there is already a significant amount of research on how a diagnostic delay burdens the economy, healthcare systems, and how it can lead to a reduced quality of life. However, our understanding is limited on how a diagnostic delay affects patient autonomy and how they choose to live their lives. The survey was generated and stored anonymously using REDcap (Research Electronic Data Capture)[117] a GDPR-compliant site recommended by the University of Oxford's Medical Sciences Division. The survey employed a combination of Visual Analogue Scales (VAS), single-best-answer questions, and open-ended questions.

Before release, the survey was reviewed by the university survey advice service and had ethical approval (REC 22/SC/0130). Between November 2022 and March 2023, the online

survey was advertised on Endometriosis UK's social media page (**Figure 5**) to recruit individuals with suspected or confirmed endometriosis to participate in.

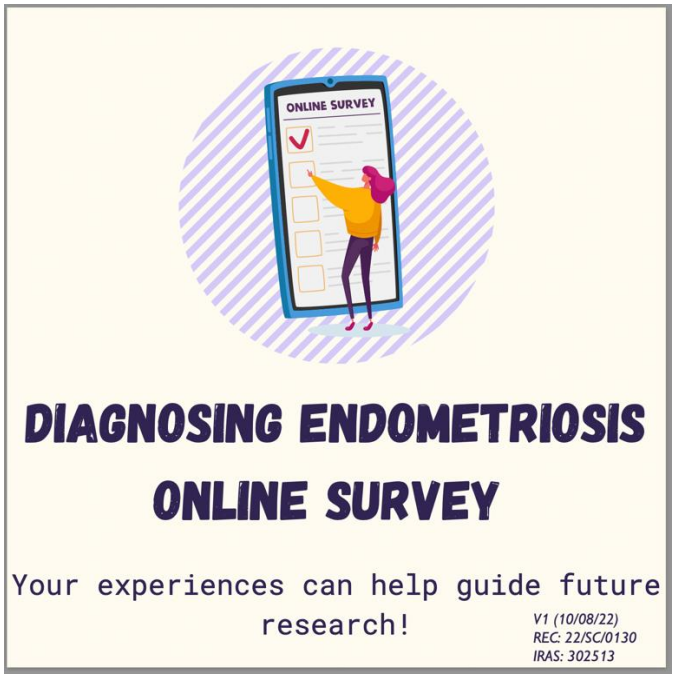


Figure 5: Diagnosing endometriosis survey recruitment social media post

The statistical analysis of quantitative data was performed using REDCap.[117] Qualitative data were thematically analysed using Braun and Clarke's reflexive analysis method[118].

Qualitative responses were extracted to Excel for the completion of the 6 steps within Braun and Clarke's method. Firstly, I familiarised myself with the data by repeated reading. Then I generated initial codes and used those to develop themes. The themes were defined, refined and finalised. The themes and responses were then considered within the context of gaps in healthcare frameworks.

DETECT: an exploratory phase 2 diagnostic study

The DETECT (Detecting Endometriosis inTEgrins using teChneTium-99m) imaging study was a collaborative project with EndoCaRE, Serac Healthcare Ltd (owners of the imaging marker) and two hospital sites (Oxford University Hospital (OUH) and Royal United Hospital (RUH)) (see **contributions**).

Sponsorship and approval

The study was sponsored by the University of Oxford (OU). Health Research Authority decision tools were used to determine the nature of the planned research and to guide the types of approvals required. I generated the study documents using OU document templates (**Appendix 1**), which were then refined with support from the sponsor R&D team and submitted within the Integrated Research Application System (IRAS) to seek ethical approval. I obtained a risk assessment by an independent nuclear medicine expert from OUH and an Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) license for the scanning site. The Oxford South Research Ethics Committee granted ethical approval following an interview and the submission of study documents. The final approval was provided by OUH and the Research and Development team at the RUH, who confirmed that they had the capacity and capability to conduct the study. Studies were conducted at RUH due to delays in OUH fitting the SPECT-CT scanner required for the study.

Funding

The study was funded by the developers of the imaging marker (Serac Healthcare LTD) and a grant from the NIHR Oxford Biomedical Research Centre.

Study aim

To confirm whether αvβ3 integrins can be detected in endometriotic lesions using ^{99m}Tc-maraciclatide and SPECT-CT imaging. The outcome was assessed by the level of agreement between radiologist-assessed ^{99m}Tc-maraciclatide uptake on SPECT-CT and clinician-assessed areas of active endometriosis on surgery.

Sample size

The study planned to recruit 20 people with known or suspected (pelvic or thoracic) endometriosis who had a planned surgery to investigate or treat endometriosis as part of their routine clinical management.

A sample size of 20 was chosen by our research group to balance safety (participant radiation exposure) with the chance of missing the diagnostic potential of the scan. Given that 50% of women undergoing diagnostic laparoscopy are found to have endometriosis[119], by recruiting 20 participants, a minimum of 10 people with surgically confirmed endometriosis would be imaged. We agreed that if no diagnostic potential was seen between the surgical and scan findings in 10 participants with endometriosis, it would be acceptable to rule out any realistic utility of the scan. Withdrawn participants were replaced until a minimum of 10 women with surgically confirmed peritoneal or deep endometriosis had completed the study, with at least four participants in each of the four

planned timepoints. ‘Complete’ meant that the participant was recruited, scanned and completed surgery for diagnostic confirmation.

Recruitment

People who fulfilled the inclusion and exclusion criteria were identified at the Endometriosis CaRe Centre during clinic appointments and by analysis of the planned surgical list by the study CI. I then contacted potential participants to discuss the study in more detail and to offer to send the participant information sheet (PIS). If the potential participant were interested in participating, sufficient time would be provided for them to read the PIS, consider the risks and benefits, and ask any questions. Subsequently, informed consent was obtained using consent forms designed in accordance with the OU study document templates.

Inclusion and exclusion criteria

Willing individuals of female sex aged 18 years or above with symptoms consistent with endometriosis and therefore due to undergo surgery for diagnostic (+/- therapeutic) purposes. Participants who were pregnant, lactating, had known significant renal or hepatic impairment or any other significant disease or disorder, such as gynaecological cancers, that may either put the participants at risk or may influence the result of the study were excluded. In addition, those who had high-dose steroids in the past 12 weeks were excluded, as it could reduce marker uptake. Finally, individuals with a known allergy to technetium or those who had recently participated in another research study, which may affect the study's results, were also excluded.

Overview of trial procedures

The study included a SPECT-CT scan with intravenous ^{99m}Tc-maraciclatide prior to planned surgery. During surgery, endometriosis Regions of Interest (ROI) were recorded on the WERF EPHect Standard Surgical Form (SSF)[120], and corresponding tissue samples were collected. Subsequently, a radiologist assessed the SPECT-CT for clinically relevant signals, which were compared to surgical findings. Participants were asked to complete a WERF EPHect Baseline Questionnaire and an end-of-study questionnaire. Finally, an immunohistochemical analysis (IHC) was performed on sampled ROIs to assess the presence of angiogenic markers. See a schematic overview in **Figure 6.**

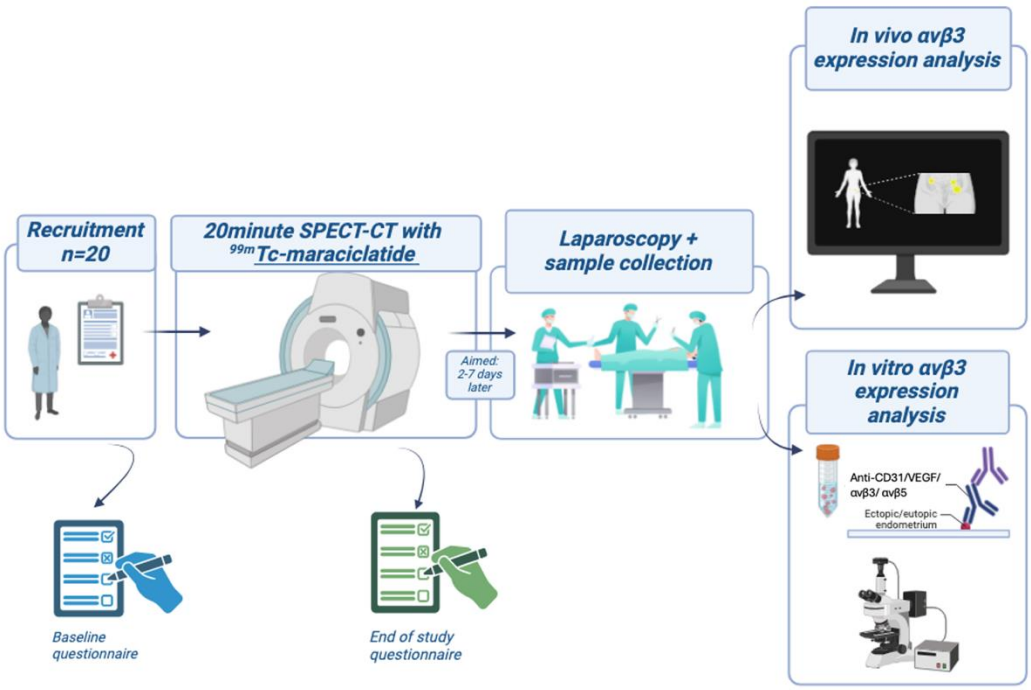


Figure 6: Overview of the DETECT trial procedures.

^{99m}Tc-maraciclatide

Maraciclatide is a chelate-peptide conjugate containing an Arginine-Glycine-Aspartic (RGD) amino-acid motif in such a configuration that it specifically binds with nanomolar affinity to the integrin receptor αvβ3 (**Figure 7**).

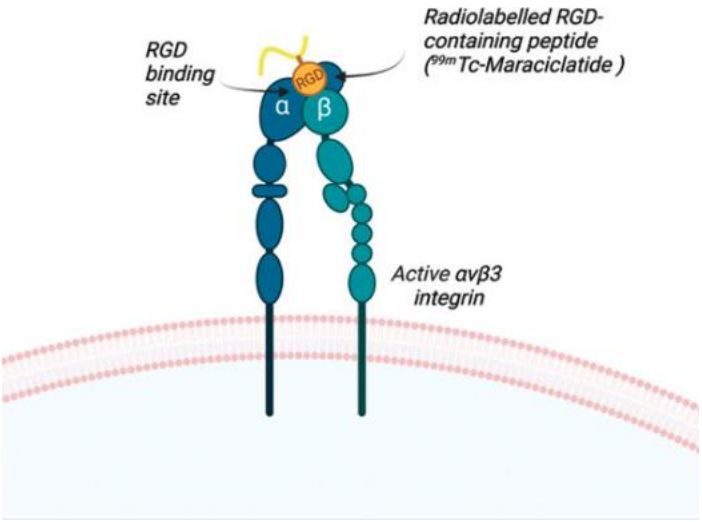


Figure 7: Maraciclatide αvβ3 binding [112]

It is an unlicensed radiopharmaceutical produced by aseptically reconstituting Maraciclatide Kits. The lyophilised Maraciclatide kits were delivered and stored at 2-8 °C. On the day of the scan, radiolabelling was performed under aseptic conditions in OUH radiopharmacy. Each vial produced contained 75 µg maraciclatide (approximately 44 nmol maraciclatide (molecular weight 1697)) and a maximum Sodium Pertechnetate (99m Tc) activity of approximately 740 MBq. The radiolabelled product could be used for up to 6 hours post-reconstitution. The radiochemical purity of the product was tested using instant thin-layer chromatography. All the preparations used in the study had a radiochemical purity ≥90%. The SPECT-CT scan was performed on a Veriton 360 CZT scanner ideally two to seven days prior to the participant's planned operation, but with a

maximum of three months. It is still unclear how quickly lesions develop, but if endometriosis is a progressive disease, it is thought to progress slowly, with one study finding the annual growth rate of DE to be +0.09 mm/year (range: −6.65 – +6.45).[121] Therefore, a limit of 3 months was deemed clinically acceptable by the research group.

SPECT-CT imaging

To develop the imaging protocols and scanning windows, I assessed and collated the data from a previously unpublished Phase 1 dosimetry and biodistribution study for ^{99m}Tc-maraciclatide conducted in 2005. It demonstrated the excretion pathway of the agent and measured the amount of radiation absorbed by different tissues to ensure safety and effective dosing. The study conducted various assessments at different time points, ranging from 5 minutes to 24 hours (**Figure 8**). The findings were published in Nuclear Medicine Communications in 2024.[112]

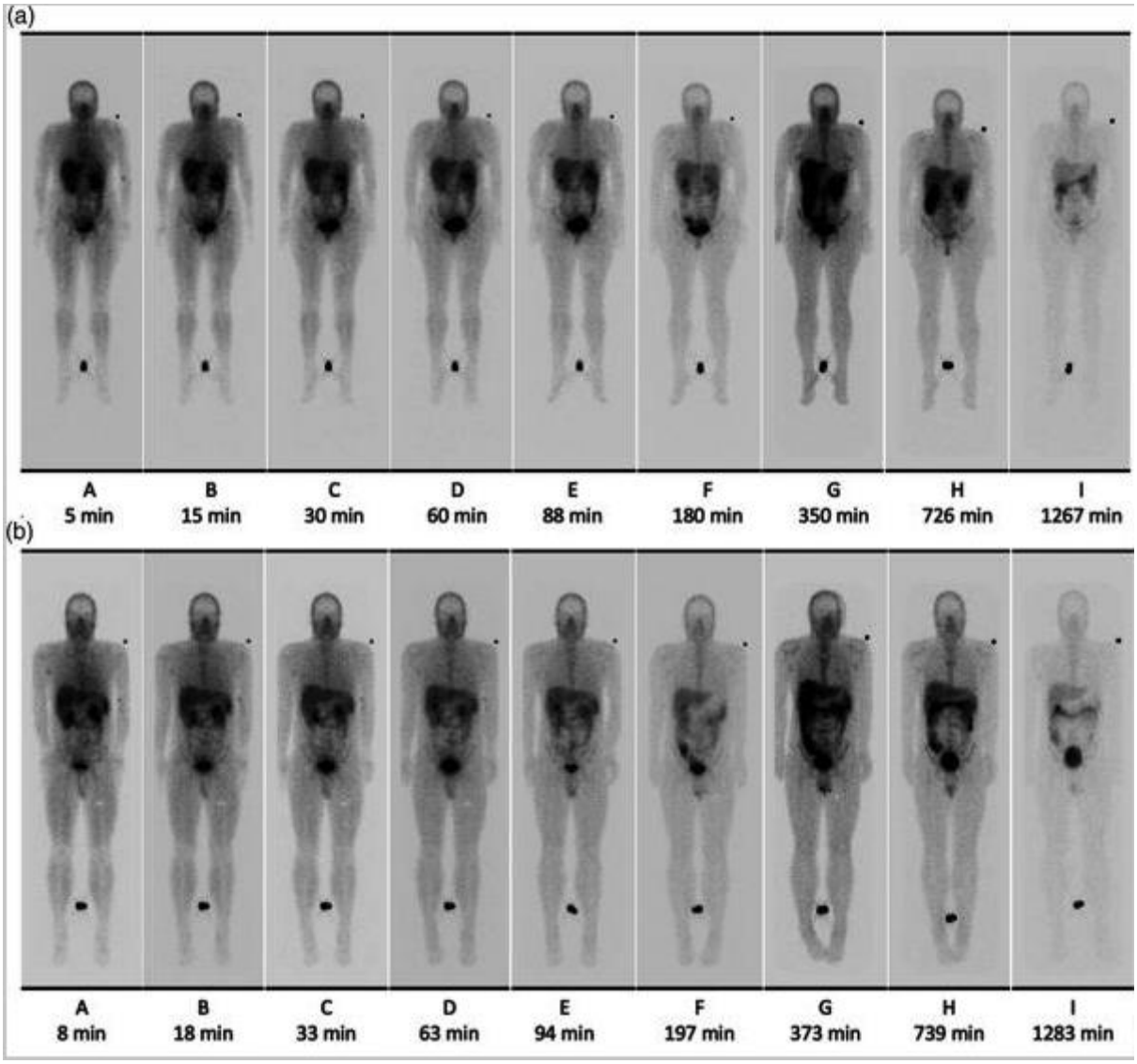


Figure 8: Whole body SPECT-CT scans in two healthy participants, one female (a) and one male (b), within the Phase 1 dosimetry study, imaged at various points after injection with ^{99m}Tc-maraciclatide.

Most importantly, the study demonstrated that ^{99m}Tc-maraciclatide was well-tolerated, with a side effect profile similar to that of the placebo. The majority of ^{99m}Tc-maraciclatide activity was excreted through the urinary pathway and gastrointestinal tract (GI), accounting for 55% and 16%, respectively.

The mean terminal elimination half-life of ^{99m}Tc-maraciclatide was approximately 1 hour, with a systemic clearance of 6.7 mL/min/kg. Compared with bone scanning agents such

as ^{99m}Tc-MDP, which typically exhibit plasma half-lives of 2–3 hours, ^{99m}Tc-maraciclatide showed a similar clearance rate but faster systemic washout. This pharmacokinetic profile is expected to reduce background activity, improve image contrast, and lower radiation exposure to non-target tissues.[122]

The study demonstrated that GI uptake of ^{99m}Tc-maraciclatide occurred rapidly in the first 90 minutes in the tissue walls, which then quickly decreased as the tracer cleared. This indicated that, theoretically, early timepoints should still be suitable for visualising endometriosis, so long as the background uptake does not obstruct visualisation. However, to ensure the best time point after imaging was selected, we split the study into two cohorts.

The first cohort would determine the optimal imaging by imaging participants at multiple time points after injection: 30 minutes, 90 minutes, 120 minutes, 240 minutes and 720 minutes. Each participant could have a maximum of six scans as per the medical physics expert's risk assessment. Compared to the later timepoints, the images obtained at 30 minutes demonstrated lower dynamic artefacts, e.g., bladder filling or gut peristalsis signals produced by gastrointestinal activity. Moreover, it was more tolerable for the patient and the scanning department, as the injection and scan could be performed within a single appointment. The visualisation of lesions did not show a considerable difference between the cohort 1 imaging timepoints. Therefore, after evaluation by the nuclear medicine radiologists within the research group, we decided that cohort two would be imaged only once, between 10 and 30 minutes post-injection, with a preference for earlier imaging to further reduce dynamic artefacts, especially from bladder filling.

The total protocol dose was 14 mSv for Cohort 1 (if 6 scans were performed). This is equivalent to nearly 6 years of average natural background radiation in the UK and translates to a 0.08% maximum risk of developing cancer as a consequence of taking part in the study. Cohort 2 total protocol dose was 9 mSv, which is equivalent to nearly 4 years of average natural background radiation in the UK and a 0.05% maximum risk of developing cancer as a consequence of taking part in the study (**Table 3**).

Table 3: Acquired radiation exposure by cohort and by number of scans completed.

Procedure	Routine	Additional	Effective Dose (millisievert)
Cohort 1 - Localisation CT as part of SPECT	0	1	3
Cohort 1 - Ultra low dose CT	0	5	1
Cohort 2 - Localisation CT as part of SPECT	0	1	3

Traditional SPECT-CT scans require 20-30 minutes to complete trunk scans; however, the scanner used in this study, the Veriton 360° CZT, requires only 10 minutes for its scans.[123] All included participants were scanned for 20 minutes to match traditional imaging protocols to reduce the chance of lesions being missed. The initial participants' scans were performed as a single 20-minute scan. However, the nuclear medicine experts within the research team confirmed that the imaging quality was sufficient to reduce the scans to two contiguous 10-minute image sets, ensuring a data set that reflects standard Vertion practices. By reducing the length of imaging acquisition, the dynamic artefacts

should also reduce. Where two 10-minute image sets were acquired, the first set was used in the data analysis again due to reduced dynamic artefacts. The second 10-minute scan was used to validate any uncertainties surrounding the disease signal.

Surgery and the WERF EPHect questionnaire

Six endometriosis specialists conducted the laparoscopies included in the DETECT study in a BSGE-accredited endometriosis centre (EndoCaRe, Oxford University Hospitals, UK). The two thoracoscopies were performed by a single thoracic surgeon with extensive experience in thoracic endometriosis within the Oxford University Hospital NHS Foundation Trust. If possible, interoperative photos and videos of the surgeon-defined ROIs were captured. As per routine practice, endometriosis ROI samples were sent to a histopathologist for confirmation of endometriosis. These reports were reviewed to provide the first level of histological evidence for the presence of endometriosis. If the participant consented, surgical samples were either halved or additional samples were taken (including a pipelle endometrial biopsy) for IHC analysis as part of the study. Surgeons were asked to complete a WERF EPHect Standard Surgical Form (SSF) after surgery to classify the lesion by region, subtype, size, and colour[120]. Lesion definitions, including the distinction between SPE and DE, were guided by the International Terminology on Endometriosis[124] and categorised by the surgeon's visual assessment and experience.

Immunohistochemical analysis

Samples were collected and stored according to the WERF EPHect Standard Operating Procedures (SOP).[125,126] Tissue samples were snap-frozen with isopropyl alcohol and

stored in -80 °C freezers awaiting staining. Once ready for processing, the samples were thawed and fixed in formaldehyde, then embedded in paraffin before being sectioned into 5µm thick slices. Processing and staining were conducted by an independent research lab (The Translational Histopathology Laboratory, Oxford). The tissue was stained with H&E (+/- CD10) until a histopathologist was able to identify epithelial glands and stroma. Then, sections were stained for angiogenic markers: αvβ3, αvβ5, CD31 and VEGF. αvβ3/5 confirmed the presence of the integrins detected by the scan, CD31 allowed for mean vessel density calculations, and VEGF, being the most commonly used angiogenic marker, also provided data on the angiogenic potential of the lesions. I examined images of the slides taken at x20 magnification, blinded to the participant from which the sample was obtained. I assessed each side for positive marker staining and for αvβ3, and calculated an endothelial Immunoreactivity score (IRS) by visual assessment. The IRS score was calculated by recording the sample's vessel staining intensity on a 4-point scale: 0 (negative), 1+, 2+, 3+ and the proportion of positive vessels; P = 1 (<15% of vessels), P = 2 (15–50% of vessels), P = 3 (50–85% of vessels), P = 4 (>85%). The endothelial IRS was calculated as follows: Intensity × Proportion of positive vessels.

End of study questionnaire

Participants were asked to complete an anonymous electronic survey after the study to assess the acceptability of the test as a diagnostic and disease monitoring tool and to compare it with other diagnostic methods currently used. Responses were captured on REDCap software.[117] This data was analysed and used within the acceptability and tolerability analysis, along with the captured adverse event data.

Data collection

To provide a standardised approach to the region-level analysis, regions on the WERF EPHect SSF[120] were used. However, after discussions with the radiologist and the initial scans, it became clear that it would not be possible at this stage to distinguish signal in or on the pelvic wall from the uterosacral ligaments. As such, the regions were merged into the pelvic wall. I also included the parietal pleura as a region because, although diaphragmatic endometriosis is listed on the WERF EPHect form, it is designed for pelvic laparoscopy. To date, there is no standardised form for completing thoracoscopic surgery for endometriosis.

Data was extracted from the completed WERF EPHect forms into Excel. Where there was missing data or uncertainty on the forms, efforts were made to clarify it with the operating surgeon, including reviewing the operation report. However, in cases where this was not possible, the study's CI (blinded to the SPECT-CT findings) was consulted using the interoperative video recordings and photos. Missing data most often included the colour or size of the lesion, whereas the disease subtype was often included in the operation report if it was missed on the form.

A single nuclear imaging radiology specialist assessed all the SPECT-CT images after surgery, in blocks of 3-4 participants. The scans were reviewed during a Zoom call, where the surgical findings were discussed. If necessary, additional regions were reassessed by the radiologist to identify any meaningful diagnostic signals missed during his initial review. There are, of course, limitations with this approach, which are outlined in the discussion. However, this approach was necessary for the exploratory nature of the

study. Despite SPECT-CT with technetium being one of the most common imaging methods in nuclear medicine, it is a novel approach for endometriosis, and ^{99m}Tc-maraciclatide is a novel tracer; therefore, iterative learning was needed. Through this process, the radiologist developed a systematic approach to reading the SPECT-CT scans. This will be included as learning materials within a subsequent Phase 3 study, where the aim will be to measure diagnostic accuracy rather than to assess whether the signals are of diagnostic relevance.

The participant's medical records were reviewed with consent to look for prior imaging results. The latest MRI and US report was used if obtained within 12 months of the SPECT-CT scan. This data was used to compare the utility of ^{99m}Tc-maraciclatide in detecting endometriosis at the participant and region levels.

Data analysis and statistical plan

Two categories of analyses were planned: (1) diagnostic performance of ^{99m}Tc-maraciclatide against the surgical reference standard, laparoscopy, and (2) association analyses relating detection to lesion characteristics or hormonal influences (anatomical region, size, colour, subtype, exogenous hormone use and menstrual cycle).

To reduce uncertainty whilst performing analysis, the following hierarchical guideline was followed:

1) The participant or region was confirmed to have endometriosis if it was observed on histology in any sample (participant level analysis) or in any pelvic or extrapelvic region (region level analysis).

2) If the participant's histology was negative or unavailable, endometriosis at the participant level or regional level was confirmed or excluded based on the operating surgeon's visual findings.

Diagnostic performance

Diagnostic performance studies were planned on the two levels used to assess diagnostic imaging methods within the Cochrane systematic review[64] on non-invasive imaging tests:

1) Participant level – Diagnostic performance per number of participants

2) Region level – Diagnostic performance in anatomical regions per number of participants

Diagnostic performance at a participant level was determined by diagnostic agreement and accuracy metrics. Cohen's kappa statistic was used to assess the level of agreement between the radiologist and surgeons in detecting endometriosis. Sensitivity and specificity were then used to calculate the diagnostic accuracy. The sample size of the

study was not powered for these diagnostic performance tests, which should be considered when interpreting the results.

Cohen's kappa statistic was calculated using GraphPad and was presented along with the 95% confidence intervals. Kappa values were interpreted as: < 0.2; Poor, 0.21 – 0.4; Fair, 0.41 – 0.6; Moderate, 0.61 – 0.8; Good, 0.81 – 1.0; Very good. Sensitivity (Se) and specificity (Sp) calculations were performed using GraphPad and presented along with 95% confidence intervals. The Positive Predictive Value and Negative Predictive Value were planned but not discussed as part of the diagnostic accuracy metrics due to the low number of negative cases (n=2). The precision and interpretability of PPV and NPV are poor in small, non-representative samples, as they are prevalence-dependent metrics. In contrast, Se and Sp do not depend on disease frequency and are therefore more stable with small sample sizes.

A two-sided p-value <0.05 was considered statistically significant, and all were reported to two decimal places. Continuous results were presented as mean ± standard deviation (SD). All analyses were performed on GraphPad.

I compared the Se and Sp to the diagnostic accuracy requirements for non-invasive endometriosis tests proposed in the 2016 Cochrane systematic review.[64] The authors pre-specified diagnostic accuracy thresholds for endometriosis diagnostic tests based on clinical usefulness. The review stated a SpPin triage (rule-in) test should have specificity ≥0.95 with sensitivity ≥0.50; a SnNout triage (rule-out) test should have

sensitivity ≥0.95 with specificity ≥0.50; and a replacement test (to substitute for diagnostic surgery) should achieve sensitivity ≥0.94 and specificity ≥0.79%

The Cochrane review assessed diagnostic accuracy by subtype and found that for SPE, no imaging method could replace surgery or reliably triage for endometriosis. However, TVUS qualified as a SpPin triage for OE TVUS, and MRI had begun to demonstrate sufficient accuracy to suggest utility as a replacement test. Therefore, I planned to conduct a diagnostic accuracy sub-analysis by disease subtype to facilitate a more accurate comparison with current imaging modalities. It was only possible to present sensitivity values, as it is not currently possible to distinguish between subtypes using ^{99m}Tc-maraciclatide.

Due to the limited number of regions affected by endometriosis and the small sample size of participants, it was not possible to perform the planned diagnostic accuracy statistics at a region-level. Instead, I described the diagnostic performance in (**Table 14**) presents each affected region alongside available histology results and whether the affected region was detected on prior imaging (US and MRI). Within the association analysis, I also explored whether the region affected detection rates and presented post-hoc Adjusted Standardised Residual (ASR) values in (**Table 14**). For the same reason, I did not complete the planned subtype diagnostic accuracy studies at a region-level. However, the planned association studies described below explored the effect of subtype on regional detection. A summary of the planned and completed analysis can be found in **Table 4**.

Table 4: Summary of planned and completed analysis on the diagnostic performance of ^{99m}Tc-maraciclatide.

Planned analysis	Completed at a participant level	Completed at a region level
Cohen's kappa	Yes	No, sample size too small for meaningful conclusions to be made.
Sensitivity	Yes	No, but the effect of region on detection rate was assessed within the association studies and the Adjusted Standardised Residual was calculated by region.
Specificity	Yes, but not the subtype sub analysis at this point in time ^{99m}Tc-maraciclatide is unable to distinguish between subtypes.	No, ^{99m}Tc-maraciclatide at this point in time is unable to distinguish between subtypes.

Association analysis of lesion characteristics and hormonal variables

The second category of analysis performed was an association analysis, in which I examined whether detection was associated with certain lesion characteristics or hormonal variables. The lesion characteristic association study was conducted at the region level. In contrast, hormonal variables were analysed at the participant level, as the influence of exogenous and endogenous hormones was expected to have an effect at the participant level. ROIs obstructed by physiological activity were excluded in all the association analyses, except for the anatomical region analysis, where it was relevant to include them. This was performed to provide a more accurate understanding of the lesions in which ^{99m}Tc-maraciclatide showed activity despite the small sample size. The 8 obstructed ROIs were bladder (n=2) and uterovesicular fold (n=5) due to bladder accumulation, and the left ovary in one participant, as ROI visualisation was masked by physiological activity in the urethra.

I selected the lesion characteristics most likely to influence detection based on the current literature and the data collected on the WERF EPHect form. This resulted in four characteristics, and performed the statistical analysis plan below to answer the following questions:

1) Is detection associated with anatomical region?

2) Is detection associated with lesion size?

3) Is detection associated with lesion colour?

4) Is detection associated with lesion subtype?

The studies on lesion characteristics were performed at the region level, but as data were obtained from the WERF EPHect form, thoracic regions were excluded.

Prior literature suggested that detection is likely to be influenced by hormonal variables, most notably the use of hormonal therapies and the menstrual phase. Therefore, I performed an association analysis at a participant level to answer the following:

1) Is detection associated with exogenous hormone use?

2) Is detection associated with the menstrual cycle phase?

To assess whether the six variables had influenced detection rates, contingency tables were generated, and Fisher's exact test was performed using GraphPad to calculate a p-value (significance set to <0.05). For groups with over 5 values in more than 80% of cells, a chi-squared test was also performed, and if it was found to be significant, χ^2 was used to calculate Cramér's V to estimate the size of the effect using the equation below.

$$V = \sqrt{\frac{\chi^2}{N \cdot \min(r-1, c-1)}}$$

Finally, if the chi-squared test found a significant association, the diagnostic odds ratio DOR was calculated to provide clinically relevant information on the associations found. If the groups were too small (i.e., more than 80% of cells had fewer than 5 values), they were merged if a meaningful merge was possible. For example, a post hoc analysis was conducted on lesion colour, grouping lesions into 'active' and 'inactive' based on previously established literature.[16] Whereas, within the region association study, the groups could not be meaningfully merged, as a lateral asymmetry was identified, with lesions detected more frequently on the right side than on the left. Therefore, it was not possible to make logical merges, such as left and right pelvic side walls, into the pelvic side wall. Consequently, a post-hoc Adjusted Standardised Residual analysis (ASR) was performed to determine which regions were driving the significant association between region and detection.

Table 5 describes the planned tests that were ultimately performed.

Table 5: The planned statistical tests that were performed in the association studies.

Assossication studies	Fishers exact test or chi-squared test	Cramér's V	Diagnostic odds ratio	Additional post-hoc tests
Anatomical region	Fishers exact test	No, sample size too small		Adjusted standardised residuals
Lesion size	Fishers exact test	No assosciation was found so no further tests were completed		Not completed
Lesion colour	Only Fishers before grouping. Both after grouping into 'active' and 'inactive colours'	Yes, but only after grouping into 'active' and 'inactive colours'		Grouping into 'active' and 'inactive colours' as described
Exogenous hormone use	Fishers exact test	No assosciation was found so no further tests were completed		Grouping into exogenous hormones vs no exogenous hormones. Sample size too small to evaluate hormone types e.g. COP vs POP
Menstrual cycle phase	Fishers exact test	No assosciation was found so no further tests were completed		Not completed

Results

Diagnostic survey

Overview of respondents

1,121 respondents completed the survey on RedCap between November 2022 and March 2023. The mean age of respondents was 31.6 (8.5 SD), and 77.6% had a confirmed diagnosis, 18.3% were under investigation for endometriosis, and 4.1% had not yet begun their investigations.

Healthcare framework gaps that exist prior to seeking medical attention

To better understand the gaps in healthcare frameworks before a patient seeks medical attention, I asked respondents the following questions:

1) *Was there a delay in your seeking medical attention for your symptoms, and why?*

2) *Who first suggested that you might have endometriosis?*

3) *What was the main priority when seeking medical attention?*

These questions aimed to reveal whether delays and barriers occur both within and outside the healthcare setting and to evaluate the importance of improving awareness of endometriosis among healthcare professionals and within society.

Responses to 'Was there a delay in your seeking medical attention for your symptoms, and why?'

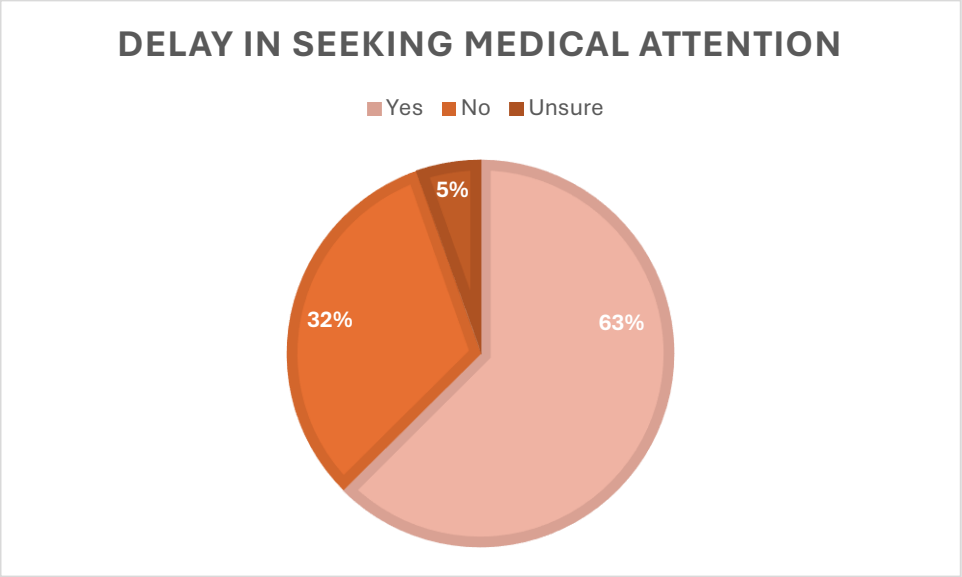


Figure 9: The proportion of respondents who delayed seeking medical attention (n=1,088)

Figure 9 demonstrates that 62% of respondents reported a delay in seeking medical advice for their symptoms. To understand the reasons for this, I conducted a thematic analysis of the open answers, which revealed that a significantly large number of respondents believed or were led to believe that their symptoms were normal; however, various types of normalisation occurred, including societal normalisation (which was interwoven with menstrual stigmatisation), patient normalisation, familial normalisation, and healthcare normalisation.

Theme 1: Societal normalisation and stigmatisation

The theme of societal normalisation included the consequence of societal menstrual health stigmatisation, whereby "Women and girls are brought up being told. Period pain is normal. Just get on with it. Go to work. Go to school. It's normal". Moreover, as periods from a young age are often seen as embarrassing and not frequently discussed, even

when something is wrong, some may not want to seek medical attention. One respondent commented, “I was a teenager and didn't want to discuss my periods with GPs”.

Theme 2: Healthcare normalisation and menstrual health stigma

A disappointing number of responses commented that healthcare professionals told them that they were “only a teenager and told it was normal.” This theme is also coupled with menstrual health stigma, as there is a belief that periods are painful as a teen but will improve. Although this is true in some cases, it has been reported that two-thirds of those with endometriosis developed symptoms before the age of 20 and the earlier the onset, the more severe the disease is thought to become, so these complaints must be taken seriously.[127]

Theme 3: Patient normalisation

Normalisation was also attributed to the patient, and causative factors included the age at which symptoms presented. One respondent commented, " At 11 I was too young to know what was normal.” If this is all they know, and if what is normal and abnormal are not discussed, it is clear how the symptoms could persist for many years without patients knowing any different. Another issue is knowing how severe a period must be to be considered abnormal, which makes it easy to explain away symptoms. One respondent commented, “Most women get pain on their period, and a lot of women get pain during sex due to anxiety, so I thought the pain was normal. It also wasn't initially severe enough that I needed a doctor to help me manage.”

Theme 4: Familial normalisation

As there is a recognised heritability of endometriosis, the 'normalising' of symptoms can also be passed down if mothers and daughters share the same symptoms. One respondent commented, "my mom had the same problems so I thought it was normal." Another stated, "I thought these symptoms were normal, in my family they ARE normal."

These results demonstrated that efforts are needed both within the healthcare setting and society more broadly to address the normalisation of symptoms and reduce the global diagnostic delay.

Responses to 'Who first suggested that you might have endometriosis?'

This question aimed to further understand the role of healthcare professionals and societal awareness of endometriosis in obtaining a diagnosis and reducing diagnostic delays.

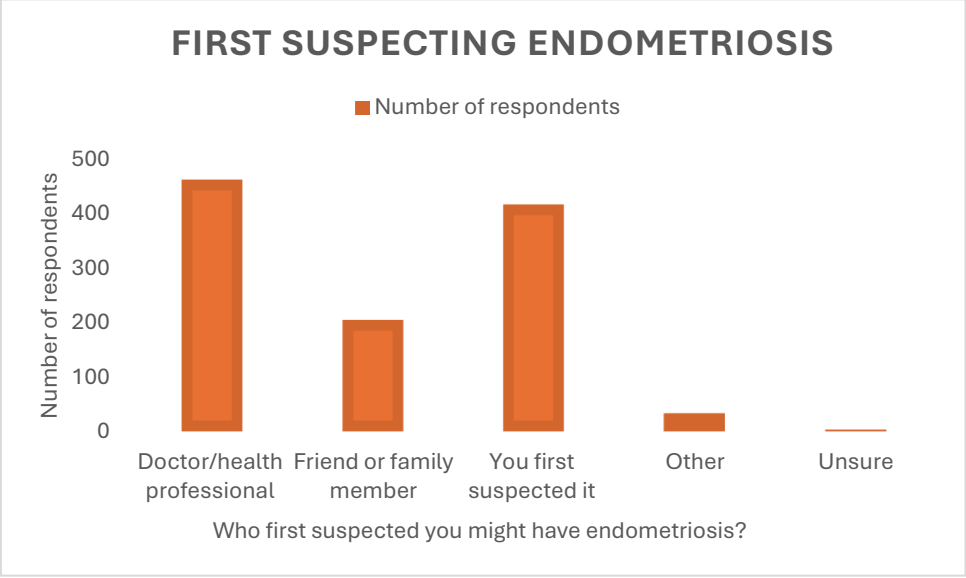


Figure 10: Individual who first suspected that the respondent had endometriosis (n=1,117)

Figure 10 demonstrates that patients and healthcare professionals are most often the first to suspect endometriosis. This reinforces the need to improve awareness within healthcare systems and society, as patients are often their own advocates in obtaining the correct diagnosis.

Responses to 'What was the main priority when seeking medical attention?'

This question aimed to clarify the priority when a patient seeks medical attention and to ensure that we, as health professionals, address what is most important to them.

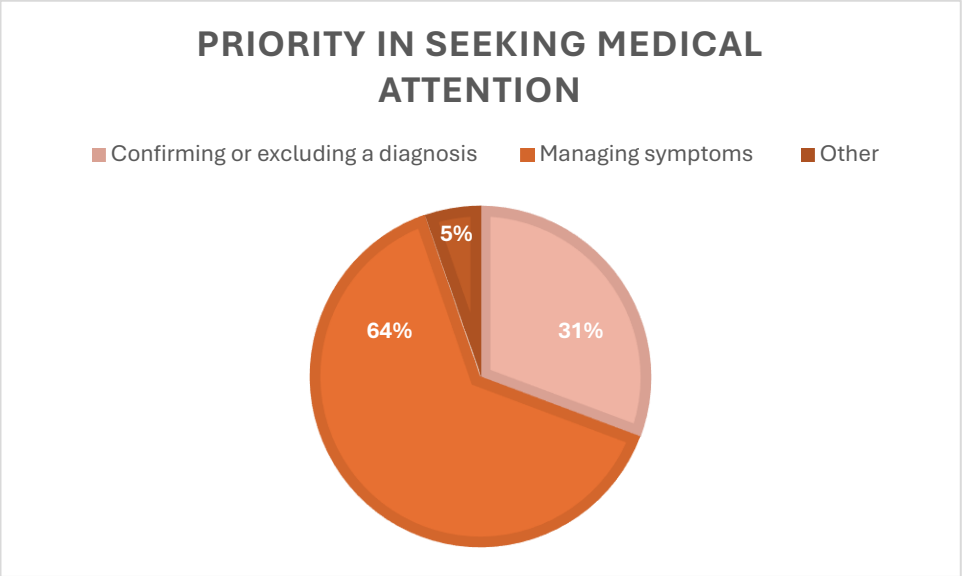


Figure 11 : Assessing why respondents first sought medical advice (n = 1,120)

Figure 11 shows that managing their symptoms is the most common reason patients ultimately seek medical care. Within the discussion, I will argue that this finding conflicts with our current prioritisation of time to diagnosis, as time to treatment may be more important for patients.

Healthcare framework gaps after seeking medical attention

The next set of questions aimed to assess gaps in this healthcare framework once a patient has sought medical attention. Many of the questions helped to build an understanding of the experiences of those undergoing investigations for endometriosis. Moreover, I explored respondents' acceptability of novel diagnostic tests which might overcome our current diagnostic limitations.

To assess this, I asked the following:

1) *How many appointments did you have with a GP regarding your symptoms before you were referred to a gynaecologist?*

2) *Have you had an ultrasound scan/MRI/laparoscopy to investigate a diagnosis of endometriosis?*

3) *How many ultrasound scans/MRI/laparoscopies have you had to investigate a diagnosis of endometriosis?*

4) *Was endometriosis detected or seen during your ultrasound scan/MRI/laparoscopy?*

5) *Please rank your satisfaction with the overall experience(s) of undergoing an ultrasound scan/MRI/laparoscopy to investigate a diagnosis of endometriosis and why.*

Responses to 'How many appointments did you have with a GP regarding your symptoms before you were referred to a gynaecologist?'

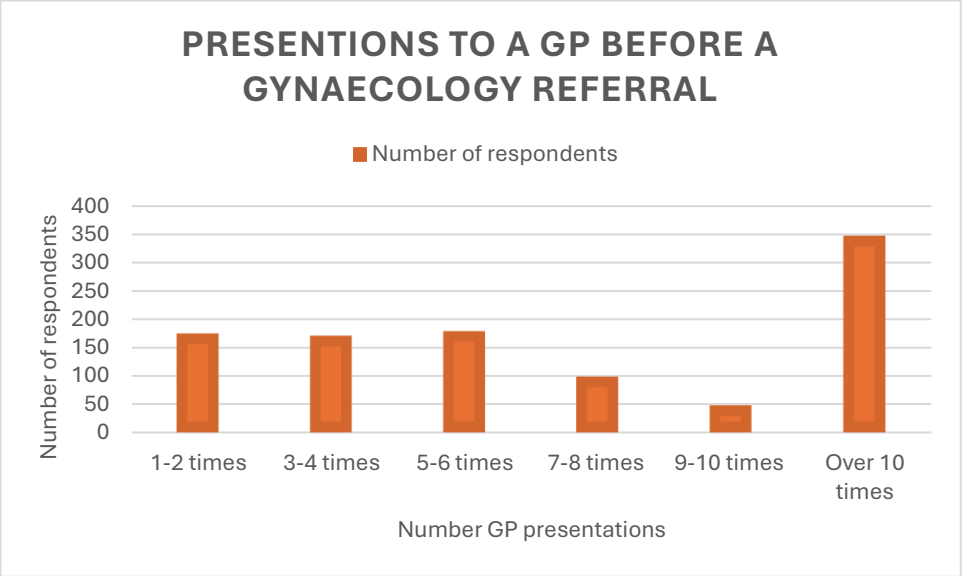


Figure 12: Number of times seen by a GP before being referred to a gynaecologist (n=1,110)

Figure 12 demonstrates a major gap within our healthcare framework and a probable cause of delay, as a large proportion of patients repeatedly present to a GP before being referred to a gynaecologist.

Responses to questions regarding the current diagnostic pathway

Table 6: Respondents' diagnostic experiences of current diagnostic methods

Investigation	Proportion of respondents having undertaken the investigation	Mean (SD) number of investigations undertaken per respondent	Proportion of respondents where the investigation identified disease	Satisfaction mean VAS (SD)
Ultrasound	958/1118 (86 %)	3.3 (3.0) N=954	232/955 (24%)	33.8 (28.6) N=855
MRI	414/1115 (37 %)	0.6 (1.0) N=413	215/413 (52%)	56.9 (33.0) N=344
Laparoscopy	769/1117 (69 %)	1.2 (1.3) N=768	741/767 (97%)	68.1 (28.0) N=700

Responses within the diagnostic questionnaire describing the current diagnostic experiences of those undergoing an investigation for endometriosis, including: uptake of investigations, mean number of investigations per respondent, diagnostic accuracy, and satisfaction using the visual analogue scale (VAS). Values are shown as x/N (%) for proportions and mean (SD), N= for continuous measures. Denominators vary by item due to missing data and skip patterns; the denominator for "identified disease" is respondents who underwent that investigation. Percentages are rounded to the nearest whole number.

Table 6 demonstrates a high usage of investigative methods among those seeking a diagnosis of endometriosis, but unfortunately, a low level of satisfaction with the methods currently available. I conducted a thematic analysis of the open-ended questions for each diagnostic approach to gain a deeper understanding of the respondents' experiences and identify gaps within our diagnostic frameworks.

Responses to ultrasound investigations

The mean US satisfaction score was 33.8 (28.6 SD) using a 0-100 VAS score (N=855). The thematic analysis of the open-ended answers provided more clarity on the low scores and identified three key themes: diagnostic gatekeeping, diagnostic limitations, and pain.

Theme 1: Diagnostic gatekeeping

Respondents often remarked that they felt the US results heavily determined the next steps in their investigation and care. As such, a negative US for some prevented further investigation. One respondent commented, “They said nothing showed up no shadows and wouldn't take it further.” Moreover, for some, although it did prompt further investigation, the US in itself was thought to be a step that needed to be completed, instead of a diagnostic tool. For example, a respondent commented, “it's rare to spot on a ultrasound so I felt it was a tickbox exercise that I needed to do to get to the next stage which was MRI.”

Theme 2: Diagnostic limitations

It is well established that US is highly operator dependent and a negative scan doesn’t exclude endometriosis. However, some felt that these limitations led to their symptoms being dismissed, making the challenge to get diagnosed more difficult. One respondent, who had endometriosis diagnosed surgically, commented, “My symptoms were all dismissed as nothing was found, even though finding endo on an ultrasound is rare.” Moreover, another respondent with surgically confirmed endometriosis commented “Told all was normal and made me feel as if I was overreacting” and another commented it left her feeling “I had wasted everyones time.” This crucially highlights the expectations that need to be set when conducting these tests and that patients (and health professionals) need to be aware of the limitations of US in detecting endometriosis.

Theme 3: Pain

A common complaint was that the US was painful, which questions our belief that this is a non-invasive diagnostic method. For many with endometriosis, pelvic pain and

dyspareunia are common features, making a US a potentially painful and unpleasant experience. One respondent commented, “You're there because your pelvic area hurts, a transvaginal doesn't help, especially when you cramp with insertion and holding urine. Also, learning that ultrasounds are not the best way to diagnose endometriosis, it felt like unnecessary pain.” However, pain elicited from the scan can also be a useful diagnostic tool; this should be explained to the patient, and once identified, methods should be employed to reduce the pain associated with the procedure.

Responses to MRI investigations

MRI is often conducted as the next step following US, especially if bowel or bladder involvement is suspected. The respondents gave MRI a mean satisfaction rating of 56.9 (SD 33.0, VAS 0-100, n = 344). In analysing the open-ended answers to the MRI satisfaction score, I identified three key themes: gateway to specialist care, identification of comorbidities, and caustrophobia.

Theme 1: Gateway to specialist care

Many respondents commented that an MRI allowed for the extent of endometriosis to be determined and led to specialist care, such as endometriosis surgery with the addition of bowel or urology surgeons. This suggests that, for many, it meets the aims of performing an MRI prior to surgery, which respondents were satisfied with.

Theme 2: Identification of concurrent diseases

Many respondents also commented that they had rated MRI highly because it had identified concurrent disease, most commonly adenomyosis. This is important prior to

surgery to be able to manage expectations and to provide additional clarification for the symptoms patients are experiencing, particularly as treating endometriosis surgically will not resolve their pain if it is driven by adenomyosis.

Theme 3: Caustrophobia

Many of the negative experiences with MRI stemmed from respondents finding the MRI to induce caustrophobia.

Although respondents were not asked to compare interventions, some volunteered their opinions. For example, MRI was “less painful than transvaginal ultrasound but hard to know which is right when MRI and ultrasound show different things” and MRI was “less invasive than surgery to detect but also worried as it may not have picked it all up or the extent of it.” The first comment raises a crucial point of the confusion that can occur by having multiple methods of investigation if the findings are not fully explained to the patient, and the diagnostic uncertainty that can persist.

Responses to diagnostic laparoscopy

Laparoscopy is often the final diagnostic approach and was the final method assessed. The mean satisfaction of laparoscopy as a diagnostic method was 68.1 (SD 28.0, VAS, 0-100, n=700). This score meant that laparoscopy was rated higher than US and MRI, the two non-invasive techniques. A thematic analysis of the responses resulted in three key themes: ‘definitive diagnosis’, ‘diagnostic and therapeutic’ and ‘invasive.’

Theme 1: A conclusive diagnosis

There was an overwhelming amount of responses sharing the relief that laparoscopy offered a 'conclusive diagnosis.' For example, "They found it and I was able to get answers and advice I desperately needed", "it confirmed what I'd waited 20+ years ,for" and "Nice to be told have it and not going mad." These powerful responses highlight the crucial importance of a diagnosis for patients and the need to improve the validation of patients' symptoms before making a definitive diagnosis. This could be achieved by strengthening the value of a clinical diagnosis of endometriosis, so patients don't feel like they need to fight to prove their symptoms.

Theme 2: Diagnostic and therapeutic

Respondents reported being pleased that laparoscopy could also provide symptomatic relief. For example, "Was really happy to get answers as to why I'm in so much pain. I have had relief from symptoms since the surgery." However, the duration of the relief was varied, with some stating it only offered a "Short term cure."

Theme 3: Invasive

It is important to highlight that surgery is an invasive procedure, despite minimally invasive techniques being utilised, and for many, it is unfortunate that only an invasive method can diagnose a common condition. One respondent commented that laparoscopy was "Very invasive surgery with a long recovery time but at least it was able to prove endometriosis"

Additional themes were identified in all three investigation techniques, such as ‘communication barriers’ (where the results and the implications were not clearly explained), ‘poor-aftercare’ (leaving patients with more concerns and questions) and ‘long waiting-times’, which highlight important infrastructural issues that exist throughout all diagnostic techniques but were not included as key themes as they are not specific to the investigative method in question.

It is clear that there are concerns with the diagnostic methods we use today, especially regarding their diagnostic limitations. Next, I assessed respondents’ acceptability of some novel diagnostic methods being investigated within the research field, as these may, in the future, bridge the gaps within our current diagnostic framework. Although CT is not currently used to investigate endometriosis, I included it in the assessment of novel tests to determine whether CT with radiation would be acceptable for patients before conducting the DETECT study.

Acceptability of novel diagnostic tests

Respondents’ acceptability of novel diagnostic tests is shown in **Table 7** and later reviewed in the discussion.

Table 7: Acceptability of novel diagnostic tests

Novel diagnostic technique	Number of respondents	Acceptability VAS 0-100 Mean (SD)
Blood test	973	87.51 (20.08)
Urine test	976	82.54 (23.70)
CT scan (20-minute scan with low dose radiation)	959	81.09 (22.19)
Menstrual fluid test	945	79.57 (24.86)
Symptom analysis (e.g. app or questionnaire)	954	63.76 (32.13)

The impact of a diagnostic delay on life choices

To deepen the understanding of why efforts are needed to address the diagnostic delay, beyond the economic factors which have been repeatedly demonstrated, I asked respondents how the delay had affected their life choices.

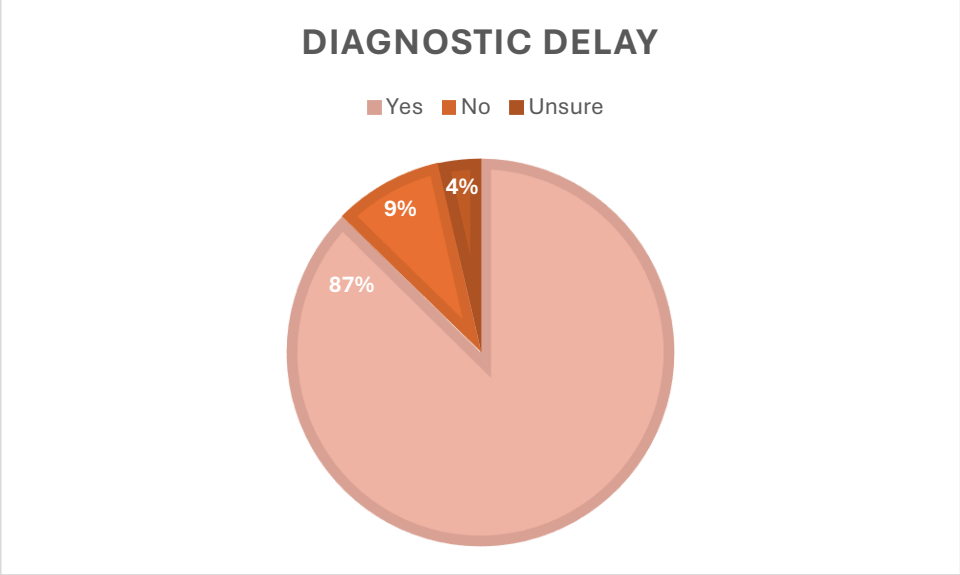


Figure 13: Percentage of respondents who believed that they had experienced a diagnostic delay (n=1,117)

87% of respondents reported experiencing a delay in their diagnosis (**Figure 13)**. 72% of respondents stated that an earlier diagnosis would have altered their life choices. A thematic analysis of the open-ended responses led to the identification of five powerful themes (fertility choices, self-awareness and self-acceptance, lifestyle choices, career decisions, and healthcare options) in response to life decisions that respondents would have changed had they received a diagnosis sooner.

Theme 1: Fertility choices

The most frequent response is that an earlier diagnosis would have given them time to consider their fertility options sooner. Many remarked that they were facing infertility at an older age, and with an earlier diagnosis, they would have had fertility discussions with a partner, tried sooner for children or frozen eggs.

Theme 2: Self-awareness and self-acceptance

Many respondents stated crucially that an earlier diagnosis would have helped them better understand themselves and their symptoms, enabling them to distinguish the two. For example, one respondent commented, “I would have had a better understanding of my body. An explanation for all my symptoms. Better mental health knowing there is an underlying medical condition.” Another commented, “My mental health would have been significantly improved had I realised I wasn't the problem and that it wasn't my fault. I wasn't lazy or unlovable.” Within this theme, many remarked on the importance of “being able to explain to a partner why it hurt during intercourse, which would have greatly helped the breakdown of relationships.”

Theme 3: Lifestyle choices

Respondents also remarked that knowing there is a disease behind their symptoms would have encouraged them to make "better lifestyle choices, e.g. diet, products, exercise." For example. "I would have focused sooner on dietary and working arrangements that may have helped me manage the condition."

Theme 4: Career decisions

Respondents also commented that understanding that their symptoms were part of a chronic disease would have helped them reassess their career decisions to ensure they chose a path that could accommodate the needs of their condition. For example, one respondent commented that they would have "chosen a less stressful career that enables my body to rest as I have a chronic pain but was always told it was just period pain."

Theme 5: Healthcare options

Many respondents commented that an earlier diagnosis would have helped them avoid unnecessary treatments and their side effects, and enabled them to receive the correct treatment sooner. Moreover, within this theme, many said they would have taken out health insurance sooner and looked into specialists earlier who could help with their various needs.

It was clear from the survey that there is a need to develop new diagnostic methods to help overcome the limitations of our current methods and to reduce the diagnostic delay,

which has a huge impact on the way patients choose to live their lives. The survey demonstrated that patients are highly accepting of novel tests, including CT.

DETECT imaging study

DETECT overview

The DETECT study aimed to address the need for novel diagnostic tests that can reduce diagnostic uncertainty before patients resort to surgery, thereby potentially reducing diagnostic delay and its associated socioeconomic consequences. As discussed in the **Methods**, various steps were completed from study design to the approval of the study for recruitment of its first participant in November 2022 (**Figure 14**). However, due to hospital winter pressures, RUH approved capacity to begin recruitment in March 2023. After gaining ethical approval for the study protocol, various protocol amendments (**Appendix 2**) were required to meet the study's aims and to adjust for unexpected events, such as two global Molybdenum-99 supply shortages (the precursor isotope to technetium-99m).



Figure 14: Timeline of events in the design and set-up of DETECT

Participants

Between March 2023 and September 2024, 20 participants were recruited (**Figure 15**). 18 participants had pelvic scans, with 17 of them undergoing subsequent laparoscopy. One participant decided against surgery; therefore, her data were excluded from the study. Two participants had thoracic scans with subsequent thoracoscopic surgery. Endometriosis was detected surgically in 17 of the 19 participants who completed the study. 18 of the participants who had surgery had it within the protocolled time of under 3 months, with a mean of 18 days after SPECT-CT. One participant had surgery outside the protocolled time, 154 days, due to surgical cancellations. Details on the detection of participant ROI by ^{99m}Tc-maraciclatide, MRI and US can be found in **Appendix 3.**

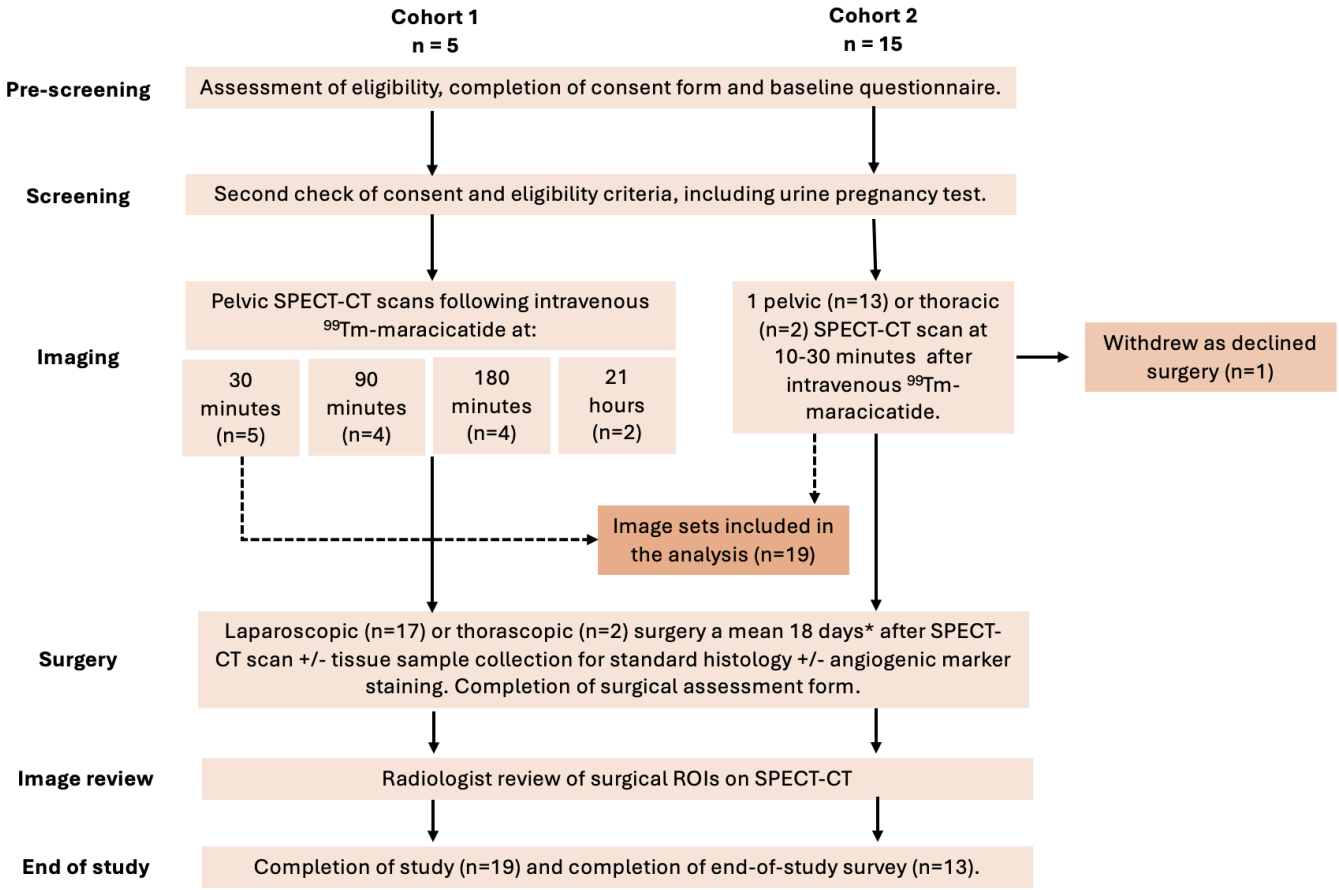


Figure 15: Patient flow and schematic of study events.

The baseline characteristics of the included participants are shown in **Table 8**

Table 8: Baseline characteristics of included participants.

Characteristics	**Included participants**
Age	Mean 34.2 (SD 8.89) Range 20-59
Ethnicity	White n=18 Asian (Indian) n=2
Previous surgical diagnosis	n=9
Prior non-invasive imaging in the 12months prior to their participation in the study	TVUS: n=14 (5 advanced scans) MRI: n=7
Concurrent exogenous hormones at the time of the scan	POP: n=4 Mirena: n=4 GnRH-a: n=1 HRT: n=1 None: n=10
Menstrual phase of the endometrium	Proliferative: n=4 Secretory: n=4 Menstrual: n=1 Unable to comment: n=10 Missing questionnaire data: n=1
Endometriosis subtypes	SPE: n=12 DE: n=9 OE: n=3 Thoracic endometriosis: n=2
Additional pathology	Adenomyosis: n=6 Salpingosis: n=1 Fibroids: n=1

Characteristics of recruited participants. The data in the table pertain to the 19 participants who completed the study. The table includes MRI or US scans taken within the 12 months before surgery. Advanced scans include those where the scan was performed by an endometriosis specialist using advanced scanning protocols.

Diagnostic performance of ^{99}Tm-maraciclatide

Participant-level analysis

^{99m}Tc-maraciclatide signal agreed with the participant-level diagnosis or exclusion of endometriosis in 16 out of 19 cases. In the two cases where endometriosis was not observed during diagnostic surgery (negative cases), the ^{99m}Tc-maraciclatide scan did not

reveal any areas of non-physiological uptake. Endometriosis was correctly visualised in 14 of the 17 cases of endometriosis seen during surgery (**Table 9**).

Table 9 Alignment between surgery and SPECT-CT imaging at a participant level

Completed Study	N=19[a]		
	Surgery +ve for endometriosis	Surgery -ve for endometriosis	Totals
^{99m}Tc-maraciclatide +ve for endometriosis	14	0	14
^{99m}Tc-maraciclatide -ve for endometriosis	3[b]	2	6
Totals	17	2	19

a.19/20 participants underwent pelvic or thoracic surgery after imaging with ^{99m}Tc-maraciclatide (one participant withdrew from surgery after scanning)
b. One participant with a fibrotic rectovaginal nodule; one participant receiving GnRHa with an inactive superficial lesion on her bladder that was histologically negative for endometriosis; one participant with SPE in the uterovesicular fold, which was obscured by bladder background. However, uptake was seen in the left fallopian tube, where endosalpingosis was seen on surgery.

Participant level - Diagnostic agreement

As per protocol, I calculated Cohen's Kappa statistic using the counts in **Table 9 .** Intra-observer agreement was 84.2% (16/19), compared with 68.7% expected by chance. Cohen's κ = 0.50 (SE = 0.23; 95% CI 0.04–0.95; z = 2.15; p = 0.032), indicating moderate agreement beyond chance. The unbalanced groups (positive n=17 vs negative n=2) have likely caused an underestimation in perceived agreement, commonly known as the kappa paradox.[128] This presents as a high percentage of observed agreements (84.21% in this case) but an unexpectedly low kappa value (Cohen's κ = 0.50, moderate agreement).

Participant level - Diagnostic accuracy

The study was not powered to complete a sensitivity and specificity analysis, but was completed to provide a better overview of the diagnostic potential of the scan. The sensitivity and specificity of ^{99m}Tc-maraciclatide for the detection of endometriosis at a participant level were calculated to be 82.4% and 100%.

Participant-level subtype sub-analysis

^{99m}Tc-maraciclatide was shown to be able to detect OE (**Table 10**), SPE (**Table 11**) and DE (**Table 12**) (see images in **Figure 16**).

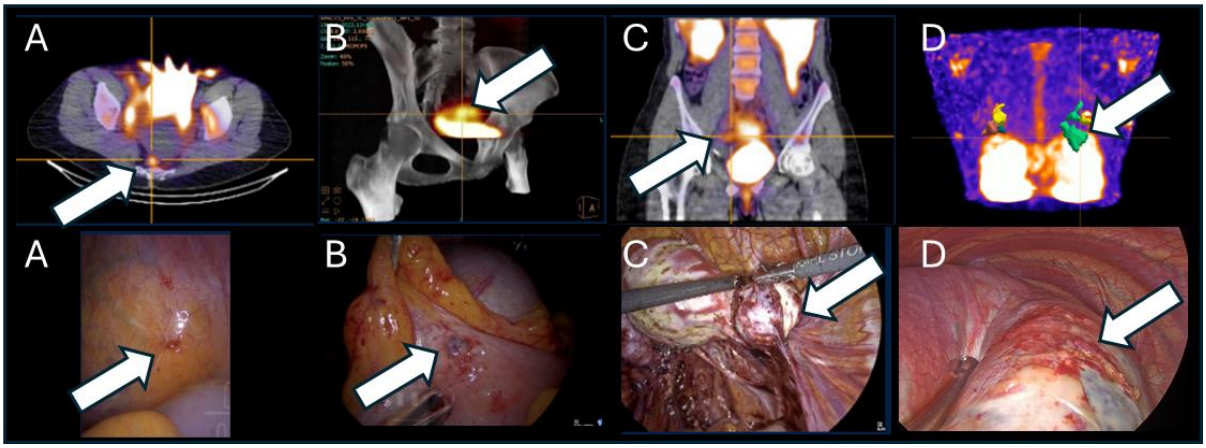


Figure 16: Detection of endometriosis subtypes using SPECT-CT images with ^{99m}Tc-maraciclatide with paired surgical images: A) SPE, B) DE, C) OE and D) Thoracic endometriosis.
White arrows indicate the paired ROIs. A) The white arrow points to uptake in a SPE lesion classified as 1-3cm within the POD**;** the lesion was not identified on prior advanced US. There is no uptake seen within the 9cm endometrioma. Both lesions were positive for endometriosis on histopathology and for IHC staining of CD31, αvβ3, and VEGF but not αvβ5. B) The white arrow points to 1-3cm DE within the upper sigmoid colon**,** classified as blue/black. The lesion was not excised. C) Arrow points to a 2cm endometrioma covered with red SP**E,** which demonstrated ^{99m}Tc-maraciclatide uptake despite being negative on histology for endometriosis. D) Arrow points to thoracic endometriosis seen on the parietal pleura and stained positively for endometriosis, CD31 and αvβ3, but not VEGF and αvβ5.

Table 10: Alignment between pelvic laparoscopy and SPECT-CT imaging with 99mTc-maraciclatide for participants with endometriomas (OE).

Completed Study	**N=17[a]**		
	Laparoscopy +ve for OE	**Laparoscopy -ve for OE**	**Totals**

^{99m}Tc-maraciclatide +ve	1[a]	0	1
^{99m}Tc-maraciclatide -ve	2	14	16
Totals	3	14	17

[a]The one endometrioma detected was surrounded by SPE; therefore, it is uncertain if the angiogenesis detected is driven by SPE, the endometrioma or both.

Table 11 : Alignment between pelvic laparoscopy and SPECT-CT imaging for superficial peritoneal endometriosis (SPE).

Completed Study	**N=17[a]**		
	Laparoscopy +ve for SPE	**Laparoscopy -ve for SPE**	**Totals**
^{99m}Tc-maraciclatide +ve	9[a]	0	9
^{99m}Tc-maraciclatide -ve	3[b]	5	8
Totals	12	5	17

[a] Two participants with SPE also had concurrent subtypes within the detected ROI; therefore, it is uncertain which subtype is driving the angiogenesis or whether it was a combination of the two.
[b] One participant received GnRHa with an inactive (fibrotic) superficial lesion on her bladder that was histologically negative for endometriosis; one participant with SPE on the uterovesical fold, which was obscured by bladder background. However, uptake was seen in the left Fallopian tube, where endosalpingiosis was seen during surgery; one participant had SPE on the left pelvic side wall and left ovary, with uptake seen in the DE lesion in the Pouch of Douglas.

Table 12: Alignment between pelvic laparoscopy and SPECT-CT imaging for deep endometriosis (DE).

Completed Study	**N=17[a]**		
	Laparoscopy +ve for DE	**Laparoscopy -ve for DE**	**Totals**
^{99m}Tc-maraciclatide +ve	5[a]	0	5
^{99m}Tc-maraciclatide -ve	3	9	12
Totals	8	9	17

[a]One participant with DE also had SPE within the ROI; therefore, it is uncertain if the angiogenesis detected is driven by SPE, the endometrioma or both.

Table 13: Summary of detection of endometriosis subtypes at a participant level

Subtype	**Participants (n)**	**Detected (n)**	**Sensitivity % (95% CI)**
Endometrioma	3	1[a]	33.3 (6.1–79.2)
Superficial endometriosis	12	9[b]	75.0 (46.8–91.1)
Deep endometriosis	8	5[c]	62.5 (30.6–86.3)
Overall	**23**	**15**	**65.2 (44.9–81.2)**

Per-subtype sensitivity analysis of ^{99m}Tc-maraciclatide to detect endometriosis, with 95% confidence intervals calculated using the Wilson method. As discussed in the methods, specificity was not calculated as it is not possible for ^{99m}Tc-maraciclatide to distinguish between subtypes. CI = confidence interval.
[b]The one endometrioma detected was surrounded by SPE; therefore, it is uncertain if the angiogenesis detected is driven by SPE, the endometrioma or both.
[c]Two participants with SPE also had concurrent subtypes within the detected ROI; therefore, it is uncertain which subtype is driving the angiogenesis or whether it was a combination of the two.
[a]One participant with DE also had SPE within the ROI; therefore, it is uncertain if the angiogenesis detected is driven by SPE, the endometrioma or both.

Although the sample size was small, ^{99m}Tc-maraciclatide appears to be able to detect SPE with higher accuracy compared to OE and DE (**Table 13**). The detection of SPE demonstrates ^{99m}Tc-maraciclatide potential in being able to improve the current diagnostic pathway, which relies on surgery to exclude SPE, as discussed further in the discussion.

Diagnostic accuracy at a region-level

After extracting data from the WERF EPHect forms, a total of 57 ROIs (49 pelvic and 8 thoracic) were identified (**Table 14**). Each participant had a mean of 3.35 ROIs (SD 2.55, 2.04 to 4.66, 95% CI) identified at surgery. Between 1 and 3 samples from 41 ROIs (multiple samples from one lesion) were sent for histopathological assessment, and 30 ROIs (73%) were positive for endometriosis. By subtype, the 57 surgically confirmed ROIs were classified as: SPE 29/57 (50.9%), DE 15/57 (26.3%), SPE & DE 2/57 (3.5%), OE 2/57 (3.5%), OE & SPE 1/57 (1.8%), and Thoracic endometriosis 8/57 (14.0%). ^{99m}Tc-maraciclatide identified 17 of the 57 (30%) endometriosis ROIs, 9 of which had histological confirmation of endometriosis.

Region of interest identified on surgery	Region confirmed on histology	Identified on US	Identified on MRI	Identified using ^{99m}Tc-maraciclatide	
					Adjusted standardized residuals
Uterus:					
n=2	0/1	0/1	0/1	2/2[a]	**+2.21**
Right ovary:					
n=5	1/2	2/5[b]	NA	1/5	−0.50
Left ovary:					
n=5	1/1	1/5	1/2	0/5	−1.53
Right fallopian tube:					
n=1	NA	0/1	NA	0/1	−0.66
Right pelvic side wall:					
n=8	6/8	0/6	0/2	5/8	**+2.18**
Left pelvic side wall:					
n=6	5/6	0/6	0/1	0/6	−1.64
Abdominal wall:					
n=1	1/1	0/1	NA	0/1	−0.66
Left parametrium:					
n=1	1/1	NA	NA	1/1	+1.55
Pouch of Douglas:					
n=9	8/9	0/6	0/3	5/9	+1.84
Uterovesicular fold:					
n=5	4/5	0/3	1/2	0/5[c]	−1.53
Bladder:					
n=2	0/2	0/1	NA	0/2[c]	−0.94
Rectovaginal septum:					
n=2	1/1	0/1	1/1	0/2[d]	−0.94
Sigmoid colon:					
n=1	NA	0/1	NA	1/1	+1.55
Mesenteric fat					
n=1	NA	0/1	NA	0/1	−0.66
Right diaphragm:					
n=2	1/2	NA	NA	1/2	+0.63
Left diaphragm:					
n=1	0/1	NA	NA	0/1	−0.66
Right parietal pleural:					
n=2	2/2	NA	NA	0/2	−0.94
Left parietal pleural:					
n=2	0/1	NA	NA	1/2	+0.63
Liver wedge					
n=1	0/1	NA	NA	0/1	−0.66

Table 14: Detection of ROIs by anatomical region

Regions identified by the operating surgeon to be affected by endometriosis and the number of regions positively identified by previous imaging (<12 months of surgery), ^{99m}Tc-maraciclatide and histology (n=number of affected regions). Regions were determined by the WERF SSF. However, regions that could not be distinguished using SPECT-CT were combined (uterosacral ligament into pelvic sidewall). 'NA' indicates where there was no available data, e.g. prior US. The number of positive US, MRI and histology findings is out of the available cases, e.g. 0/1 means that endometriosis was not found on histology in the 1 sample sent to histology. Adjusted standardised residual values were calculated, and values were bolded to indicate if the ASR was significantly higher or lower than expected (>2 or <-2)

[a] The participant had SPE surrounding the uterus, but also had adenomyosis. As discussed in a subsequent section, adenomyosis may have been driving the uptake of the signal.
[b] Although the US identified both right endometriomas, one was incorrectly diagnosed as a haemorrhagic cyst.
[c] Due to the proximity to the bladder, any signal present in this region would not have been able to be distinguished from bladder accumulation.
[d] Both lesions in this region were classified as a fibrotic disease, which is not expected to take up the signal.

Association analysis of lesion characteristics and hormonal variables

As the DETECT study was a small exploratory study, I wasn't able to control for factors that were likely to influence the rate of detection. Therefore, I performed association studies to assess the influence of various factors on the detection rate. These studies aimed to provide more data on αvβ3 expression patterns, ^{99m}Tc-maraciclatide uptake patterns, and to offer hypotheses that could be further developed in future studies.

Question 1: Is detection associated with anatomical region?

A Fisher–Freeman–Halton exact test on the 19×2 table demonstrated a significant association between region and detection ($p = 0.02$). As a chi-square test was not possible due to the low number of results in each cell, I calculated the adjusted standardised residuals (ASR) post hoc to determine which regions were driving this significance. The ASR identified higher-than-expected detection in the uterus (ASR=+2.21) and right pelvic side wall (ASR=+2.18), and lower-than-expected in left pelvic side wall (ASR=−1.69) and ovaries/uterovesicular fold (ASR=−1.5) (**Table 14**)

Question 2: Is detection associated with lesion size?

Table 15: Detection by ROI size.

Lesion size	Detected	Not detected	Total	Detection rate
<1 cm	2	6	8	**25%**
1–3 cm	11	15	26	**42 %**
>3 cm	2	5	7	**29 %**
Totals	**15**	**26**	**41**	**37 %**

Data obtained from the completed WERF EPHect SSF forms.

A Fisher–Freeman–Halton exact test on the 3×2 table (**Table 15**) revealed that, in the current dataset, there was no evidence of a difference in detection rates by size (p = 0.65).

Question 3: Is detection associated with lesion colour?

Table 16: Detection of ROI by lesion colour

Colour	Detected	Not detected	Total	Detection rate
Blue/black ± white	1	10	11	**9 %**
White	2	8	10	**20 %**
Red or red mixed	5	3	8	**63 %**
Brown	2	1	3	**67 %**
Clear	3	0	3	**100 %**
Blue	1	0	1	**100 %**
Yellow/white	1	1	2	**50 %**
Totals	**15**	**23**	**38**	**40 %**

Data obtained from the completed WERF EPHect SSF forms.

A Fisher–Freeman–Halton exact test on a 7×2 contingency based on the values in **Table** 16 found a significant association between lesion colour and detection (p =0.01). The sample was too small for a valid chi squared test to as per the protocol meaningful groups were merged. Given the belief that red/clear lesions represent early angiogenic 'active' lesions, these groups were merged along with any mixed lesion with a red or clear component. The remaining coloured groups (blue, black, brown, yellow and white) were merged to 'inactive' lesions. After grouping, detection was much higher for 'active' (red/clear) lesions (8/11 = 72.7%) than for inactive (blue/black/yellow/brown/white)

lesions (7/27 = 25.9%), an absolute difference of 46.8 percentage points (**Table 16**). Grouping the lesions made performing a chi-squared test possible, but a significant association was still seen on a Fisher's exact test (p=0.01). On a 2×2 table, Pearson's chi-square test determined that detection and colour group were significantly associated, $\chi^2(1)=7.17$, p=0.01. To assess the strength of this association, I conducted Cramér's V to measure the effect size, which revealed a moderate association, with Cramér's V/ϕ = 0.43 (0–1 scale).

$$V = sqrt\sqrt{(\chi^2/N \min(\mathrm{r}-1, \mathrm{c}-1))} = \sqrt{\left(\frac{7.1653}{38x1}\right)} = 0.434$$

$\chi^2 = 7.165$

N = 38

min(2−1,2−1)=1

To provide clinically relevant metrics to the results, I calculated the odds ratio, which found that the odds of detecting active lesions were 7.62× higher (OR 7.62; 95% CI 1.57–37.05) than detecting inactive lesions.

Question 4: Is detection associated with lesion subtype?

Of the ROIs that demonstrated ^{99m}Tc-maraciclatide activity, SPE was the most common subtype detected (SPE 9/17 (52.9%), DE 4/17 (23.5%), SPE & DE 1/17 (5.9%), Endometrioma & SPE 1/17 (5.9%) and Thoracic endometriosis 2/17 (11.8%)). However, Fisher's exact test found no association between subtype and detection (p = 0.50).

Question 5: Is detection associated with exogenous hormone use?

17 participants were found to be positive for endometriosis on surgery, 8 of whom had been using exogenous hormones over the past 3 months (POP: n=3, Mirena: n=3 GnRH-a: n=1, HRT: n=1). Due to the small sample size, participants were grouped into exogenous hormone users or non-users. A Fisher–Freeman–Halton exact test on the current dataset revealed no association between the hormonal variability of exogenous hormones and the detection of endometriosis using ^{99m}Tc-maraciclatide (p = > 0.99).

Question 6: Is detection associated with the menstrual cycle phase?

Information on the menstrual phase was available for 9 participants not using exogenous hormones. Among participants with a known endometrial phase (n=9), phases were evenly split between secretory (4/9, 44.4%) and proliferative (4/9, 44.4%) phases, with 1/9 in the menstrual phase (11.2%). Secretory cases were 1 early (D17), 1 mid (D21), and 2 late (n=2 D24); proliferative cases were 1 early (D7), 2 mid (D9, D10), and 1 late (D13). A Fisher–Freeman–Halton exact test on the current dataset found no association between the hormonal variability induced by the menstrual cycle and detection of endometriosis using ^{99m}Tc-maraciclatide (p = >0.9999)

Exploratory Ancillary Signals

Based on the findings of the Phase 1 study, physiological activity was expected within the urinary tract and bowel as these were the main excretion pathways. Varying degrees of activity were observed in the bowel and urinary tract of each participant. Within the urinary tract, no clinically relevant signals could be distinguished due to the large amount of tracer excretion. As previously discussed, this resulted in the obstruction of detecting lesions on the bladder, the uterovesicular fold and even the ovary in one participant. Within the bowel, physiological activity appeared diffuse and linear, whereas the presence of focal activity suggested pathological uptake. The radiologist identified two ROIs of focal activity that were deemed clinically relevant; one was confirmed by laparoscopy (**Figure 16**), but the other region could not be confirmed (**Figure 17**).

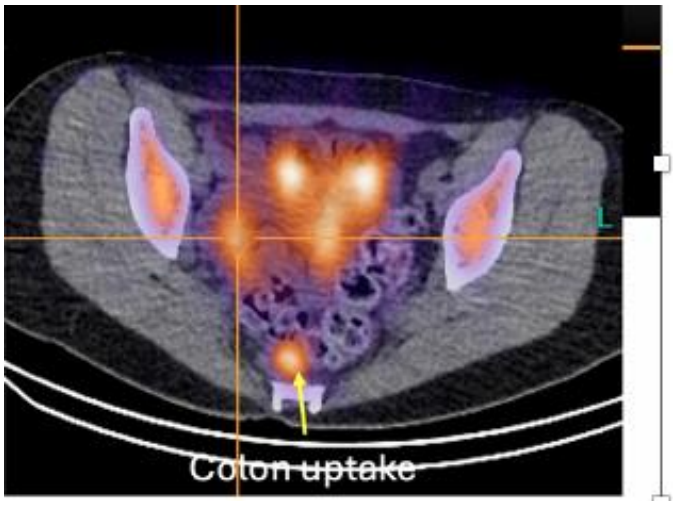


Figure 17: Focal vs diffuse colon uptake of ^{99m}Tc-maraciclatide

The yellow arrow demonstrates focal bowel uptake, whereas the crosshairs demonstrate diffuse bowel uptake. Uptake can also be seen within the bone marrow, bladder and ureters.

Activity was also observed in one participant with endosalpingiosis, a condition not believed to be inflammatory (**Figure 18**).

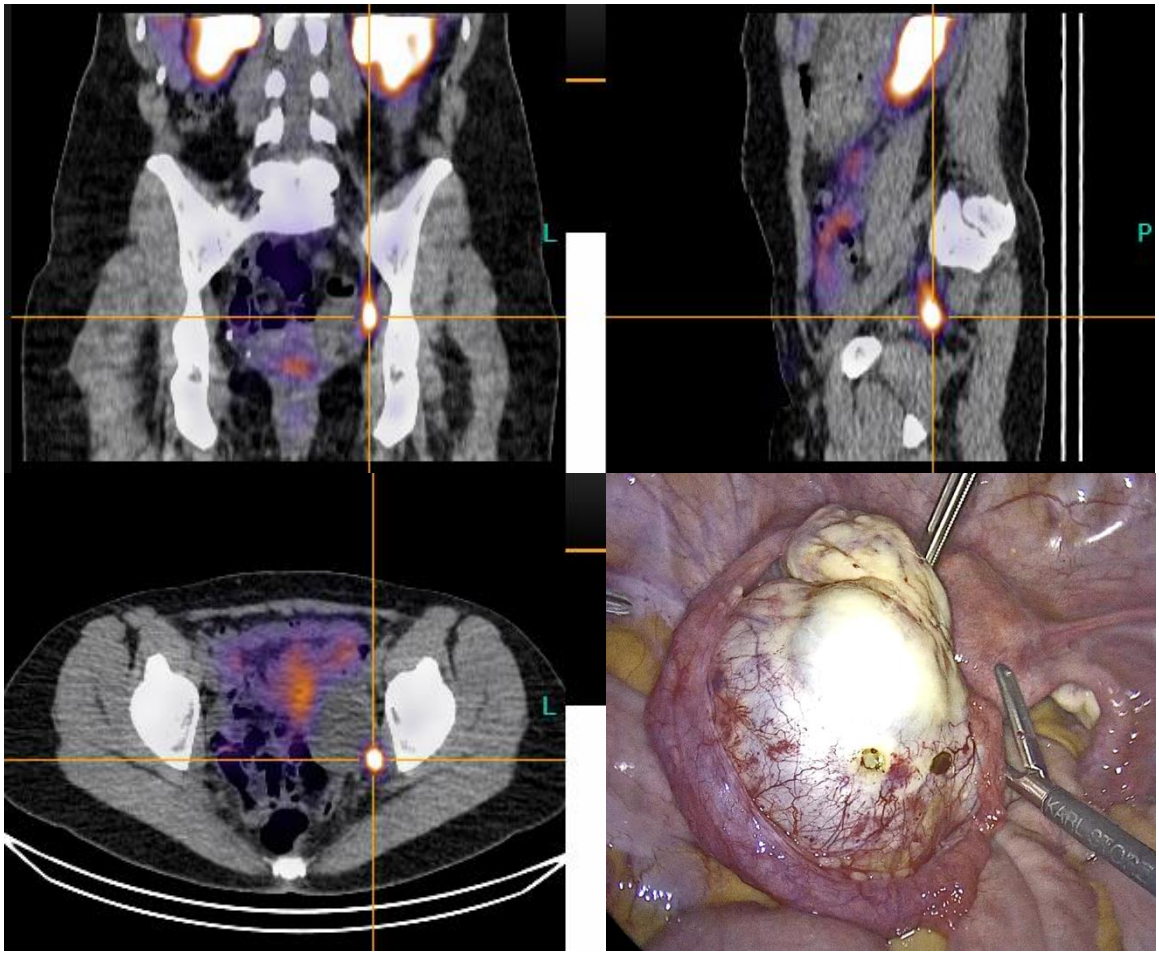


Figure 18: ^{99m}Tc-maraciclatide uptake within a patient with endosalpingiosis and a para-ovarian mucinous cystadenoma

Uterine activity was visualised within 10/18 participants (assessment of one uterus was not possible due to CT scatter obscuring the visualisation). Assessing the expression pattern within the uterus revealed two distinct patterns: diffuse (n=3) and focal (n=7) (**Figure 19**). 4/7 participants with focal uptake showed localised activity around their IUD (n=3) or IUS (n=1). After removing those with focal uptake due to the coil, I considered other pathologies that may be affecting uterine uptake. Eight participants without a coil had an imaging plus surgical (visual appearance or histology) confirmed or excluded diagnosis of adenomyosis. ^{99m}Tc-maraciclatide uptake agreed with the presence (n=4) or exclusion (n=3) of adenomyosis in 7/8 cases. Meaning in all cases where adenomyosis was confirmed on surgery and imaging, the uterus displayed activity (n=2 diffuse and n=2

focal), and the four participants where adenomyosis had been excluded, one participant displayed focal uterine uptake.

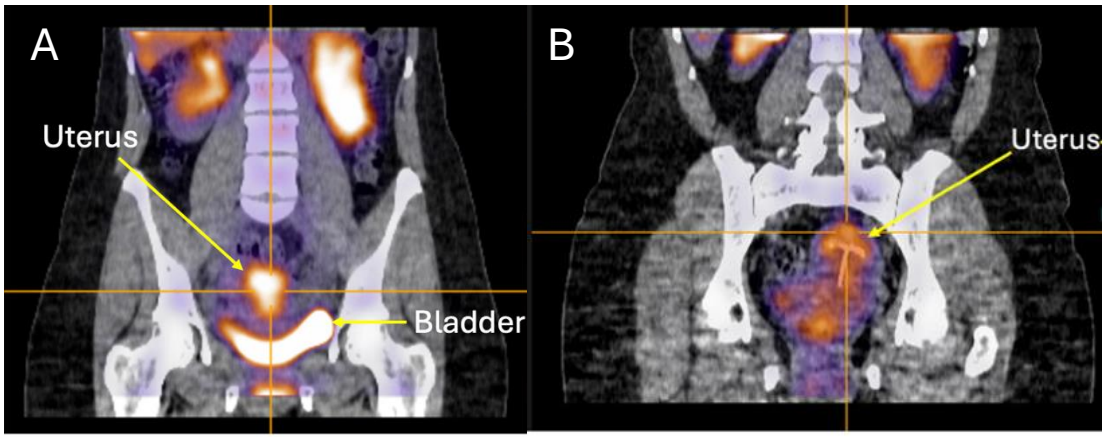


Figure 19: Uterine ^{99m}Tc-maraciclatide uptake.

A) Diffuse uptake pattern of ^{99m}Tc-maraciclatide B) Focal uptake pattern surrounding a Mirena coil.

End of DETECT study participant survey

Completed surveys were retrieved from 13/20 participants. The scan's acceptability as a diagnostic test (mean 97.4, SD 5.7 (VAS 0-100), n=13) and disease monitoring tool (VAS mean 97.7, SD 7.1, n=13) was high. The open questions were assessed to look for reasons for the scores. Many found the SPECT-CT scan to be a similar or better experience than MRI, but they also commented on the downside of radiation, especially if multiple scans were needed. Nevertheless, SPECT-CT was rated highly compared to other diagnostic methods in **Figure 20.**

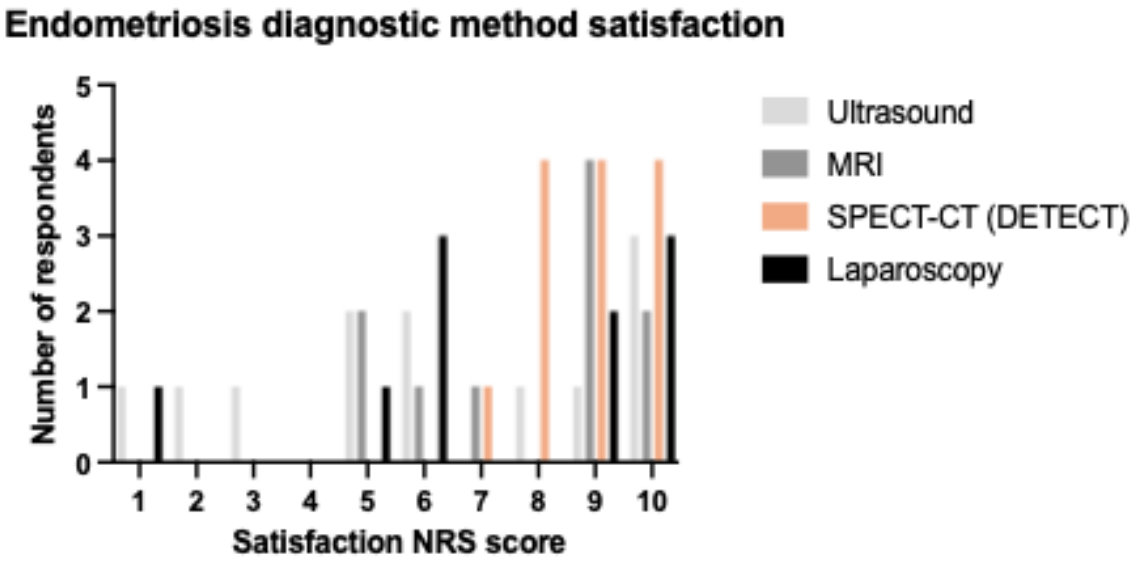


Figure 20: Satisfaction of various methods of investigation experienced by included DETECT participants, n=13, Numerical Rating Score (NRS) 0-10.

One participant reported abdominal pain, diarrhoea and nausea within the first 3 hours following injection of the marker. The patient was followed up until the symptoms resolved within 24 hours. This ^{99m}Tc-maraciclatide attributed adverse event was also experienced by one participant within the phase 1 study of ^{99m}Tc-maraciclatide participants on healthy volunteers.[112] Another participant reported arm pain following the scan. This was attributed to the position in which the arms were held during repeated scans, not to ^{99m}Tc-maraciclatide itself. No other adverse events related to the study were noted.

IHC analysis

49 samples of eutopic and ectopic endometrium and negative peritoneum were sent for IHC staining with αvβ3, αvβ5, CD31 and VEGF (**Figure 21**).

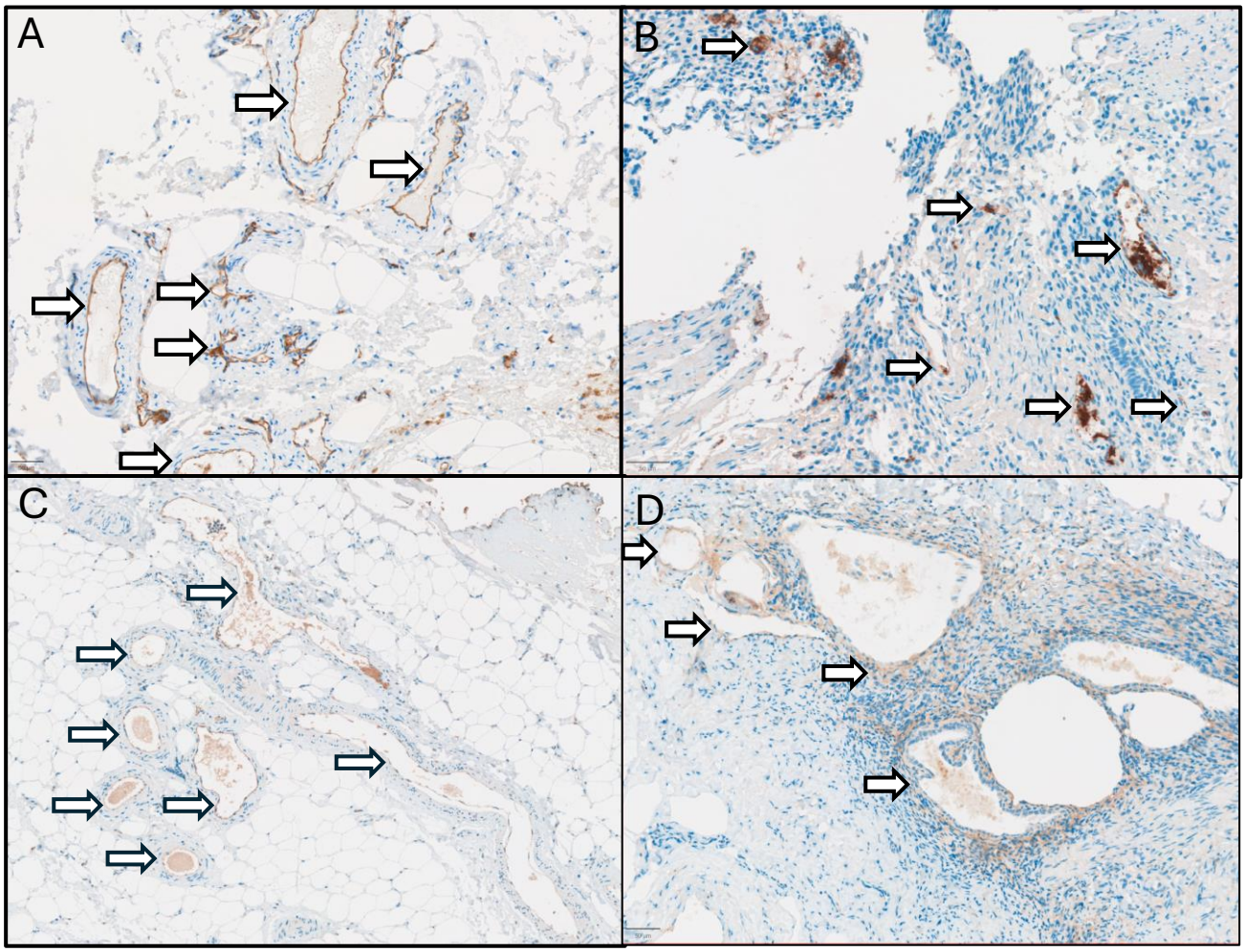


Figure 21: Tissue sample staining with angiogenic markers.

A) Endothelial uptake of CD31 was visualised within a 1-3cm yellow/white SPE lesion within the pelvic side wall and graded as 3+ (intensity scale 1-3). This sample was used to determine the number of blood vessels present within the sample to determine the proportion of blood vessels stained with αvβ3 for the blood vessel immunoreactivity score (IRS). It did not demonstrate ^{99m}Tc-maraciclatide uptake. B) αvβ3 staining within the same lesion as A), endothelial uptake was also visualised and graded as 3+ intensity and P2 proportion of staining (15-50% of blood vessels). This provided a blood vessel IRS score of 6. C) Endothelial VEGF uptake was seen within a blue/black SPE lesion >3cm in size. It did not demonstrate ^{99m}Tc-maraciclatide uptake. D) Endothelial uptake of αvβ5 was seen within a brown 1-3cm DE lesion within the pouch of Douglas, which demonstrated ^{99m}Tc-maraciclatide uptake on SPECT-CT.

Table 17: IHC tissue staining with angiogenic markers

Sample type	N	CD31	αvβ3	αvβ5	VEGF	αvβ3 & VEGF
DE	11	11 (100%)	8 (73%)	5 (45%)	9 (82%)	7 (64%)
OE	2	2 (100%)	2 (100%)	0 (0%)	2 (100%)	2 (100%)
SPE	13	13 (100%)	8 (62%)	2 (15%)	11 (85%)	8 (62%)
Negative peritoneum	3	3 (100%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)
Thoracic	4	4 (100%)	3 (75%)	1 (25%)	1 (25%)	1 (25%)
Endometrium	13	13 (100%)	10 (77%)	1 (8%)	11 (85%)	9 (69%)
Negative endometrium	2	2 (100%)	1 (50%)	0 (0%)	1 (50%)	1 (50%)
Salpingosis	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)

The table describes the proportion of samples (n=49) that were positively stained for various angiogenic markers. Negative samples were obtained from the two participants, where endometriosis was not seen on surgery, but were taken as the surgeon was uncertain. Following the negative histopathology results, the surgeon concluded that the patient was negative for endometriosis.

The table demonstrated that all tissue samples (positive or negative for endometriosis), except for the salpingosis sample, were positive for CD31, a known endothelial marker. αvβ3 positivity was frequent in pelvic (69%) and thoracic endometriosis (75%), but absent in peritoneal tissues from a participant without endometriosis, which was used as a negative control. In contrast, αvβ5 positivity was generally uncommon but highest in DE (45%) compared to endometrium (8%), SPE (15%), OE (0%), and thoracic endometriosis (25%). VEGF was widely expressed in endometrium (80%) and pelvic lesions (85%) but low in thoracic disease (25%). Co-expression of αvβ3 with VEGF mirrored these patterns, being common in pelvic endometriosis (65%) but less so in thoracic endometriosis (25%).

Table 18: In vivo and in vitro expression of αvβ3 in ectopic endometrial lesions

Maraciclatide uptake	αvβ3 positive	αvβ3 negative
Positive	8	3
Negative	13	8

αvβ3 IHC staining and 99mTc-maraciclatide uptake in ectopic endometrial lesions (n = 30) were compared. Two lesions within the uterovescular fold were excluded as maraciclatide uptake could not be assessed.

Table 19: In vivo and in vitro expression of αvβ3 in ectopic endometrial lesions and eutopic endometrial lesions

Maraciclatide uptake	αvβ3 positive	αvβ3 negative
Positive	5	3
Negative	5	1

αvβ3 IHC staining and 99mTc-maraciclatide uptake in eutopic endometrial lesions (n = 14) were compared. One pair was excluded as CT scatter obstructed interpretation of the uterus for 99mTc-maraciclatide uptake.

In the current data set, there does not appear to be an association between ^{99m}Tc-maraciclatide uptake and αvβ3 positive staining of ectopic (Fisher's exact test of **Table 18,** p = 0.70) or eutopic endometrium (Fisher's exact test, **Table 19**, p = 0.58). As such, ^{99m}Tc-maraciclatide uptake is observed in lesions and endometrium that are not IHC positive for αvβ3. Additionally, endometrium and lesions can show no uptake of ^{99m}Tc-maraciclatide despite being positive for αvβ3 on IHC.

Table 20: Endothelial αvβ3 Immunoreactivity scores (IRS) of various sample types

Sample type	Number of samples	Mean (SD) Vessel IRS Score
SPE	13	1.7 (2.2)
DE	11	1.1 (1.5)
OE	2	2.5 (2.1)
Negative peritoneum	3	0.0 (0.0)
Endometriosis endometrium	13	0.6 (1.2)
Negative endometrium	2	2.0 (2.8)
Thoracic endometriosis	4	2.0 (1.4)
Salpingosis	1	0.0 (0.0)
Active lesions	6	0.33 (0.5)
Inactive lesions	13	1.8 (2.0)

The Immunoreactivity score (IRS) was calculated by visual inspection of various tissue samples (n=49). Tissues were then grouped into active and inactive based on the WERF EPHect SSF where lesion colours were recorded. Active lesions included any clear, red, or clear/red lesions mixed with other colours. Inactive lesions were any other colour lesions (e.g. blue, black, white, brown, yellow or mixed lesions without a clear or red component).

Endothelial αvβ3 IRS scores (**Table 20**) were generally low across groups, with differences by subtype. OE showed the highest mean signal (2.5, SD 2.1, n=2), followed by SPE (1.7, SD 2.2, n=13) and DE (1.2, SD 1.4, n=11). These regions of ectopic endometriosis had a higher score than the eutopic endometrium from women with endometriosis (0.6, SD 1.2, n=13). The two participants who were negative for endometriosis, in fact, had a higher eutopic endometrium mean vessel IRS Score (2.0, SD 2.8, n=2). Lesions determined as 'active' or 'inactive' demonstrated an unexpected pattern with higher vessel IRS scores in 'inactive' lesions (1.94, SD 2.01, n=13) than active lesions (0.33, SD 0.52, n=6). However, as demonstrated in the IRS Scores by histological compartment (**Appendix 4**), strong staining is also localised to perivascular smooth muscle/pericytes and immune cells in addition to the endothelium, which may also contribute to the lesions' angiogenic activity.

Discussion

Diagnostic survey

Health framework gaps that exist prior to seeking medical attention

87% of respondents reported experiencing a delay in their diagnosis; however, the cause of the delay is multifactorial and results from various gaps in existing healthcare frameworks. For example, 62% of respondent reported a delay in seeking medical advice for their symptoms. A thematic analysis found various forms of normalisation and menstrual health stigmatisation to be contributors to respondents delaying them in seeking help, which are recognised contributors to endometriosis diagnostic delays.[75,129,130] The concerns with normalisation can be addressed by increasing efforts to raise societal awareness of endometriosis.

When exploring who was the first to suspect that respondents had endometriosis, only 41% reported that a health professional, such as a doctor, had first suspected their endometriosis, again supporting the importance of rising societal awareness, as endometriosis is often first considered out of the healthcare setting. This is reflective of a survey[131] conducted in Israel, where 42% of respondents stated that endometriosis was first suspected by health professionals, while the remaining respondents suspected they might have endometriosis through media forms, association's actions, independent online research, or conversations with peers. However, as the amount of information on endometriosis is rising, so is the amount of misinformation[132] and there needs to be efforts to develop robust health information systems to educate and support those with endometriosis and those around them. This is particularly important for adolescents, as

endometriosis symptoms often begin at an early age, and it is important that those around them, those that they feel comfortable speaking with, are well informed on what is normal and what is abnormal when it comes to menstrual symptoms. This support may come from family and friends, but schools can also serve as an ideal setting to provide menstrual education and support.

Nevertheless, 42% is still a large number of respondents whose endometriosis was first suspected by healthcare professionals. Thus, it is crucial that when a patient presents to a healthcare system, they are met by knowledgeable and well-trained healthcare staff who can identify the signs and symptoms of endometriosis and don't dismiss their symptoms as normal. Global initiatives to raise societal and healthcare awareness of endometriosis and the development of health information infrastructures are explored further within **Chapter 4**.

The survey found that when respondents first sought medical advice, their highest priority was to receive treatment for their symptoms (64.8%), as opposed to obtaining a diagnosis (30.1%). This raises the question of whether we understand the most important metric for patients when we are measuring healthcare delays. Should we instead be assessing the time from symptom onset to the first therapeutic intervention? Many patients begin treatment on a clinical (working) diagnosis of endometriosis or on the suspicion of a gynaecological disorder. From clinical experience GP's can be understandably hesitant in labelling someone with endometriosis until they have been seen by a gynaecologist. However, there are extensive delays in seeing a gynaecologist. NICE guidelines[56] recommend GPs to begin medical management whilst arranging investigations and

referrals in parallel. Therefore, measuring the delay to treatment may represent a more accurate measure of the delays experienced. Nevertheless, as discussed later, it is crucial for patients to understand why they have the symptoms they do and obtaining a diagnosis (whether working, diagnostic, or surgical) is a key outcome that patients expect when they seek medical attention.

Healthcare framework gaps that exist after medical attention is sought

Even after an individual suspects endometriosis, a delay occurs for many before endometriosis is considered or investigated. The survey found that before referral to a gynaecologist, 32% had presented to their GP at least ten times, and 28% had presented to A&E at least three times. This supports the findings of the 2023 Endometriosis UK Diagnostic survey, which found that 47% of respondents visited their GP 10 or more times before endometriosis was even considered as a possible cause of their symptoms. A limitation of this comparison is that the same respondents may have answered both surveys, as they were both promoted by Endometriosis UK. However, similar findings have been reported in other countries, such as Sweden, where 24% of the 1,000 women questioned in a national survey had visited general practitioners more than 10 times before being referred to a gynaecologist.[133]

US was reported as the most common investigation undertaken to investigate endometriosis (86%), with an average of 3.3 (3.0 SD) per respondent. Moreover, only 24% of respondents with surgically confirmed endometriosis stated that the US had correctly identified the disease.

Although the survey did not explore the reasons for the repeated scans, whether or not they were advanced scans (as respondents are not likely to know), and some may have been performed after a diagnosis was made, it is well recognised that US is extremely operator-dependent and often requires repeating by more specialised clinicians. For example, a Canadian study found the sensitivity of routine US in detecting endometriosis to be 25% (10/40), compared to 78% (31/40) when the scan was repeated by a tertiary centre specialising in the diagnosis and management of endometriosis ($P < 0.01$)[134]. Unfortunately, the survey did not distinguish between endometriosis detection by routine or advanced imaging, but it begins to explain the low satisfaction with US (mean 34 (29 SD) using a 0-100 VAS) and the responses that were given whilst assessing the reasons behind the low satisfaction, especially within the theme of diagnostic gatekeeping and diagnostic limitations.

Fortunately, satisfaction with MRI was higher than with US (Mean VAS 0-100: MRI 57 vs. US 34). Surprisingly, laparoscopy had the highest satisfaction (68 mean VAS) despite being the most invasive method. The responses under the theme of 'conclusive diagnosis' described the 'fight' many patients had been through for their symptoms to be taken seriously and the 'relief' a confirmed diagnosis had provided them. These results highlight the gaps and limitations of non-invasive diagnostics in providing patients with a confirmed diagnosis prior to surgery, but also concerningly, the societal environment where patients feel they need to prove themselves to be taken seriously. Again, this highlights the importance of improving non-invasive diagnostics, as well as enhancing society's (including health professionals') understanding of endometriosis and the

limitations we face in diagnosing it. Unfortunately, with current methods, a negative scan does not exclude endometriosis.

Can novel diagnostic tests address gaps in the diagnostic framework?

The acceptability of diagnostic tests is influenced by several factors, including the patient's attitude towards the test, the perceived burden, previous experiences, and the perceived effectiveness.[135] These factors can likely explain the rating of the novel diagnostic test acceptability (**Table 7**). Although open answers were not requested, it was not surprising that a blood test was rated the highest due to its low perceived burden and its status as a diagnostic method ingrained into most diagnostic pathways for other diseases, such as diabetes or infections. Interestingly, the least physically invasive test, 'symptom analysis', had the lowest acceptability. As already discussed, many respondents felt relieved to have the diagnosis confirmed, as it proved "I wasn't crazy." Perhaps a diagnosis without 'proof' wouldn't be satisfactory enough for the individual personally and may risk not being socially accepted, for example, when seeking support from the workplace. An international retrospective cohort study found higher scores in feelings of control and lower feelings of powerlessness in patients who received a diagnosis via imaging (ultrasound/MRI; n = 120) compared to those who had received a clinical diagnosis (n = 121)($p = 0.049$). Although this didn't reach clinical significance when covariates were controlled for ($p = 0.054$), the trend towards significance (which may be more profound in larger patient groups, demonstrates the importance of appreciating the effect the type of diagnosis has on the person and the potential social implications.

Importantly for the DETECT study, which will be discussed shortly, a CT scan was highly acceptable (mean VAS 0-100, 81, SD 22, n = 959). Again, this is likely due to the perceived knowledge that CT is a well-established method of diagnosing other structural diseases and that MRI is already integrated within the diagnostic pathway. The end-of-study survey presented on page 96 further explored patients' perspectives on having a CT to investigate endometriosis.

The impact of a diagnostic delay on life choices

There are numerous social and economic implications associated with a diagnostic delay; for instance, individuals with longer diagnostic delays incur higher healthcare costs due to increased rates of emergency hospital visits and inpatient stays.[104] Moreover, for some, a diagnostic delay can lead to increased pain and disease severity.[136] The survey found that another important reason why efforts should be increased to reduce the diagnostic delay is that 72% felt that an earlier diagnosis would have changed their life choices. These choices included decisions that would allow them to cope with endometriosis better, like choosing a different career path or taking better care of themselves, with the knowledge that a disease was responsible for their symptoms. A cohort study questionnaire on 100 participants with chronic pelvic pain due to causes such as endometriosis found that 68% had identified triggers for their pain flares.[137] An earlier diagnosis could help those with endometriosis identify and potentially avoid their flare triggers sooner. Other choices included addressing the consequences of endometriosis, such as discussing and considering their fertility options sooner.

In summary, the survey has crucially demonstrated that there are inherent concerns with the existing diagnostic pathway and the methods used to diagnose endometriosis. Moreover, a diagnostic delay continues to significantly affect those with endometriosis, beyond just increased healthcare and economic factors, but also the way those with endometriosis hold autonomy over their lives and their decisions in life. Therefore, it is paramount that the diagnostic pathway improves, either by enhancing existing non-invasive techniques or by developing novel ones. As patient satisfaction is a crucial marker of service provision, the results demonstrate the need for novel tests that may enhance satisfaction scores and improve the patient experience.[138]

DETECT study

Diagnostic accuracy of 99mTc-maraciclatide

^{99m}Tc-maraciclatide demonstrated a high diagnostic performance in detecting endometriosis at the participant level, in terms of agreement with surgery and diagnostic accuracy. The sensitivity and specificity of ^{99m}Tc-maraciclatide (Se 82% and Sp 100%) exceeded the parameters set by the 2016 Cochrane review[64] for a SpPin triage (Se ≥ 50% **and** Sp ≥ 95%). However, the requirements for a SnNout triage test (Se ≥ 95% **and** Sp ≥ 50%) or as a replacement to laparoscopy (Se ≥ 94% **and** Sp ≥ 79%) were not met. Although caution is needed when interpreting these results, given the study's small sample size, particularly as only two participants were negative for endometriosis, these findings are important as the Cochrane review found that neither US nor MRI met the requirements for SpPin or SnNout triage, nor could they serve as a surgery replacement

test, when all endometriosis subtypes were considered. If these results could be confirmed in a larger population with a larger inclusion of negative participants, it could demonstrate a place for ^{99m}Tc-maraciclatide within the current diagnostic pathway.

Although the study found that ^{99m}Tc-maraciclatide cannot currently distinguish between subtypes, it has demonstrated a clear benefit in the detection of SPE (se 75%), which is currently a crucial diagnostic challenge. An angiogenic marker is an exciting target for SPE, given that SPE has been repeatedly shown to express high levels of angiogenic markers and higher levels of angiogenic markers in SPE than in other endometriosis subtypes. Yerlikaya et al. found that at an MRNA level, compared to DE and OE, SPE lesions express significantly higher levels of the angiogenic markers VEGFR2, HGF, PDGFB, NRP1, and EPHB4. This study was supported by the findings of Braza-Boïls, who found significantly higher levels of VEGF-A MRNA in SPE lesions than endometrioma samples. Although, this finding was not supported by the αvβ3 IHC vessel IRS conducted within this thesis, possible reasons for this will be discussed shortly.

A sensitivity of 75% at a participant-level represents a higher diagnostic accuracy than other reported advances in non-invasive imaging of SPE. TVUS has seen advances in detecting SPE within the POD. For instance, an approach called sonoPODography passed the SpPin criteria for detecting SPE in the POD (Se 64% and 100%).[139] Moreover, using advanced TVUS scanning techniques, a specialist centre reported a 51 % sensitivity and 94% specificity.[68] The benefit of TVUS over SPECT-CT is the accessibility, lower cost, no radiation, being able to distinguish between subtypes, and to get better details on sizing and affected surrounding structures, such as an obliterated POD. However, there is likely

a place for ^{99m}Tc-maraciclatide in detecting imaging-negative SPE, especially in regions other than the POD as SPE was not detected within the current study set on prior imaging. Moreover, the region-level analysis demonstrated that ^{99m}Tc-maraciclatide appears to be detecting SPE based on its angiogenic status, as angiogenically 'active' lesions (clear, red or mixed with clear or red) demonstrated a 7.62× higher odds of being detected than 'inactive' lesions. All of these 'active' lesions were classified as SPE. However, as these results were derived from a post-hoc analysis of grouping lesions, this hypothesis will need to be confirmed in a larger dataset.

The usefulness of ^{99m}Tc-maraciclatide in detecting other subtypes is less clear. From the data obtained from this study, it is uncertain whether ^{99m}Tc-maraciclatide can truly detect endometriomas. In fact, not detecting endometriomas was expected, as endometriomas are believed to be relatively avascular structures surrounded by a fibrotic cortical wall. The 2cm endometrioma detected was surrounded by SPE (which has been proven to demonstrate uptake); however, the 9cm and 3cm endometrioma in two other participants were missed, despite them both being positive for αvβ3 on IHC. Brosens' pathophysiology model[140] suggests that an ovarian endometrioma forms when endometriotic implants on the ovarian surface create an inflammatory and pro-angiogenic response, which can be confirmed by visible neoangiogenesis at laparoscopy[141]. This leads to the formation of adhesions, which cause the ovarian cortex to invaginate, resulting in the production of a pseudocyst. It is possible that ^{99m}Tc-maraciclatide captured the endometrioma undergoing this inflammatory process. A US Doppler study[142] found an association between higher vascularisation and dense pelvic adhesions, again suggesting the uptake seen within the endometrioma on ^{99m}Tc-

maraciclatide represents a higher inflammatory load. However, it is also likely that the 2cm endometrioma would have been better perfused than the 9cm endometrioma, as endometrioma volume is positively related to US Doppler RI and PI ($r = 0.382$ and 0.335; both $p < 0.05$)[143], meaning smaller cysts have lower vascular resistance and therefore better access to intravascular ^{99m}Tc-maraciclatide. Although by that logic, one would expect the 3cm endometrioma to show activity too. Unfortunately, the sample size is too small to draw any conclusions, and future larger studies will need to be powered to explore this further. However, as all endometriomas were previously identified on imaging, it is unlikely that ^{99m}Tc-maraciclatide would enhance the current diagnostic pathway for detecting endometriomas.

Neovascularisation is a key mechanism in DE progression and microvessel density (MVD) is thought to be higher in DE than in SPE.[144] ^{99m}Tc-maraciclatide detected DE in five out of eight participants with DE (although one participant also had concurrent SPE within the region). This provided an Se of 62%, which again exceeded the triage test Se requirements, however, again the sample size is small. At a region-level, only 4/17 DE ROIs were detected (mixed subtype ROIs were excluded), and all were classified as 'inactive' by lesion colour. As the detection cannot be explained by lesion colour, it is possible that there was a regional difference in angiogenic activity. For example, higher levels of the angiogenic marker VEGF are typically found in DE lesions in the bowel compared to those in the bladder.[144] Nevertheless, within this study group, ^{99m}Tc-maraciclatide did provide more diagnostic information on DE than prior imaging. However, all participants with DE had prior imaging (US n=6 and MRI n=2), only one participant's DE, a large fibrotic rectovaginal nodule that was palpable on vaginal exam,

was detected on prior MRI. The DE lesion on the upper sigmoid in **Figure 16** was not anticipated and therefore was not excised, however prior knowledge of its presences could have led to discussions with bowel surgeons. The participant did not have a prior MRI, so it is unclear whether this lesion would also have been seen on MRI. Although the sample size is too small to draw clinically meaningful conclusions about the diagnostic accuracy of ^{99m}Tc-maraciclatide in detecting DE, the study suggests that 99mTc-maraciclatide may have a complementary role in detecting US and MRI-negative DE.

Association analysis of lesion characteristics and hormonal variables

The association analysis was conducted to assess whether key variables would influence the detection rate; however, the sample size was small with many confounders which could not be controlled for due to the small sample size for example the influence of the menstrual cycle, so no conclusions could be drawn but the results may help in developing hypotheses for the later phase 3 study.

Firstly, although an association was found between anatomical region and detection, the sample size is too small to draw meaningful conclusions. For instance, it was unexpected that the right pelvic side wall showed significantly higher levels of uptake than expected (ASR=+2.18), and there was non-significant but lower-than-expected activity in the left pelvic side wall (ASR=−1.69). This is likely due to the small sample size and can't be easily explained due to anatomical or physiological reasons, and in fact, endometriosis is actually believed to show a left asymmetry with most lesions (SPE, DE or OE) occurring on the left. This phenomenon occurs as the peritoneal fluid moves clockwise from the wider right paracolic gutter to the right subphrenic space, whilst leftward flow is limited

by the phrenicocolic/falciform ligaments. Meanwhile, the sigmoid colon slows clearance on the left hemipelvis, resulting in fluid stasis and a left-sided predominance of endometriosis.[145]

Although it was not significant, a lower-than-expected rate of detection within the UVF (ASR = -1.5) was expected and will likely be confirmed in larger studies. The phase 1 biodistribution and dosimetry study[112] that revealed that the urinary tract served as the primary excretory pathway for ^{99m}Tc-maraciclatide and thus will obscure lesions in regions such as the UVF. In fact, 8/57 ROIs within the study were masked due to the urinary tract, which presents a major limitation of ^{99m}Tc-maraciclatide, as the detection of urinary tract endometriosis is currently limited, and it is known to affect between 0.3% and 12% of those with endometriosis, with bladder endometriosis being the most common site[146]. However, 90% of those with bladder endometriosis also have at least one other site affected, providing an opportunity for endometriosis detection using ^{99m}Tc-maraciclatide.[147]

Bladder accumulation is a common concern with nuclear imaging markers, for example, in prostate scans, and advances in imaging software are hoping to mitigate this issue. The imaging protocol, based upon the European Association of Nuclear Medicine's (EANM) CT imaging guidelines[148] attempted to reduce the effect of the urinary tract activity by asking participants to pre-hydrate to dilute the marker and to urinate just before the scan to empty the bladder. Moreover, participants were scanned caudally to cranially to reduce bladder filling artefacts. Future studies on the detection of endometriosis using ^{99m}Tc-maraciclatide should consider the next step within EANM's guidelines, which

include offering diuretics or a urinary catheter to reduce bladder activity obstructing visualisation of surrounding lesions.

Another unexpected regional finding was that despite each participant having a mean of 3.35 (SD 2.55, 2.04 to 4.66 95% CI) affected ROIs, ^{99m}Tc-maraciclatide only demonstrated activity in more than one region in one participant. This is another reason methods to reduce bladder signal should be considered within the next study as high physiological activity especially by the bladder is known to result in smaller less active lesions being missed within the pelvis.[149]

The lack of association between lesion size and detection was also expected due to the small sample but also, given the limitations in the data collection method. Firstly, the lesions weren't accurately measured, as we are using the surgeon's best visual guess of the lesion and distinguishing between 1 or 2cm lesions is likely to be very subjective and possibly inaccurate. Moreover, although the WERF EPHect questionnaire was completed as soon as possible after surgery, it is likely that the surgeon may not remember the exact sizing of the lesion, especially as a few millimetres difference can place the lesions into different categories. In fact, given the recognised ambiguity over measuring endometriosis lesions, the AAGL consensus meeting intentionally 'ignored' sizing within their endometriosis staging system.[150] However, in the context of this study, sizing is an important variable. In future studies, intraoperative measuring tools could be used, and the measurements should be recorded on the WERF EPHect form during surgery.

The association between lesion colour as a marker of lesion angiogenic activity and detection supported the hypothesis that as an angiogenic marker ^{99m}Tc-maraciclatide is detecting angiogenic lesions. Developing a marker for angiogenically active disease would change the way we think, classify, investigate and treat endometriosis. However, the implications of detecting angiogenic disease is still unknown. What is known is that it could support the detection of disease in younger people as they have been found to have higher levels of red and clear lesions. Moreover, it may be beneficial in monitoring the effects of treatment and may support the development of novel angiogenic therapies. However, it is not yet clear whether angiogenic lesions present or affect a participant differently to inactive and thereby missing inactive lesions may still hold consequence. This study has provided new insights into clear lesions, which are deemed atypical subtle lesions, and were not traditionally included in endometriosis definitions, as they were believed to be cleared by the immune system. Clear lesions are thought to represent a very early stage of endometriosis, the stage before neoangiogenesis turns the lesion red. However, its detection with ^{99m}Tc-maraciclatide suggests these regions, despite not being red, are still highly angiogenically active which is supported by a study of transplantation of human endometrial tissue into a chick chorioallantoic membrane model that demonstrated early implantation (within 3-4 days) relies upon early angiogenic responses.[151,152]

If ^{99m}Tc-maraciclatide is truly detecting active, angiogenic tissue, then detection within white-fibrotic lesions should not occur. However, activity was seen in two 1-3 cm white lesions of the right ovarian fossa in two separate participants. Unfortunately, the video for one participant was incorrectly saved during surgery. However, the other lesion appears

to be surrounded by inflammatory processes. It is possible that ^{99m}Tc-maraciclatide activity in this ROI can be explained by the angiogenesis marker, detecting the surrounding inflammation. More research is needed to understand the significance and composition of coloured lesions. Future studies investigating ^{99m}Tc-maraciclatide in endometriosis will need to develop a standardised method for classifying lesion colour so the significance of lesion colour and detection can be confirmed.

Again, due to the sample size no conclusions could be drawn on the influence of remaining factors investigated such as menstrual cycle and exogenous hormones. However, it is positive that the scan detect endometriosis despite the use of exogenous hormones potentially allowing patients to continue on the treatments that are controlling their symptoms. These association studies has allowed for the generation of hypotheses and to assess how the methodology of phase 3 study with a larger sample to test these hypotheses can be optimsed.

Exploratory Ancillary Signals

Based on the phase 1 study[112], physiological activity in the bladder and bowel were expected. Three participants were found to have non-physiological activity within the bowel. One was attributed to endometriosis, but two were found to have activity was seen beyond the bowel wall, which cannot be assessed laparoscopically. Both presented as a focal lesions and was present at both the 10minute and 20minute timepoints reducing their chances of being an artefact or due to physiological filling. On reviewing the WERF EPHect baseline questionnaire, one participant reported pain opening bowels

as one of the symptoms leading to her diagnostic laparoscopy. Furthermore, the participant reported constipation and pain getting worse after opening bowels 'most of the time' during their period over the past 3 months. Moreover, 'sometimes' the pain improved after a bowel movement and 'sometimes' had more frequent bowel movements. The other participant reported bowel symptoms (including dyschezia, diarrhoea and constipation related to her periods) as the main reason for the diagnostic laparoscopy. She also reported being investigated by a gastroenterologist due to her symptoms, but no diagnosis had been given. Various studies have found dyschezia to be an important indicator of bowel DE.[153,154] Unfortunately, the SPECT-CT ROIs was identified after surgery was undertaken, so it is not possible to confirm whether abnormalities within this region were seen during surgery, as the full length of the bowel is not reviewed. It is also possible that the region was assessed and no disease was seen. However, histological studies of regions that appear 'normal' on visual inspection can contain endometriosis, known as occult microscopic endometriosis (OME).[155,156] It is possible that the colon ROI was demonstrating angiogenesis within a region of OME. ^{99m}Tc-maraciclatide has proved to be able to identify lesions smaller than 1cm, likely due to ^{99m}Tc-maraciclatide detecting the area of surrounding angiogenesis (rather than the lesion), which is larger than the lesion itself. Although detecting OME may be beneficial for providing patients with a more accurate diagnosis, the significance of identifying and removing bowel OME is uncertain.[157]

Physiological uterine uptake was seen within the Phase 1 study but 4.8x lower than the bladder wall. Thus, it was possible that the uterus would be visualised in this study but it was expected to be consistent throughout participants. FGD-CT studies have shown that

uptake within the uterus in pre-menopausal women should be expected and physiological uterine uptake appears to be diffuse and uniform in pattern whereas uptake due to disease such as cancer appears to be focal. Moreover, that diffuse uptake is also identified and has been found to be menstrual cycle dependent, with higher rates in the menstrual and ovulatory phase than in the proliferative and secretory.[149] Within the DETECT study, although there was diffuse uptake seen in the one participant on the menstrual phase (day 3) of her cycle, diffuse uptake was also seen in a participant within the secretory phase (day 24) and in one participant where the phase couldn't be determined as she was using the POP. Previous histological studies[42] on the endometrial vasculature found higher difference in blood vessels stained for αvβ3 in endometriosis patients compared to control during the secretory phase than proliferative suggesting there may be an element of cycle variability to diffuse uptake however our study's sample size is likely too small to detect any differences. Moreover, the IHC studies conducted within this study found the endometrium of those without endometriosis (N=2) to have a higher αvβ3 IRS (2.0) that then endometrium of those with endometriosis (IRS 0.6, N=13). However, the sample size is too small to draw any meaningful conclusions and the cycle of the negative endometrium could not be determined due to exogenous hormone use.

Focal uptake was seen in all those with an intrauterine device or system (IUD/IUS). Three participants had a Mirena coil (LNG-IUS), and one had a copper coil (IUD) in situ. The SPECT-CT images demonstrated focal activity in the uterus of all four uteri, localised around the IUS/IUD, specifically around the arms of the coils, where levonorgestrel or copper ions are released, respectively. Multiple studies have demonstrated that LNG within IUDs, in addition to thickening cervical mucus thickening and preventing

endometrial ripening, LNG induces a localised inflammatory response. Histologic and immunologic studies have demonstrated endometrial leukocyte infiltration, cytokine and immune changes, reflective of this inflammatory response, known as a foreign-body reaction.[158–160] Moreover, transcriptomic profiling of endometrial samples from women with LNG-IUDs identified 2509 differentially expressed genes, predominantly mapped to immune and inflammatory pathways.[161] This foreign body reaction has also been visualised in vivo on PET imaging, where focal uptake of fluorodeoxyglucose was seen in glucose-avid inflammatory endometrial cells surrounding a copper IUD.[162] This argues against the transcriptomic profiling of endometrial samples of patients with a copper IUD, where no significant differences in gene expression were observed compared to controls. The authors concluded that inflammatory signals and 'foreign body reaction' were only driven by progestin. On the contrary, the DETECT study found similar focal activity patterns in the copper IUD and LNG IUS, demonstrating *in vivo* that both the copper IUDs and LNG-IUS can induce a localised inflammatory response. This result conflicts with the transcriptomic study, which could be due to the authors analysing the effect in the global endometrial transcriptome, whereas it appears that changes are likely to be focal, localised to the endometrial tissue surrounding the IUD/IUS. Visualisation of this focal reaction in vivo within LNG-IUS, to my knowledge, is the first time the foreign body reaction has been seen in vivo in response to an LNG-IUS. Also, it strengthens the *in vivo* evidence of the copper coil as ^{99m}Tc-maraciclatide is a more specific marker for inflammation.

Finally, a region of incidental uptake was within a participant with endosalpingosis. Endosalpingiosis is one of four benign müllerian diseases (adenomyosis, endometriosis,

endosalpingiosis, and endocervicosis). The müllerianosis theory suggests that misplaced embryonic müllerian tissue leads to the development of müllerian diseases, and whilst each may occur independently, they often occur together.[163] During laparoscopy, endosalpingosis is often mistaken for endometriosis unless very visually obvious (as in this case) with the presence of multiple white to yellow, translucent to opaque, punctate, fluid-filled cystic lesions.[164] A report of 64 peritoneal samples thought to be endometriosis, where 31% were in fact only endosalpingosis and 11% were a combination of both endosalpingosis and endometriosis.[164] Endosalpingosis is not believed to be associated with inflammation or neovascularisation.[165] With the exception of when it is associated with other inflammatory conditions, such as salpingitis. For example, a case study discussed how endosalpingosis was mistaken for malignancy on a PET scan due to high FDG uptake, which the authors explained was due to concurrent salpingitis.[166]

High levels of ^{99m}Tc-maraciclatide activity in the endosalpingosis, represented a significant presence of inflammation. As this is not believed to be typical for endosalpingosis, it brings into question what could have been driving the inflammatory response. One possibility is that there was concurrent endometriosis, as the patient was found to have endometriosis within the uterovesicular fold. However, two samples of the salpingosis were sent to two different histopathologists, both of whom performed microscopic and macroscopic IHC, including CD10. Neither sample contained glands or stroma, and both were negative for CD10. Alternatively, despite mucinous cystadenomas and endosalpingosis being thought to be non-inflammatory, the reactive stroma around both the mucinous cystadenoma and the endosalpingiosis may have been undergoing

neoangiogenesis and vascular remodelling. Fallopian tube epithelial cells are known to express αvβ3 consistently throughout the menstrual cycle.[167] It is possible that endosalpingosis allowed for the tubal epithelium to be misplaced or overexpressed within the cysts, which was detected by ^{99m}Tc-maraciclatide, whereas in most patients it is not. Another possibility is that it is the mucinous cystadenoma driving the uptake, as some mucinous cystadenomas express low levels of VEGF on the ovarian epithelial surface.[168] The findings in this patient highlight the importance of interpreting the findings of ^{99m}Tc-maraciclatide SPECT-CT as a test for angiogenesis and not an endometriosis-specific scan, as other causes of inflammation are expected to be detected. This participant's data was recorded as a missed diagnosis (false negative) as the endometriosis within the UVF was not identified. However, in a blinded study, it is likely this lesion would have represented a false positive.

Immunohistochemistry

The IHC studies of angiogenic markers across 50 samples was conducted to develop a clearer understanding of the Maraciclatide scan in detecting angiogenesis. CD31 was present in almost every tissue confirming that the sampled tissues contained endothelial-lined vessels. αvβ3 was commonly expressed the pelvic, thoracic and eutopic endometrium of included participants. To my knowledge this represents the first study to locate αvβ3 within ectopic lesions. With samples only from one participant negative for endometriosis no comparisons in expression could be made.

VEGF was widely expressed in endometrium and pelvic lesions but not in the three thoracic endometriosis samples, however all samples were from the same participant. Co-expression of αvβ3 with VEGF was common in pelvic endometriosis which supports

the hypothesis of synergistic angiogenic action. OE showed the highest IRS score followed SPE and DE. The sample is too small to draw conclusions but is surprising considering that neither of the OEs stained showed Maraciclatide uptake, suggesting that Maraciclatide was either unable to reach both OEs or could not bind. It was also surprising that αvβ3 vessel staining did not follow the scan findings with 'active' lesions stainining more positively for αvβ3 vessel staining than angiogenically inactive lesions. There are various explanations for this counter-intuitive finding that may be useful to consider in the phase 3 study. It is possible that Maraciclatide is not only detecting endothelial αvβ3 but also αvβ3 expressed in perivascular smooth muscle/pericytes and stromal immune cells which were also strongly expressed but not included within the IRS. Moreover, it is highly likely that a lesions angiogenic activity at a molecular level can not be as easily measured as just looking at the intensity score of αvβ3 alone. In addition, whereas in surgery the whole lesion can be examined to assess the angiogenic activity, unfortunately the samples that have been used only represent a small fraction of the lesion. This may also explain why Maraciclatide was still able to detect lesions despite lesions being them being negative for αvβ3 on IHC.

We also do not know enough on how confounding factors such as hormonal influence effect αvβ3 expression. Studies indicate that vascular αvβ3 expression in eutopic endometrium and αvβ5 expression in ectopic lesions show limited or no significant menstrual cycle–related variation, in contrast to the marked cyclical regulation observed for epithelial αvβ3.[42,169]. However, this could not be investigated within the DETECT study as it would have been too logistically challenging to match the participants surgery and scan to the same menstrual phase, so it is unclear whether the samples and SPECT-CT

provide accurately matched *in vivo* and *in vitro* data on αvβ3 expression. Finally, previous IHC αvβ3 studies tend to control for exogenous hormone use which we have not. We have shown that αvβ3 is expressed despite exogenous hormone use but the impact of hormones on expression and IRS could not be determined.

Strengths

The diagnostic survey received over 1000 responses, allowing for a broad variety of views and experiences to be heard. Despite the large sample, recurring concepts were observed, enabling themes and conclusions to be drawn that represented a substantial proportion of views. It looked beyond just the accuracy of diagnostic tests, but the experiences patients are having with them, especially in relation to the test's perceived accuracy. Moreover, it novelly assessed patients' acceptability to the novel methods being explored, which is an important consideration to those within the research field.

The strengths of the DETECT study begin with its origins. It answered the World Endometriosis Society's call to explore other fields of advanced imaging in hopes of advancing diagnostics for endometriosis.[76] ^{99m}Tc-maraciclatide had been investigated within other inflammatory conditions, but the DETECT study was the first time it was applied to a gynaecological disease. In fact, nuclear medicine is not a field often utilised within gynaecology, but it holds the benefit of providing insights into anatomical and physiological changes. Conditions such as endometriosis extend beyond structural changes seen, and therefore, developing tests and treatments based on its known pathophysiology, such as angiogenesis, is a crucial approach to advancing this field.

The study has been designed and placed within the diagnostic pathway, where, in practice, it is likely to serve best, as a step before surgery, likely in those with negative imaging who want to avoid surgery. The study has demonstrated that ^{99m}Tc-maraciclatide can provide vital information prior to surgery for example the detection of SPE which for some may help them determine whether or not to proceed with surgery. The diagnostic survey showed that although many who contact health professionals prioritise symptom relief, many are also seeking a diagnosis. A delay in this diagnosis, as shown by the survey, can have life-changing implications for their life choices and provide more autonomy over the decisions they make.

The broad inclusion criteria enabled the testing of various hypotheses. For example, the use of exogenous hormones was anticipated to prevent lesion detection, but on the contrary, lesions were detected in more participants on hormones than not. This is a clear benefit as it would allow patients to continue with their treatment whilst being investigated for endometriosis. It is however still likely that factors such as exogenous hormones and menstrual phase will influence uptake of the marker and future studies can assess the clinical impact of this. Moreover, endometriosis was detected in participants aged 20 to 59, making it potentially applicable to a wider range of patients. This range is further expanded by the fact that two cases of extrapelvic endometriosis was also detected. Extrapelvic endometriosis is often overlooked but is also a key diagnostic challenge, which may be supported by ^{99m}Tc-maraciclatide, especially as whole body planar CTs can be performed within the same imaging session.

The largest strength of the study has been demonstrating the potential of ^{99m}Tc-maraciclatide as a novel diagnostic test for SPE, a subtype which can not be reliably detected or ruled out using current imaging techniques. If this can be confirmed in larger studies it has the possibility to revolutionise the diagnostic pathway for those living with endometriosis by offering an earlier diagnosis and providing them with more information before they decide whether or not to have surgery.

Limitations

The weakness of the questionnaire was the limited amount of information obtained from respondents, which could provide better contextual information. For example, it is likely that scans performed in general sonography would have a different satisfaction score to those performed within tertiary endometriosis centres if a major concern was it the diagnostic accuracy and it causing delays to further interventions. Moreover, recruiting participants from an advocacy group page introduces a risk of selection bias. It is possible that those who follow the page are those who have needed additional support due to failures within their healthcare system to provide support, and care. Therefore, they may represent those who have had a longer diagnostic delay and had more negative experiences with healthcare. Another limitation is that the survey did not compare the acceptability of a saliva test to other novel diagnostic methods. The ZWIG saliva test is now being used in many countries across the world and represents a biomarker test that has reached one of the most advanced stages within the biomarker discovery chain.

Despite the DETECT study's strengths, there are key limitations which need to be considered whilst interpreting the study's results. Firstly, the study was designed as an exploratory study to assess whether ^{99m}Tc-maraciclatide holds potential to supplement the diagnostic pathway for endometriosis. In that sense the study has reached its objectives. However, the sample size was small and not powered to complete diagnostic accuracy studies. Moreover, with only two negative cases diagnostic metrics such as specificity can not be relied upon. Furthermore, as it was the first time this marker has been applied to endometriosis, there was no training set for the radiologist, and thus iterative learning was required, and therefore the radiologist was not blinded. Using a single, highly trained reader ensured interpretation consistency and avoided inter-observer variability, which can confound results in small samples but this approach raised several methodological concerns.

Reliance on a single reader introduces subjectivity and risks confirmation bias which may inflate concordance between imaging and operative outcomes. It is therefore unclear whether these signals would have been detected if the radiologist was blinded or whether they would have been dismissed as artefacts. Similarly, whether artefacts would have led to more false positives. Instead, this exploratory study prioritised understanding whether there is a meaningful signal of diagnostic value, rather than producing definitive diagnostic accuracy metrics, as the latter will be assessed in subsequent studies powered specifically for diagnostic accuracy.

It has already been discussed that a major limitation will be in the detection of endometriosis in regions obstructed by physiological uptake such as the urinary bladder

and that future studies should try to mitigate for these limitations with imaging technologies or by using methods to empty the bladder before imaging. A final limitation is that although it appears that ^{99m}Tc-maraciclatide is detecting angiogenic lesions the clinical significance of this and of missing inactive lesions is currently unclear.

Phase 3 planning

This chapter has discussed the development and completion of an exploratory phase 2 study aimed to investigate the diagnostic potential of ^{99m}Tc-maraciclatide. The next step will be a phase 3 study to confirm the findings of this study and to move closer to clinical application. It will need to be suitably sized to perform diagnostic accuracy studies, and there will need to be a minimum number of negative participants to act as controls. Efforts should be made to expand its utility to extrapelvic endometriosis as it presents a benefit to detect 'uncommon' ROIs which are often missed. In terms of recruitment, it is clinically beneficial to continue recruiting participants on and off exogenous hormones to reduce the burden placed on patients if they have to come off their therapeutic treatment to have a scan. Efforts should be made to ensure ethnical diversity in the participants included, as this is a known limitation in many research studies, including this one, as all but two participants identified as white.

As it appears ^{99m}Tc-maraciclatide is detecting 'active' lesions, research is needed to develop a standardised classification of lesions and to determine the significance of 'active' lesions. Even once a consensus is reached videos and lesion imaging should still be taken and assessed by various surgeons to ensure this consensus is consistent in

practice. As discussed, the phase 3 study needs an improved standardised operating procedure and improved method for collecting information on the WERF EPHect form. The WERF EPHect form should also be updated or modified to reduce uncertainty surrounding lesion characteristics such as sizing and colour.

Concerning imaging, the scans must be interpreted by blinded radiologists and likely by various radiologists so interrater variability can be assessed. After the surgeon has performed their primary survey, ROIs detected on the scan should be relayed to the surgeon to check regions, so an assessment for false positives can be made. With this it can also be investigated whether ^{99m}Tc-maraciclatide can complement laparoscopy by providing more information on physiological changes occurring. Finally, it should be assessed how the addition of ^{99m}Tc-maraciclatide within the diagnostic pathway has an economic effect but also the impact on the diagnostic delay and patient satisfaction.

Conclusion

The diagnostic survey found there are multiple factors contributing to the recognised endometriosis diagnostic delay which needs to be addressed with societal and healthcare frameworks. Moreover, there low satisfaction with the investigative methods we use today but a high acceptability of novel tests including the use of CT. The DETECT study demonstrates that nuclear imaging with ^{99m}Tc-maraciclatide visualises endometriosis, accurately detecting disease missed by conventional imaging methods. These results indicate that ^{99m}Tc-maraciclatide offers a promising and highly acceptable

diagnostic and monitoring tool, particularly for SPE. A planned phase 3 study aims to validate these findings in a larger group of patients

Contributions

I would like to recognise the support of my research group including my supervisors, Christian Becker and Krina Zondervan, as well as Druin Burch and Jon Barnett, who have also provided me with crucial intellectual support on ^{99m}Tc-maraciclatide and supervision in conducting this study. The Nuclear Imaging Department within RUH (particularly Sarah Cade and Richard Grayham) was fundamental for the smooth running of the study. Radiologists Neel Patel supported the development of imaging protocol and Munir Ghesani provided crucial insights on the ROIs seen on SPECT-CT. Giuseppe Spalino assisted with collecting surgical images. Operating surgeons within OUH including Christian Becker and Francesco Di Chiaria who assisted with participant recruitment and provided vital information on the surgical ROIs. The IHC work was conducted by The Oxford Translational Histopathology Laboratory.

Chapter 3: Bridging Gaps in Endometriosis Management Frameworks

Introduction

It has been suggested that those with endometriosis face one of two major challenges: endometriosis-associated pain or infertility, or in some cases, both.[170] Endometriosis-associated pain occurs in approximately 90% of patients and can result in repeated hospital visits and investigations, in addition to high rates of school and work absenteeism, a negative impact on social relationships and a decreased quality of life(QoL)[171,172]. The umbrella term endometriosis-associated pelvic pain encompasses a myriad of more specific symptoms, including but not limited to dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, dyschezia, and chronic pelvic pain. As there is no cure for endometriosis, various approaches have been developed to address endometriosis-associated pain. To standardise these approaches, endometriosis guidelines have been developed to assist clinicians in countering clinical uncertainties.

To understand the global availability of endometriosis guidelines, I, as the second author and an international research team (see **contributions**), conducted a scoping review to map the availability of endometriosis guidelines worldwide which has been accepted for publication within the Lancet Obstetrics and Gynaecology.[173] The review found various levels of organisation within the development of frameworks for endometriosis management. For instance, some regions have implemented endometriosis-specific guidelines by governments in collaboration with academic societies, such as the UK.

However, the review also revealed a disconcerting lack of guidance in various regions, especially within LMICs (**Figure 19**). In fact, 35% of countries have no endometriosis care guidance beyond physician/clinic/hospital websites, news articles, interviews, patient advocacy websites, and social media. Thus, in many countries, there is likely no standardised evidence-based approach applied to endometriosis management.

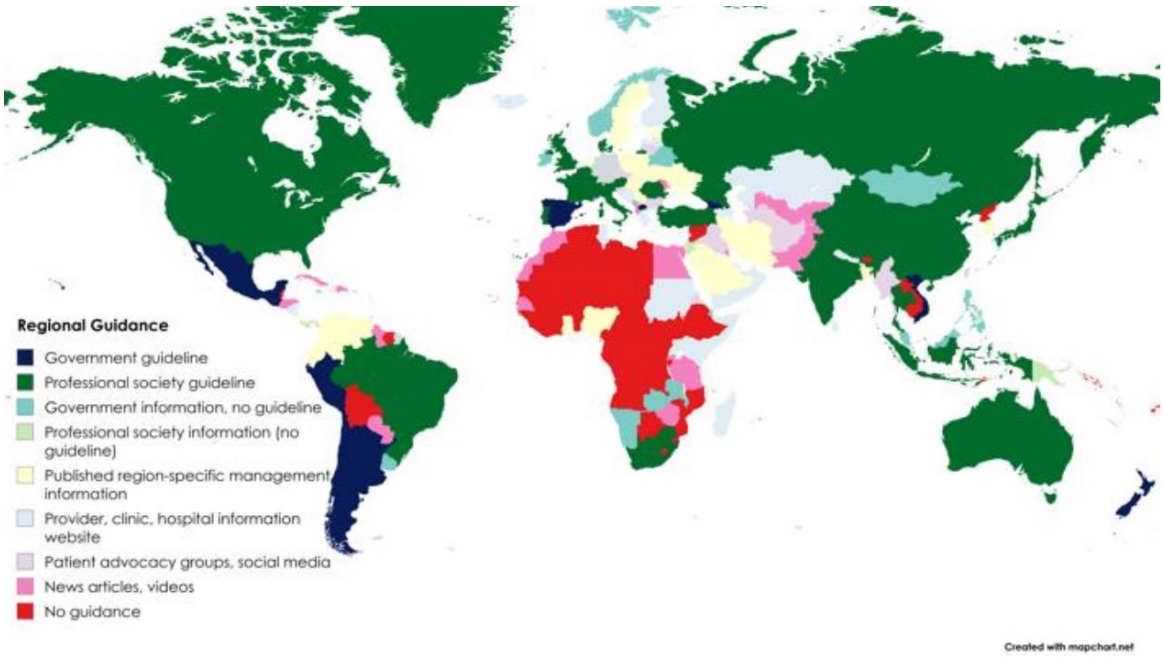


Figure 19: Map describing the availability of endometriosis guidance worldwide. Evans et al. [173]

Medical guidance in the form of guidelines is the backbone of providing evidence-based care, and a crucial instrument within the WHO Health Information Systems and Service Delivery Building Blocks of healthcare systems. The review highlighted that to address the lack of standardised, evidence-based countries can adapt guidelines from other regions to their own. Guidelines, such as those from ESHRE[57], recommend trialling medical management until failure, but highlight that it is often a trial-and-error approach, as there is no clear evidence on which treatment is most effective. This can result in

clinical uncertainty and potentially lead to treatment delays until the most effective treatment is identified. Moreover, in resource-limited settings, having stronger clarity on the most effective treatments may help to guide resource allocation and assist with countries being able to tailor international existing guidelines into their own.

Across the globe many prefer traditional or non-pharmacological treatments for example Chinese herbal medicines or Ayurvedic medicines known as Complementary and Alternative Medicines (CAMS) that are not considered standard practice in western guidelines and these approaches are also becoming increasingly popular in the western world. However, there remains clinical uncertainty regarding how these should be recommended and how they compare to traditional Western medicine. Given the uncertainties surrounding endometriosis and the various treatment options available, further research is needed to understand how these treatments compare with one another. Unfortunately, there is a recognised gender health gap and an underserving of funding for women's health research, which could address these uncertainties.[1] Given the underfunding of endometriosis research, it is crucial that research is standardised to it can be meaningfully replicated and compared. Various research standardisation approaches have already been employed. For instance, the WERF EPHect standard operating procedures[125,126], the International Terminology on Endometriosis[124] and the Endometriosis Core Outcome Set.[174]

This chapter will discuss a collaborative project aimed at supporting the development of robust, evidence-based guidance for endometriosis. The project followed a systematic review and meta-analysis conducted in 2020 by many of the same authors, which aimed

to address another clinical dilemma within the endometriosis treatment framework: 'When to do surgery and when not to do surgery for endometriosis'.[175] We decided to use a network meta-analysis (NMA) model for this project as it has the potential to address deficits in endometriosis research funding and holds the potential to develop a clinically relevant ranking of treatments, which could inform the development of treatment guidelines and guide resource allocation. I presented the results at the Society of Endometriosis and Uterine Disorders 2024 congress[176] and the manuscript has been drafted for publication.

Hypothesis

A network meta-analysis of interventions for endometriosis-related pain will allow for the comparison of treatment effectiveness and identify inconsistencies and gaps in the evidence base that may limit the development of robust clinical guidelines and inform healthcare resource prioritisation.

Aims

1. To compare and rank interventions for endometriosis-related pain by performing an NMA

2. To use the findings of the NMA to identify gaps in healthcare information frameworks that can be addressed to strengthen endometriosis guidelines

Methods

Rationale for a network meta-analysis

Numerous pairwise meta-analyses have been conducted to assess the effectiveness of endometriosis treatments in providing pain relief. However, pairwise meta-analysis can only compare evidence obtained from treatments directly compared in a randomised trial. This fragments the evidence, making it challenging for clinicians to compare and apply the research to real-world scenarios where multiple treatment options exist. This is especially challenging within endometriosis as treatments across various categories are rarely assessed in research studies (e.g. surgical vs medical interventions), but this is a common scenario clinicians face when considering whether or not a patient should have surgery.

A network meta-analysis (NMA), however, is a statistical model that allows for the comparison of multiple treatments using both direct and indirect evidence, even if the treatments have not been directly compared within clinical trials. This method can overcome the limitations of current endometriosis research, where there are too many interventions available to compare directly, particularly given the recognised underfunding of women's health research. An NMA can combine the direct and indirect evidence to estimate all pairwise comparisons, thereby maximising the use of available data and improving precision.[177–179] The benefits within the clinical setting can be further enhanced by the use of statistical methods such as Surface Under the Cumulative Ranking Curve (SUCRA), which allow treatments to be ranked and presented in a form that is meaningful for those developing guidelines, practicing clinicians and even patients. Ultimately, this method enables the selection of the most optimal therapy for

women with a clinical problem where numerous treatment options are available and the comparative effectiveness of these treatments is unclear.

Although various NMAs for the classes of endometriosis treatments have been developed, this is the first to compare all interventions (medical, surgical, and CAMs) in terms of efficacy for those with endometriosis-associated pelvic pain, thereby better informing clinical practice and health policies.

Assumptions of an NMA

To ensure an NMA is an appropriate model for this analysis, three core assumptions must be met: transitivity, consistency and homogeneity. These assumptions fundamentally mean that the model assumes that all included trials are sufficiently comparable for indirect comparisons to be valid.

Transitivity in terms of endometriosis studies refers to the fact that the participants in each study would have been eligible for any of the interventions. Although we are seeing a shift towards non-invasive diagnosis, as traditional endometriosis studies only included those with a surgical diagnosis, to ensure transitivity, we decided to only include studies where patients had a confirmed surgical diagnosis. Many recent studies, but particularly older studies, would have excluded patients with a diagnosis based solely on imaging; therefore, including studies with an imaging diagnosis within indirect comparisons does not meet the assumption of transitivity.

Consistency is the next assumption, which is an agreement between direct head-to-head evidence and the indirect evidence. This states that estimates generated from direct head-to-head comparisons should not conflict beyond chance with the estimates generated from indirect comparisons. Given the heterogeneity of endometriosis trials (different comparators, dosing regimens, and outcome measures), we actively tested for inconsistency using the Wald design-by-treatment-interaction test, as well as a side-splitting approach and clarified the inconsistency and its impact on the results.

Homogeneity assumes that trial results vary primarily due to random error rather than systematic differences. The concern with this assumption is that variation is expected within the included studies due to known variations in surgical technique, dosing regimens, co-interventions (both recorded and unrecorded), and outcome measurement. These variations were addressed by using the random-effects model. Random effects allow for less precision/confidence in the treatment effect, resulting in wider 95% confidence intervals. As residual heterogeneity remained high, the effect estimates and ranks should be interpreted with caution.

Protocol and registration

I registered the review with the International Prospective Register of Systematic Reviews[180] (PROSPERO CRD42020184429) and reported it according to PRISMA guidelines.[181]

Search strategies

I developed a comprehensive search strategy that consisted of terms relating to key concepts of “endometriosis”, “surgery”, “medical management”, “complementary and alternative management”, and “randomised controlled trials (RCT)”(**Appendix 5**). Using the search strategy, I searched the following databases from inception until October 2022: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase via OvidSP, AMED Allied and Complementary Medicine, and CINAHL. I also searched ClinicalTrials.gov for ongoing and registered trials. OpenGrey was used to search for grey literature. I configured the search on OvidSP to remove duplicate studies. In addition, reference lists of relevant articles and related reviews were manually searched to identify papers not captured by the electronic searches. Finally, members of the study team were asked to identify any papers that were not captured.

Eligibility criteria and study selection

All RCTs in those with surgically confirmed endometriosis, published and unpublished in any language at any time, were considered for inclusion. Studies were independently reviewed by a minimum of two authors, as per the eligibility criteria identified in the protocol, for selection before further data extraction for the Systematic Review and NMA. Discussions and consensus were reached when disagreements between reviewers became evident, with input from a third author provided as necessary. Abstracts, non-randomised, quasi-randomised, or crossover trials were excluded.

Types of intervention

All interventions used for the management of endometriosis were included and grouped into medical, surgical, or complementary and alternative medicine (CAM) categories. RCTs in which interventions were used in conjunction were included, as this is common clinical practice.

Surgical interventions:

Surgical interventions included operative therapy to remove superficial peritoneal or deep endometriosis by excision or ablation. To align with the clinical approach, where the choice of method depends on the specific subtype of endometriosis, the intervention was categorised based on the primary removal technique employed, such as primarily excision or primarily ablation.

Medical and Complementary and alternative interventions (CAMs):

All medical interventions and CAMs were considered and grouped depending on the class of the drug, e.g., nonsteroidal anti-inflammatory drugs or Chinese herbal medicines (CHM). Given the heterogeneity between study methodologies and interventions, interventions were grouped irrespective of their dosage or route of administration. This level of pooling was necessary to increase the information for each node and to stabilise the random-effects variance without creating multiple disconnected nodes. Moreover, each dose was expected to be in a therapeutic range. Novel interventions were also considered, e.g., CCR1 antagonists.

Outcome measures

Early work on standardising endometriosis pain research has stated that pain should be distinguished by menstrual-related pain and non-menstrual-related pain, as patients can easily distinguish the two and recommended not to combine the two types of pain.[182] However, beyond that, there are various terms used within endometriosis research, making it difficult to compare studies. In 2020, a Core Outcome Set[174] was developed to standardise future endometriosis research, which included that studies should report 'overall pain' when assessing endometriosis-associated pain. As such, the primary outcome of this project was 'overall pain'. However, we were aware that, given this outcome set was introduced recently, various other terms would be used by the included studies.

As such, we included terms synonymous with overall pain, e.g. 'chronic pelvic pain' (CPP), 'total pain', 'pelvic pain' under overall pain. To maximise consistency during the data extraction phase, overall pain was prioritised if terms synonymous with overall pain (e.g., chronic pelvic pain) were also reported, rather than recording both. Continuous (e.g., visual analogue scale) and dichotomous data (e.g., better or improved versus not better or improved) were both extracted. We also extracted data on specific pain types such as dysmenorrhea (n=78 RCTs), which will be included in a subsequent NMA. Interestingly, no studies reported the second of the core outcome, 'improvement of the most troublesome symptom'. Moreover, despite fatigue being one of the most common symptoms of endometriosis[183], only three studies have reported on fatigue outcomes.

Outcome Timepoint

In the protocol, we planned to perform the analysis on data from the 12-month post-randomisation time point. However, while extracting the data I became aware that most studies particularly the CAM studies, did not reach 12 months, possibly due to funding restraint but also perhaps due to the belief that the intervention reaches a clinical steady state sooner and reflects the typical provisions available. For example, NICE recommended offering those with chronic pain a single, time-limited course of acupuncture (≤5 hours of clinician time). This limit was informed by its cost-effectiveness model, which drew on trials where acupuncture was typically delivered as 10–15 sessions over 3 months.[184] Moreover, the United States Medicare programme provides coverage for 12 visits in 90 days coverage for chronic low back pain, but unfortunately, they do not yet provide coverage for chronic pelvic pain.[185] Furthermore, in clinical practice it is often recommended to trial a medication for 3 months before determining its effectiveness on the individual.[56,186] I noticed that for some studies that reached 12 months post-randomisation, the individuals were no longer using the treatment and again, to provide the most clinically useful data, we wanted to assess the effect of the management whilst using the treatment. Therefore, although we extracted data from each time point, the authorship group and I decided to analyse pain outcomes for the non-surgical outcome once the participants had been using the intervention for 3 months.

We did not adjust the protocolled 12-month timepoint for surgical studies, as we believe it is a clinically relevant timepoint used in guidelines, such as ESHRE[4], to assess the surgical benefits of surgery for endometriosis. However, future work will involve

performing a sensitivity analysis on 6 months post-operative data, as this time point is likely to be more comparable to the 3-month non-surgical data.

Data Extraction

I generated data extraction sheets, which were completed by a minimum of two authors, who extracted data from each article. Checks and quality assessments were conducted on the extracted data by at least one other author. The extracted data included methodological design characteristics, patient demographic profiles, endometriosis classifications, intervention classes, and outcome data. Data was manually extracted and entered into Microsoft Excel.

Data Synthesis

Dr Katie Stocking completed the statistical analysis for this project. For the primary analysis of overall pain, we analysed change and end scores separately. Studies reporting a binary measure, such as the "presence of pain," were combined with continuous end-of-study scores. Those reporting “improved” or “recurrence” outcomes were combined with continuous change scores.

Necessary protocol deviations arose from the inherent heterogeneity in the reporting methods of the included studies. Each decision was cautiously made to optimise the effectiveness of the NMA and to obtain the most clinically valuable results. For example, the decision was made not to dichotomise the data and to retain the continuous data to minimise information loss, thereby presenting standardised mean differences (SMD) instead of odds ratios as planned.

Our analysis examines the randomised comparison, regardless of concomitant therapies. The data set included various treatments, some of which were administered in conjunction with another treatment. This meant that our original network was extremely large and disconnected. For example, Long 2010 compared GnRH agonist to GnRH agonist + COC. We included this as a comparison of COC with 'no treatment' in a population that all received GnRH agonist, and combined it with studies that compared COC in other populations. Implicitly, therefore, we assumed that treatment effects are consistent across populations. Similarly, sham procedures, placebo, and no treatment were considered as the same node. Multiple studies assessed the effect of different treatment doses. To ensure that all doses were included in the analysis, the placebo group was divided by the sample size as appropriate.

Dr Stocking constructed network plots to illustrate the network's geometry, with treatment effects presented as SMD and corresponding standard errors for each intervention compared with placebo. We used the number of people analysed in each comparison, rather than the number randomised. To rank the treatments, we used the SUCRA.

Study Risk of Bias Assessment

Each study selected was assessed independently by two authors, and where disagreement occurred, discussion and consensus were achieved with input from a third team member. The Cochrane risk-of-bias (ROB) 2 tool was used to assess the risk of bias, with an overall judgment being given to each study: 1) low risk of bias, 2) some concerns, or 3) high risk of bias.

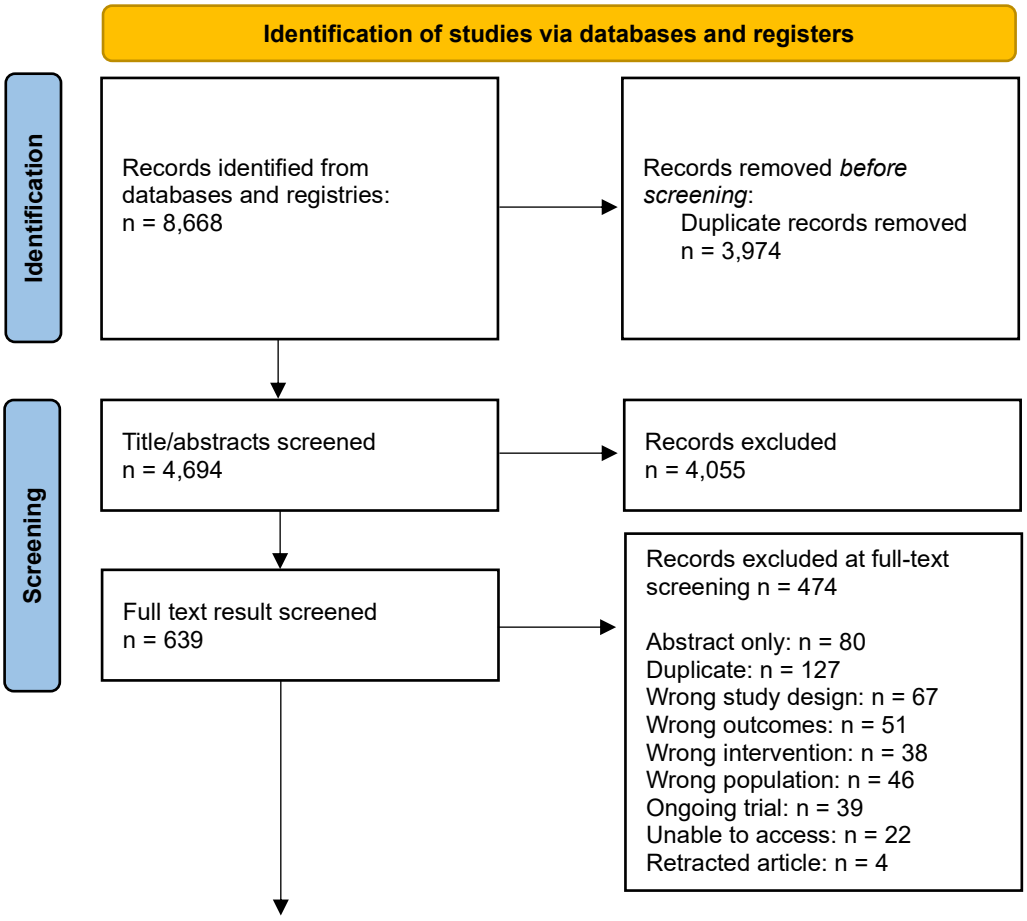
Evidence-based Quality Assessment

The GRADE approach was used to assess the quality of evidence for the outcomes. The evidence was downgraded due to study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

Results

Search Results

The literature search returned 8,668 publications (**Figure 20**). 165 RCTs fulfilled the eligibility criteria. Publication dates ranged between 1981 and 2022. Overall, there were 13,327 patients randomised to 37 interventions, including Placebo/No Treatment.



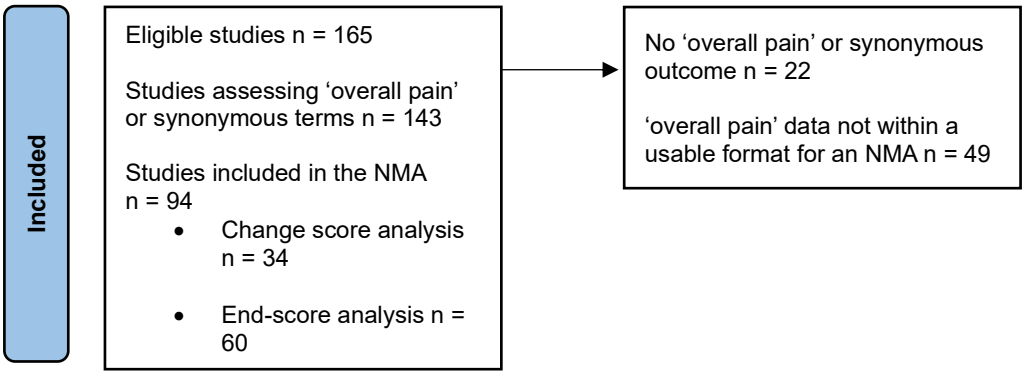


Figure 20: PRISMA flow chart of included studies

When assessing our primary outcome of overall pain (and synonymous terms) a total of 136 comparisons from 94 trials were included. Of these comparisons, 64% were classified as high risk of bias overall, 26% had some concerns, and 10% were low.

Change score analysis

There were 60 comparisons (consisting of 20 interventions) from 34 trials in the change score analysis. The most common comparisons in this analysis were Placebo versus GnRH antagonist (12 comparisons; 2224 patients) and placebo versus GnRH agonist (8 comparisons; 671 patients). Unfortunately, there were multiple comparisons in open loops (**Figure 21**). Thus, judgments were based on indirect comparisons.

Network meta-analysis showed that compared with placebo, GnRH agonist (SMD 0.59; 95% CI 0.41, 0.77), GnRH antagonists (SMD 0.45; 95% CI 0.32, 0.59), GnRH antagonists + COC (SMD 0.38; 95% CI 0.10, 0.66), progesterone (SMD 0.65; 95% 0.44, 0.87), androgenic agents (SMD 0.58; 95% CI 0.18, 0.99) and ablation +/- drainage (SMD 0.96; 95% CI 0.26, 1.67) resulted in lower overall pain (**Figure 22**). There was insufficient

evidence of a difference for any other interventions versus placebo. The results of the direct comparisons agreed with the results from the network meta-analysis. No evidence of inconsistency was identified globally or locally.

Ablation +/- drainage had a 76% probability of ranking in the top 3 treatments, followed by PEA-M+polydatin (37%)(**Table 21**).

The quality of the evidence was downgraded three times to very low-quality evidence due to the high risk of bias in the majority of the included studies, the inconsistency (high heterogeneity, which necessitated the use of the random effects model instead of the protocolled fixed effects model) and the use of a biased subset of trials (as we were unable to include all the RCTs in a single NMA due to heterogenicity in reporting methods).

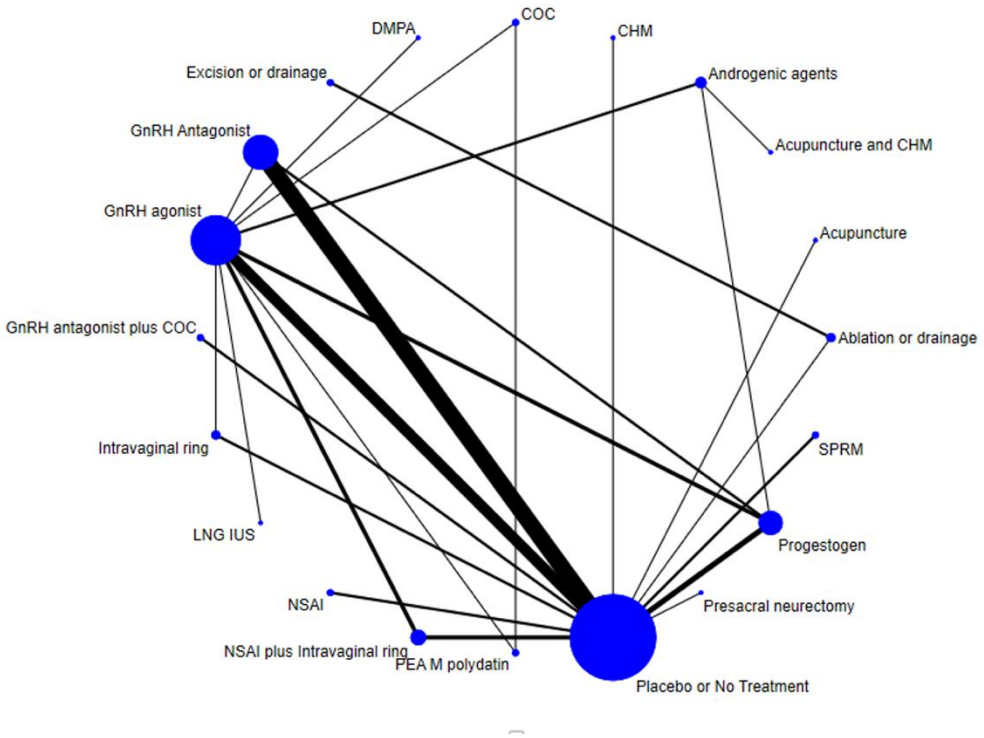


Figure 21: Network plot of overall pain change scores

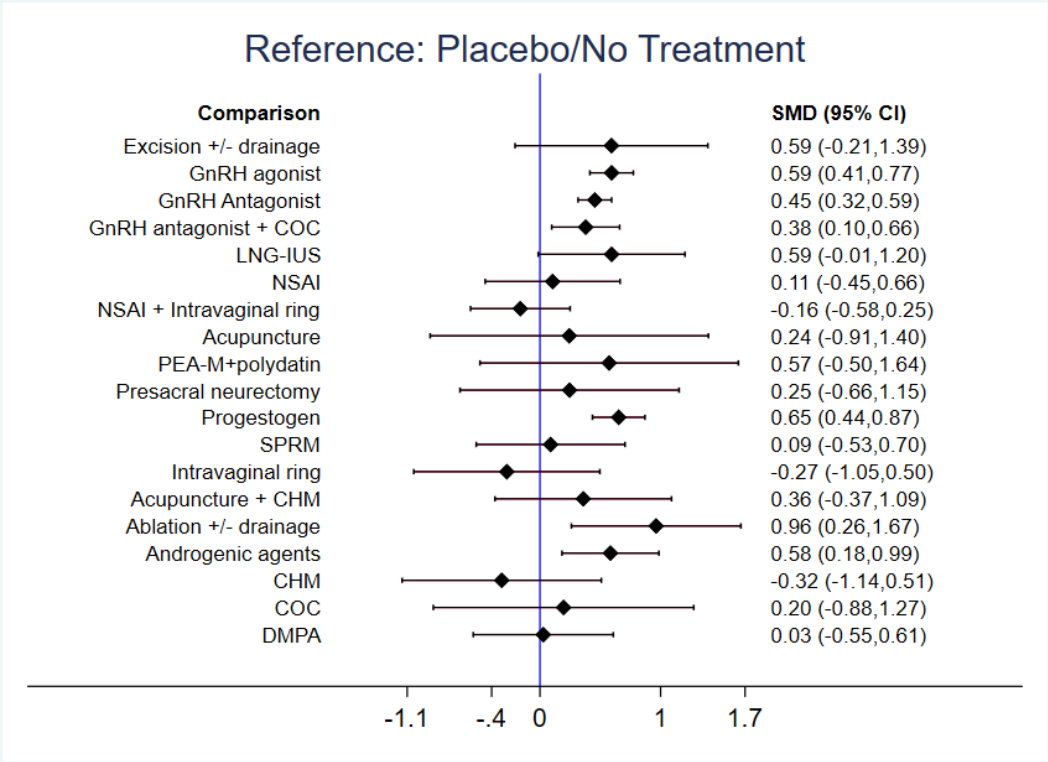


Figure 22: Forest plot of interventions for endometriosis overall pain, change scores

Table 21: Ranking of treatments (% probability best treatment, % probability in top 3 treatments, mean rank overall.)

Treatment	% probability best	% probability in top 3	Mean rank
Placebo/No Treatment	0	0	15.1
Excision +/- drainage	1.5	32.7	7.1
GnRH agonist	0.4	9.7	5.9
GnRH Antagonist	0	0.6	8.5
GnRH antagonist + COC	0.1	1.7	9.6
LNG-IUS	8.2	30.3	6.6
NSAI	0.2	1.5	13.4
NSAI + Intravaginal ring	0	0	16.7
Acupuncture	7.7	19.3	11
PEA-M+polydatin	18.1	37.4	7.4
Presacral neurectomy	4.1	13.2	11.3
Progestogen	2.6	26.3	4.9
SPRM	0.3	2	13.4
Intravaginal ring	0.1	0.5	16.9
Acupuncture + CHM	3.4	13.1	9.9
Ablation +/- drainage	46	76.3	2.8
Androgenic agents	2.7	19.7	6.3
CHM	0.1	0.5	17.1
COC	4.3	14.1	11.7
DMPA	0.1	0.9	14.3

End score analysis

There were 75 comparisons (comprising 28 interventions) from 60 trials in the end-score analysis. There was one trial, comparing the contraceptive implant and DMPA, which could not be included as it was disconnected. The most common comparisons in this analysis were between GnRH agonists and androgenic agents (14 comparisons; 1,351 patients) and between combined oral contraceptives and placebo (8 comparisons; 647

patients). There were multiple comparisons in open loops (as seen in **Figure 23**). The NMA showed that, compared with placebo, acupuncture (SMD 1.45; 95% CI 0.59, 2.31), antiprogesterones (SMD 1.27; 95% CI 0.39, 2.14), and aromatase inhibitors (SMD 1.21; 95% CI 0.33, 2.08) resulted in lower overall pain (**Figure 24**). There was insufficient evidence to demonstrate a difference for any other interventions compared to the placebo. No evidence of inconsistency was identified globally or locally. Acupuncture had a 49% probability of ranking among the top 3 treatments, followed by Excision +/- drainage (39%)(**Table 22**).

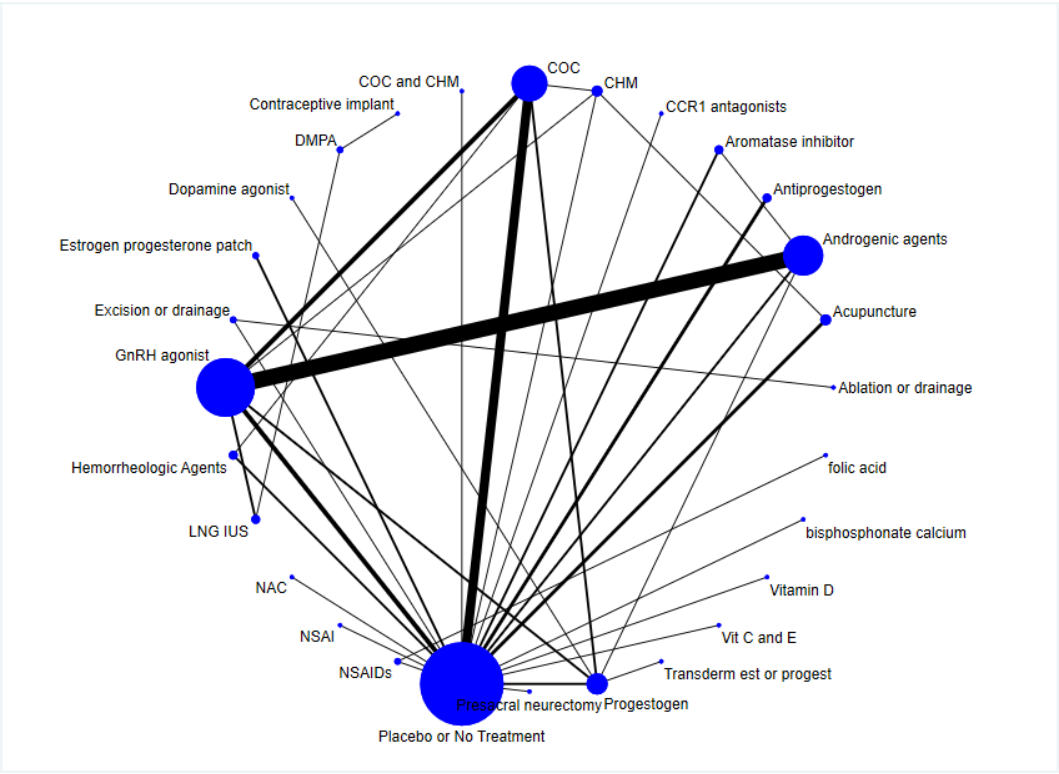


Figure 23:Network plot of overall pain end scores

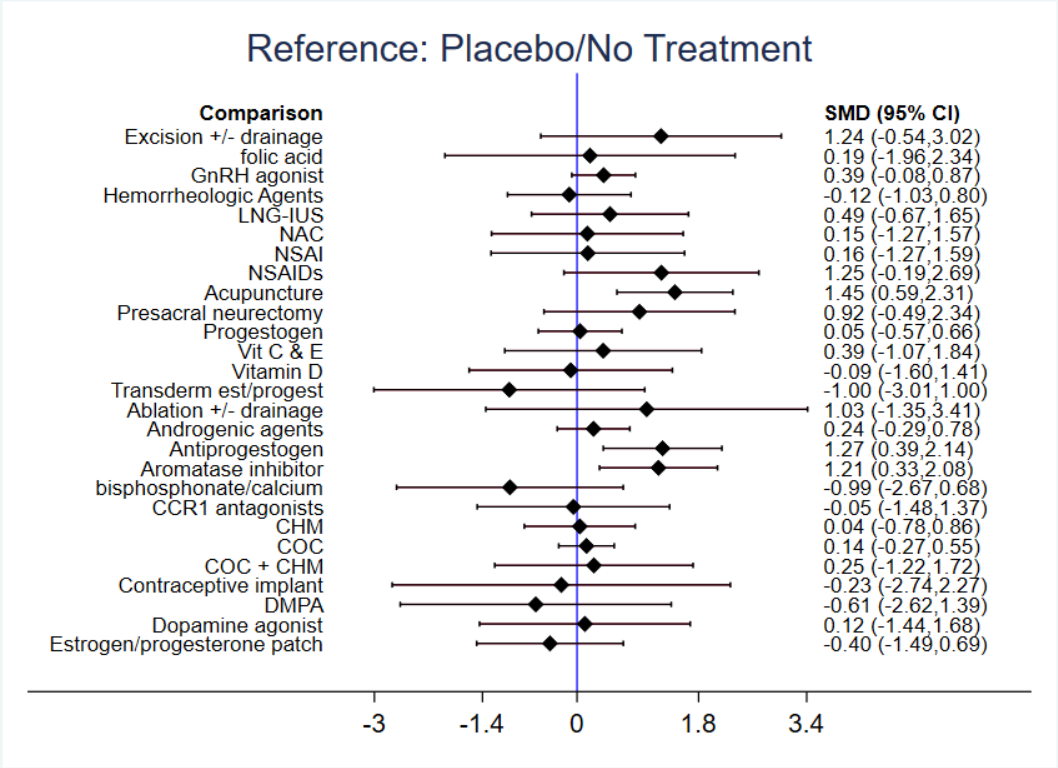


Figure 24: Forest plot for interventions for endometriosis overall pain, end scores

Table 22: Ranking of treatments (% probability best treatment, % probability in top 3 treatments, mean rank overall.)

Intervention	% probability best	% probability in top 3	Mean rank
Placebo/No Treatment	0	0	18.2
Excision +/- drainage	14.1	39.4	6.8
folic acid	3	10.3	15.4
GnRH agonist	0	0	12.3
Hemorrheologic Agents	0	0.2	18.9
LNG-IUS	0.7	4.6	12
NAC	0.7	3.7	15.7
NSAIDs + ring	0.8	3.8	15.7
NSAIDs	15.5	37.6	6.1
Acupuncture	15.6	49.2	4.1
Presacral neurectomy	7.6	22.1	8.4
Progestogen	0	0	17.3
Vit C & E	1.8	7	13.4
Vitamin D	0.4	1.8	17.9
Transderm oest/prog	0.2	0.8	23.5
Ablation +/- drainage	17.7	35	9.1
Androgenic agents	0	0	14.6
Antiprogestogen	8.4	34	5.2
Aromatase inhibitor	7.1	29.3	5.6
bisphosphonate/calcium	0	0.2	24.1
CCR1 antagonists	0.3	1.9	17.7
CHM	0	0.1	17.2
COC	0	0	16
COC + CHM	1.2	5	14.8
Contraceptive implant	3.7	8.5	17.9
DMPA	0.2	1.5	21.3
Dopamine agonist	1.1	4.4	15.9
Oestrogen/progesterone patch	0	0.1	21.3

Discussion

Summary of findings

We identified studies eligible for inclusion in a network meta-analysis for overall pain, of which 94 reported data which could be included in the primary analysis for overall pain. Of the 94 studies, 34 (36%) contained information on change from baseline pain, and 60 (64%) reported end-of-study data.

In the primary analyses, the results from the NMA were largely consistent with the direct comparisons, with no evidence of inconsistency. However, there were two occasions in the end score analysis where the results notably differed. The GnRH agonist had a much higher effect estimate using direct-only evidence compared to the NMA. Conversely, aromatase inhibitors had a higher effect estimate when incorporating indirect evidence into the NMA, compared to when it was not.

Interpretation of results

The results from our primary analysis, change from baseline in overall pain, suggest that women with endometriosis could benefit from GnRH agonists, GnRH antagonists, a combination of GnRH antagonists and COC, progesterone, androgenic agents and ablation +/- drainage. Ablation +/- Drainage was the top-ranking intervention in this analysis.

Our results are consistent with a previous NMA on medical interventions for endometriosis published by Samy et al. 2021.[187] The authors determined that at 3 months, Dienogest (progestogen), COC and Elagolix (GnRH antagonist) were the most effective for treating endometriosis-related pelvic pain. Whereas, at 6 months, GnRH-agonists, LNG and progesterone were the top-ranked. This review supported and developed these findings by adding ablation +/- drainage, which was the top-ranked intervention for treating endometriosis-related pelvic pain when assessing change scores. The reviews differ in their methodology; androgenic agents were not assessed in Samy et al., which reported the mean difference for studies using the VAS scale to assess

pelvic pain. In contrast, this review calculated the SMD, allowing data obtained from multiple scales to be analysed.

A 2020 Cochrane review stated that the effect of laparoscopic treatment on overall pain was uncertain, as only small studies of very low quality were included.[188] This review has also found a paucity of large, high-quality surgical studies, particularly when compared to the number of medical interventions. As such, our conclusions on ablation and excision must be considered cautiously, especially for excision, as the evidence for change scores is provided through indirect comparisons. However, similarly to the Cochrane review, both ablation and excision were found to be superior to placebo. Interestingly, in our NMA, ablation was found to be superior to excision in reducing overall pain. However, it is important to recognise that in clinical practice, a combination of ablation and excision is often used, depending on the type of disease being addressed which wasn't controlled for in the NMA. As highlighted by the 2022 ESHRE guidelines, papers assessing surgical interventions for endometriosis do not distinguish between disease subtypes, and ablation would not be suitable for the removal of DE, for example; therefore, excision was recommended over ablation.[57] The findings of this review do not dispute this recommendation but highlight the need for additional studies to assess the differences in surgical methods, considering disease subtype, given the high frequency of surgical interventions used for endometriosis treatment. The ESHRE guidelines also advocate for excision due to concerns that ablation may not fully remove all disease, although this has not been assessed in this NMA. Methods to reduce disease recurrence are paramount and, therefore, may again support the use of excision over ablation.

With regard to complementary medicines, a 2018 meta-analysis found acupuncture to be the only CAM approach to provide a significant benefit compared to a placebo. Our review supported this finding and went further to compare the effectiveness of acupuncture with that of surgical and medical treatments. Acupuncture was found to be extremely effective, with the highest mean rank score and percentage of being in the top three when assessing end scores, supporting its use in the holistic approach to endometriosis pain management. However, unfortunately, it was not possible to include these studies in the change score NMA, from which the majority of our conclusions were derived. Many CAM trials include patients with radiologically confirmed endometriosis, which, according to our protocol, is excluded from this review. This has limited the availability of data for CAM comparisons.

Strengths

The strengths of this NMA lie in its attempt to address the lack of research on endometriosis by employing a statistical model that enables the comparison of indirect evidence. Performing an NMA allowed for comparisons of interventions across treatment categories, which is rarely done in primary research studies, as most studies primarily compare interventions within categories. This allowed for the finding that acupuncture may be more effective than many medical and even surgical treatments for pain. Another strength was the comprehensive search strategy, which went beyond broad terms such as ‘medicine’ to also assess specific treatment terms. The international authorship group facilitated the inclusion of studies in various languages and provided access and translation of foreign texts. In addition, the effect of all dose comparisons was included, minimising the loss of data. Finally, in performing this NMA, an understanding of the

available evidence guiding endometriosis guidelines can be assessed, and recommendations can be made.

Limitations with current endometriosis research and recommendations

Unfortunately, the study was limited by inherent gaps within endometriosis research studies. Nevertheless, in identifying these gaps resulted in me considering what could be done to strengthen future endometriosis research and enhance the evidence used to develop guidelines for endometriosis.

1. **Heterogeneity in outcome reporting**

The core outcome set in 2020 stated that studies on endometriosis-associated pain should report 'overall pain' to standardise the reporting of endometriosis pain outcomes. Unfortunately, this outcome is rarely reported even after the release of the core outcome set. Also, it is in conflict with earlier work stating that pain outcomes should be separated by pain associated with menstruation and pain not associated with menstruation.[182] Therefore, within this NMA, terms we considered synonymous with overall pain were interpreted as generalised pelvic pain. However, there are limitations to this approach, as researchers and patients may have interpreted terms differently, since no standardised definition was applied. For example, overall pain could be interpreted as the combination of all pelvic pain types (menstrual and non-menstrual related), a combination of pelvic pain (non-menstrual related) or all pain types (pelvic and non-pelvic). For example, one pilot national survey (n=94) found 51% experienced endometriosis-related leg pain.[189] Assessing whether pelvic laparoscopy has an impact

on overall body pain or overall pelvic pain is two separate outcomes, but a patient suffering from extra-pelvic pain may interpret overall pain as body pain.

Uncertainty surrounding ‘overall pain' could be clarified by changing it to 'overall pelvic pain'. Multiple large clinical trials after 2020 have reported the term ‘overall pelvic pain’. This would also allow other terms such as ‘pelvic pain’ or ‘chronic pelvic pain’ to be integrated with more confidence within research such as this NMA. Another, likely alternative is to use a standardised definition within research studies. An example based on the pain patterns described within the International Terminology for Endometriosis could be:

“Overall pain” refers to the participant’s single, global rating of the intensity of all pelvic pain they believe is related to their endometriosis, regardless of location, timing, or trigger. Participants should consider that the endometriosis-associated pain originating from the pelvis may radiate to nearby areas (e.g., lower back, hips, thighs, abdomen).

These amendments to the core outcome set terminology however fail to address the inherent concerns raised by Rosenberg et al.[190] that endometriosis studies and the core outcome set have prioritised too heavily pain intensity but that this does not capture the full patient experience and crucial domains recommended by IMMPACT[191] for chronic pain trials such as other aspects of pain, rescue medication, physical functioning, emotional wellbeing, quality of life and social impact.

Consideration: Amending the core outcome sets pain intensity outcome to 'overall pelvic pain' or including a standardised definition for researchers and participants would enhance the consistency and comparability of findings across studies. In addition, including outcomes to address other aspects of pain, physical functioning, emotional wellbeing, quality of life and social impact would allow for a more comprehensive comparison of treatments and support the development of guidelines that better reflect the needs of those with endometriosis.

2. Heterogeneity in pain outcome measures

A fundamental limitation of this NMA is the need to separate the data by end-of-treatment ("end") or change-from-baseline ("change") outcomes, which splits the network and weakens indirect comparisons. This arose because studies used incompatible estimates and often didn't provide enough data to compare them (e.g., the SD change from baseline–follow-up or just the final result at follow-up). Moreover, there was also variation in the scales used, e.g., VAS, NRS, VRS, improved vs not improved, etc. For the NMA, this could be overcome by using SMD, which, although it has lower statistical power than MD, has no material differences between the two.[192]

Future trials could avoid these limitations by adopting standardised reporting of outcome measures. The 2010 report from the Art and Science of Endometriosis meeting[182] on the standardisation of endometriosis pain scoring urged the use of NRS scales, which others including the IMMPACT recommendations (along with VAS and VRS) support.[190,191] Standardising the use of NRS (0-10 or 0-100) to assess pain intensity would improve comparability between studies. To improve the accuracy of SR and MA which are often

used in guideline development, authors should report both baseline and follow-up means with SDs and numbers analysed and also report the mean change with its SD or, at a minimum, the baseline–follow-up correlation so the SD of change can be derived.

Consideration: Reporting pain intensity outcomes using NRS scores in sufficient detail may improve the accuracy and confidence of the conclusions made in MA and SRs which are used to develop guidelines.

3. **Heterogeneity in timepoints measured**

There was also heterogeneity in the time points measured, making it difficult to compare interventions as it is recognised that the effectiveness of treatments vary overtime. The 2010 report from the Art and Science of Endometriosis[182] meeting suggested researchers collect data weekly for the first 6 weeks, monthly to 6 months, then at 9, 12, 18, and 24 months, to avoid recall bias and detect transient effects. These timepoints would also improve the conclusions made in studies, such as NMAs. Given the limited funding available, treatments should be protocolled to continue for at least three months, as this is a clinically relevant time point of use for most clinicians and in guideline development. Moreover, with standardised timepoints we will better understand to which treatments the arbitrary three months duration applies and which treatments need a shorter or longer duration before an alternative therapy should be considered.

Consideration: Designing studies to investigate the therapy for a minimum three months and standardising the timepoints that outcomes are reported would allow

***for improved comparability of treatments between studies and better support recommendations made in guidelines and by clinicians*.**

4. **High risk of bias in the included studies**

Unfortunately, 64% of the included studies were assessed to be at high risk of bias and contributed to the NMA's findings being downgraded to very low-quality evidence. It is a major concern that the majority of the evidence used to develop guidelines is at such high risk of bias, and efforts are needed to improve the quality of research studies so robust clinical recommendations can be made from them. Our finding conflicts with Csirzó et al.'s NMA on medical management for endometriosis pain that reported low risk of bias for most of their studies using the same ROB2 tool.[193] This may suggest that surgical and CAM studies are driving the difference.

Increasing research funding from independent sources, such as government or NGO allocations is one approach to reduce bias and support the development of high-quality research that addresses its populations needs, this will be explored in Chapter 4. As we and Rosenberg et al. found there is vast heterogeneity in the methodology used in endometriosis studies impacting their comparability and the conclusions that can be drawn from works such as ours, resulting in us downgrading the confidence of our findings. Improving the standardization of studies is then needed however there is concern even with reporting standards such as CONSORT reporting of endometriosis RCTs is poor.[194,195]

Consideration: There is a great concern in the quality of evidence we base our guidelines and recommendations on, highlighting the need for increased funding for high quality research with standardised methodologies and reporting standards to increase the quality of research we produce.

Limitations of an NMA

As discussed, there are limitations to the available clinical research; however, there are also limitations in the approach we have taken to assess the effectiveness of endometriosis treatments for pain. Firstly, the endometriosis subtype and stage were not taken into account. We know that endometriosis subtypes pose different genetic and molecular properties, and it is likely that different interventions work differently depending on the type of disease one has. However, this approach is reflective of the standardised approach to how endometriosis is often treated. We recognise that regardless of stage or subtype, each endometriosis patient is unique; therefore, creating a ranking of treatments may not be the most effective approach for each individual however it may support allocating resources in regions with funding restraints where the 'trial and error' approach is less feasible. Relying on indirect evidence, although a good approach when research is limited, is less reliable than direct evidence. Given the paucity of data for various interventions, caution is needed when applying findings from indirect evidence to clinical practice.

Future work: A living endometriosis NMA

Although the heterogeneity in endometriosis research has limited the NMA from developing a comprehensive ranking of endometriosis treatments for pain, clarity on the

understanding of the available research on endometriosis treatments for pain has emerged, allowing adjustments to the model to be made and improving the clinical relevance of the NMA results. Furthermore, a model has been developed that will facilitate the continued inclusion of future endometriosis research, which is expected to be of higher quality and lower risk of bias, thereby strengthening the model. Various guidelines[196] are now incorporating living NMAs to facilitate the continued integration of research within clinical recommendations. Future updates of the NMA aim to develop a living NMA model to support and strengthen the evidence provided to those developing guidelines and for countries with limited resource allocation.

Conclusion

This chapter explores some of the frameworks supporting endometriosis treatment globally. The scoping review identified a lack of clear guidance in certain countries, especially in LMICs, but recommended tailoring existing guidelines to the specific needs of the country. Having a clearer understanding of the ranking of treatment effectiveness for endometriosis would not only support the updating of existing guidelines but also facilitate the development of guidelines in countries that currently lack them. Unfortunately, the NMA discussed within this chapter was unable to provide a clear ranking of endometriosis treatments due to the low quality of evidence. Nevertheless, it did suggest that surgical methods may be more effective than medical treatments. However, as the data were not analysed by disease subtype, it is likely that these conclusions are based on treating advanced-stage endometriosis. The effectiveness of surgery in treating SPE is currently unknown, but it is under investigation at other research centres. The NMA also found that when comparing CAM interventions, such as

acupuncture, to conventional treatment methods, it may be more effective than previously believed, with evidence of superiority compared to traditional treatments. This chapter has critically demonstrated the interwoven nature of frameworks, and only through collaborative efforts targeting various aspects of the WHO building blocks can improvements be achieved.

Contributions

Scoping Review on the Global Availability of Endometriosis Guidance:
Devon Evans led this project, which was conceptualised and supervised with the support of Stacey Missmer, Linda Giudice, G. David Adamson, and Krina Zondervan. Becky Skidmore contributed to the development and conducted the search strategy. I performed the second screen of the database search results, assisted with the identification of documents, and supported the development of the manuscript, which has been accepted within the Lancet Obstetrics and Gynaecology.

Endometriosis Treatment NMA:
The protocol development was led by Mathew Leonardi, Neil Johnson, Katie Stocking and me. I developed and performed the search strategy and developed the data extraction sheets. Overall pain is the primary but not the only outcome our research group is performing NMAs; therefore, we have a large group to support the screening and data extraction of the 165 included RCTs (Kevin Kuan, Isis Lunky, Marina Liu, Jasleen Sekhon, Anneke Schreurs, Aiat Shamsa, Albert Jung, Joz ong, Jessie Hao, Emily Yang, Elizabeth Glanville, Mike Amour, Adele Cave, Tal Jacobson, Louise Hull, Ruth Hodgson, Velja Mijatovic, Christian Becker, George Coundous, Neil Johnson, Mathew Leonardi and me). I managed the data and performed additional checks, such as checking the accuracy of

each studies extracted data, finding missing data and searching studies against the retraction register. I also classified each study into its intervention node and ensured the data were ready for statistical analysis, which Katie Stocking and Andy Vail performed.

Chapter 4: Bridging Gaps in Global Policy Frameworks for Endometriosis

Introduction

Despite the prevalence and the profound global socioeconomic burden of endometriosis that has been explored within the introduction, endometriosis has been underrepresented in public health discourse and policy agendas. This oversight is reflective of the gender health gap in medical care globally[1,197] and is partly attributed to the stigma surrounding the disease and all menstrual disorders.[198] Similar to endometriosis, mental health conditions present significant healthcare and socioeconomic challenges that require coordinated approaches spanning healthcare, workplace and social systems. Mental health conditions have also historically been stigmatised and neglected in policy representation. However, in response, the World Health Organisation (WHO) developed Project Atlas[199] in 2000 to map, track and promote the availability of mental health policies across the globe. A 2021 report[200] demonstrated that 75% of the 194 WHO member countries had a stand-alone policy or plan for mental health (an increase from 68% in 2014) and 57% had a mental health law (an increase from 51% in 2014). To date, there is no programme to map or track global endometriosis policy reform. Various stakeholders, including non-governmental organisations (NGOs) and governmental organisations, have made attempts to improve the political prioritisation of endometriosis. For example, in 2017, the European Parliament urged EU member states to increase funding for endometriosis research, draft clinical guidelines, establish reference centres, promote awareness-raising campaigns, support the training of specialised health professionals, and consider making endometriosis treatment free and

providing sick leave during acute periods of illness. The response of the EU governments to this call, along with those of other countries to the broader challenges of endometriosis, has not yet been systematically assessed.

This chapter describes a scoping review conducted to comprehensively map the global landscape of endometriosis policies within healthcare frameworks, shedding light on healthcare inequalities and identifying initiatives, policies, and frameworks that could be implemented globally. The review presents the first step in mapping and tracking the global progress of endometriosis policy. I presented this work at the World Congress on Endometriosis 2023, where it was awarded Best Oral Presentation from an Early Career Clinician, Highly Commended, and it has been accepted for publication within The Lancet Obstetrics and Gynaecology.

Hypothesis

The availability and maturity of endometriosis policies vary significantly across countries, as do their type, comprehensiveness, and the approaches taken by stakeholders to implement them.

Methods

Selecting a study design

Various approaches could be used to map endometriosis policies, from primary research (interviews, questionnaires) to secondary literature (literature, scoping, or systematic reviews). I chose a scoping review as the optimal method, since it allows broader questions, iteration, and adaptation to the data. Scoping reviews are particularly suited

to underexplored topics, whereas systematic reviews are more useful once data have been scoped and questions narrowed. Scoping reviews for health policy mapping have been described by Anderson et al. [201] as *'a scoping study designed to identify the main documents and statements from government agencies and professional bodies that have a bearing on the nature of practice in that area.'* Anderson et al. noted that scoping reviews are used by researchers, professional bodies, policymakers, and funding agencies to map and analyse policy documents, identify gaps, and guide future research, practice, and clinical decisions.

A scoping review framework

Once the study design was selected, I adopted the Arksey and O'Malley scoping review framework. The framework was the first to develop a systematic and reproducible approach to scoping reviews, which can be applied to different data types. This is crucial, given that endometriosis policy has not yet been mapped. The framework also supports the inclusion of grey literature and performing a thematic analysis, both of which are important for achieving a comprehensive understanding of existing policies. The five stages of the framework are outlined below:

1) **Identifying the research question**. Identifying the reason for conducting the review and what it should achieve.
2) **Identifying relevant studies.** A systematic approach is needed to identify the relevant data needed to answer the research question.
3) **Selecting studies for inclusion.** An iterative approach is encouraged to allow the review to adapt to the retrieved data.
4) **Charting the data.** To describe the data obtained.

5) **Collating, summarising, and reporting the results**. To analyse the data and how far it can answer the original research question.

An optional 6th step is stakeholder consultation, which Levac et al. in 2010[202], recommended be a requirement to increase methodological rigour and relevance. The Joanna Briggs Institute (JBI) developed a Manual for Evidence Synthesis[203] building upon these frameworks, which has been followed in the generation of this scoping review.

Defining the research question

As per the JBI Manual for Evidence Synthesis[203], the PCC framework[204] (population, concept, and context) was followed to define the scoping review question:

- **Population:** People with endometriosis
- **Concept:** Availability and maturity of healthcare policies and delivery systems
- **Context:** By country

"What is the availability and maturity of healthcare policies and delivery systems for people with endometriosis across different countries?"

The definitions of the terms used within the research question can be found in **Appendix 6.**

Identifying relevant documents

Following the JBI Manual for Evidence Synthesis, [9] I conducted a database and grey literature search to identify relevant documents and reported the results according to the

Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) checklist.[12] The database search was intentionally broad to maximise identification of endometriosis policy. Given the nature of policy documents, grey literature searching was expected to play a major role and was conducted in comprehensive stages.

Database search

The JBI Manual for Evidence Synthesis[203] recommends following McGowan et al.'s evidence-based guideline for Peer Review of Electronic Search Strategies (PRESS)[205], which recommends that the main search be done by a librarian and peer-reviewed by a second librarian. As such, I developed an initial search strategy, which was refined and expanded by a senior information specialist (funded by the International Committee Monitoring Assisted Reproductive Technologies) and then peer-reviewed by a second independent information specialist using the PRESS tool. All searches were conducted on November 7, 2022, and were updated as of July 16, 2024. Using the multifile option and deduplication tool on the Ovid platform, we searched Ovid MEDLINE® ALL, Embase, and Global Health. We also searched CINAHL and EconLit on Ebsco, Web of Science (core collection), and Global Index Medicus (all indexes). Strategies employed a combination of controlled vocabulary (e.g., "Endometriosis", "Health Policy", "Health Services Accessibility") and keywords (e.g., "endometriosis", "policy", "health care access"), with no language or date restrictions applied to any of the searches. Files were downloaded and deduplicated using EndNote version 9.3.3 (Clarivate) and then uploaded to Covidence software (Veritas Health Innovation Ltd.), where I and a colleague (Devon Evans) independently screened the results. An initial test subset of titles and

abstracts was screened to mitigate any disparities in protocol interpretation. I resolved any conflicts with my second reviewer and referred to a third author if necessary. The full search strategy is presented in **Appendix 7.**

Grey literature search

Grey literature refers to documents produced by various levels of government, academia, or the media that are not subject to commercial publishing regulations[206]. I divided the grey literature search into two key steps based on the research question and the definitions of the research questions described above.

Step 1: Searching National Action Plans (NAPs)

NAPs describe how countries prioritise and plan to tackle health conditions. I aimed to identify the NAPs that best characterise the nation's health priorities, e.g., General Health NAPs, and the NAPs most likely to include endometriosis, e.g., Women's and Reproductive Health NAPs, and whether there were stand-alone NAPs for endometriosis. Therefore, I searched for 4 types of NAP in each of the 194 WHO member countries:

1) **National Action Plans for General Health** - plans which outline a country's health targets
2) **National Action Plans for Women's Health** – plans for all women's health conditions

3) **National Action Plans for Reproductive Health** – plans to improve the reproductive health of the population.
4) **National Action Plan for Endometriosis** – plans specifically targeted to improve the infrastructure for those with endometriosis.

For each of the 194 WHO member countries, a thorough search was conducted across Google, Department of Health websites, and the WHO repository to locate each of the four National Action Plans. The search included terms in the local language, utilising Google Translate (**Table 23**). Each country was searched to assess whether it had produced any of the documents above. Once a document was located, it was recorded on an Excel sheet and screened for eligibility and the inclusion of endometriosis within the document. Google Translate was utilised to screen documents, and all searching was conducted in Oxford, United Kingdom, most recently between January and March 2024.

Table 23: Grey literature search strategy for NAPs. The first 50 results were reviewed for each search.

Search Engine or website	***Search Terms (language)***
Google (reviewed first 50 results)	Country + national health plan (English + native) Country + national health strategy (English + native) Country + endometriosis plan (English + native) Country + endometriosis strategy (English + native) Country + women's health plan (English + native) Country + women's health strategy (English + native) Country + reproductive health plan (English + native) Country + reproductive health strategy (English + native) Country + fertility plan (English + native) Country + fertility strategy (English + native) Country + department of health (English + native) à search endometriosis Country + ministry of health (English + native) à search endometriosis Country + department of health (English + native) à search documents/policies à search endometriosis Country + ministry of health (English + native) à search documents/policies à search endometriosis
Google Scholar (reviewed first 50 results)	Country + national health plan (English + native) Country + national health strategy (English + native) Country + endometriosis plan (English + native) Country + endometriosis strategy (English + native) Country + women's health plan (English + native) Country + women's health strategy (English + native) Country + reproductive health plan (English + native) Country + reproductive health strategy (English + native) Country + fertility plan (English + native)

	Country + fertility strategy (English + native)
WHO mindbank[207]	Country resources à country à General health policies Country resources à country à General health strategies and plan

Each of the 194 WHO member countries were searched.

Step 2: Searching for high-level policy documents

Acknowledging that policy and initiatives would likely exist beyond what is found in NAPs, the second phase involved identifying other forms of documents, such as interparliamentary discussions, laws, bills, and reports of NGO initiatives, through comprehensive searches on Google and Google Scholar (**Table 24**). Country-specific sources were examined, including the International Federation of Gynaecology and Obstetrics (FIGO)-registered society guidelines, WHO-mind, Endometriosis.Org listed societies, and Department of Health websites from January to May 2023.

Table 24: Grey literature search strategy for endometriosis policy and initiative documents

Search Engine or website	***Search Terms (language)***
Google (reviewed first 50 results)	Country + endometriosis + policy (English + native) Country + endometriosis + strategy (English + native) Country + endometriosis (English + native) Country + endometriosis society (English + native)
Google Scholar (reviewed first 50 results)	Country + endometriosis + policy (English + native) Country + endometriosis + strategy (English + native) Country + endometriosis (English + native)
FIGO[208]	Search of endometriosis societies, resources and endometriosis guidelines (English)
Endometriosis.org[209]	National Endometriosis Organisations (English)

Each of the 194 WHO member countries were searched.

In January to March 2024, an update of the grey literature search was conducted based on high-yield terms from the initial search (**Table 25**).

Table 25: High yield grey literature search strategy for endometriosis policy and initiative documents.

Search Engine or website	***Search Terms (language)***
Google (reviewed first 50 results)	Country + endometriosis + policy (English + native) Country + endometriosis + action plan or strategy (English + native) Country + ministry of health (English + native) à search endometriosis

Each of the 194 WHO member countries were searched.

Screening the results

Each result was screened, and if it appeared to meet the eligibility criteria, it was included with pertinent information extracted, including the date of publication, source, and a summary of the document, including the type of policy document and the initiatives included. Non-English texts were translated either as whole texts using the Google Translate plug-in or by translating the text in sections using Google Translate.

The inclusion and exclusion criteria

The review includes publications from policymakers or prominent NGOs (source) on those with endometriosis (population), referring to policy and delivery systems (concept). The data were grouped by country, defined as a WHO member state (context). All (inter)national and regional documents were included, but priority was given to national documents. There was no language or date restriction. Data not from government-commissioned working groups, prominent expert groups, advocacy groups or NGOs were excluded, as priority was given to high-level policies. 'Prominent NGOs' in the context of this review describe groups that showed evidence of influencing policy decisions or showed a considerable potential to do so. After a discussion, it was agreed to include other sources, citing extracts from parliamentary hearings in the absence of official reports.

Selecting results for inclusion

Selecting NAPs

During the search and screening process, identified NAPs were assessed for their eligibility. All national, general health, endometriosis-specific, Women's Health, and Reproductive Health NAPs (including terms such as 'Sexual Health NAPs' and 'Fertility NAPs') were recorded, so long as there was evidence that policymakers, e.g. MoH, had been involved in their generation or approved the document. The NAPs were then screened to assess whether they 1) mentioned endometriosis and 2) included an endometriosis policy or initiative.

Selecting 'endometriosis laws'

During the search and screening process, laws related to endometriosis were identified. The laws regarding endometriosis were assessed to determine whether they constitute a comprehensive endometriosis strategy referred to as an 'Endometriosis Law' or whether it was a law for a single initiative. 'Endometriosis laws' constituted an alternative strategic framework to NAPs but included similar initiatives or goals. There were also laws for endometriosis initiatives, such as a law for a national Endometriosis Day, but these were included under *ad hoc* initiatives.

Selecting ad hoc initiatives

Ad hoc initiatives were classified as all endometriosis initiatives that existed outside of a strategic framework, e.g. NAP or 'Endometriosis Law'.

Charting, collating, summarising, and reporting the results.

Data for all 194 WHO member countries were charted in EXCEL and can be found in the **Appendix 8.**

Reporting NAPs

As previously discussed, the WHO Mental Health Atlas[200] prioritises stand-alone policies, therefore stand-alone endometriosis NAPs were prioritised within the results. NAPs, including an endometriosis policy (either a stand-alone endometriosis NAP or endometriosis policy integrated within another NAP), were assessed using the PANEL approach.[210] This approach is a framework provided by the Scottish Human Rights Commission: Participation, Accountability, Non-Discrimination, Empowerment and Legality. The framework can be used to assess whether a Human Rights-based approach has been taken in the generation of policies, such as NAPs. NAPs with only a single endometriosis initiative were not assessed using the PANEL approach.

If the information was available, the NAPs were reported in the results as follows:

1) **P – Participation:** How was the NAP developed/inspired, and were endometriosis patients/voices included and represented?
2) What are the key priorities of the NAP, and are there any flagship initiatives?
3) **N – Non-discrimination:** Were measures taken to identify at-risk groups and reduce discrimination against these groups?
4) **E – Empowerment:** Were there examples of attempts included in the initiatives proposed to empower endometriosis patients? E.g., empowering patients with sufficient information and support to empower their clinical autonomy. Moreover,

empowerment was assessed by whether the policy had attempted to protect secondary human rights, such as the right to work.

5) **L- Legality:** In the context of endometriosis policy, legality included whether legal frameworks had been considered, e.g., human rights frameworks or laws.
6) **A – Accountability:** How was accountability ensured, e.g., steering groups and status reports?

Reporting 'Endometriosis Laws'

As discussed, laws that outline a comprehensive legal strategy for endometriosis were reported as 'Endometriosis Laws', while laws for single initiatives were reported as *ad hoc* initiatives. Documents constituted as comprehensive 'Endometriosis Laws' were assessed using the PANEL approach as previously described.

Reporting ad hoc initiatives

Ad hoc initiatives were described in the context of the WHO Building Blocks[107] (**Figure 4**).

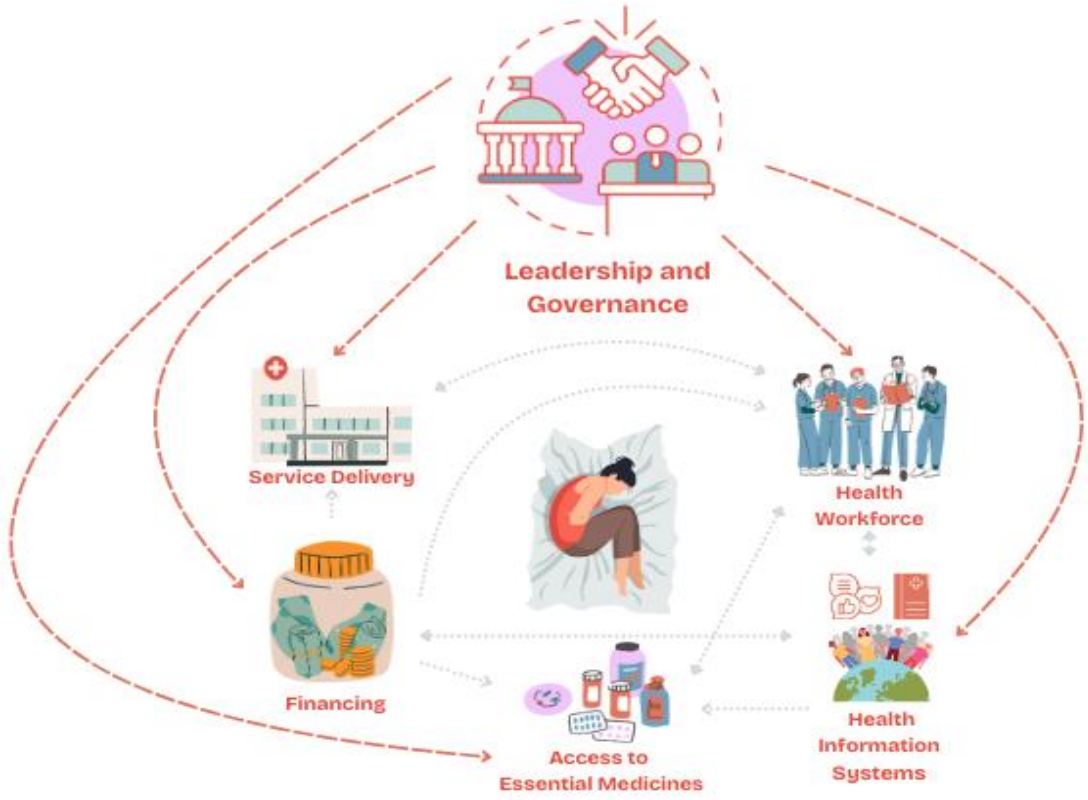


Figure 25: WHO Building Blocks mapped to the endometriosis infrastructure of care

Governance and leadership: This building block describes the strategic planning and oversight of health systems to ensure policies are implemented effectively and are accountable through monitoring practices. It is an integral building block that is interwoven into all of the remaining building blocks. **Service delivery:** This building block describes a health system comprising primary, secondary, and tertiary care to provide timely access to high-quality services, including specialised centres. **Health workforce:** This building block ensures that patients with endometriosis, when they seek support, are met with a well-trained, informed, and adequately distributed workforce. **Health information systems:** This building block builds a well-informed population, patient group and clinicians. This means patients are empowered with enough information to make autonomous decisions, and that endometriosis receives societal acceptance and understanding. **Access to essential medicines:** This building block encompasses the infrastructure necessary to develop a care system that ensures timely access to high-quality endometriosis treatments. **Financing:** This building block provides financial support and protection for the health challenges that people with endometriosis face. Health systems should support their population's ability to receive the care they need without financial hardship. Created on Canva.

A thematic analysis of the included results

A thematic analysis was conducted to summarise the initiatives identified. Using Braun and Clarke's [118] inductive and deductive approach, codes were generated, iterated, and refined as my understanding of the data developed, with similar codes collapsed to improve comparability. Coding was applied regardless of enforcement status,

recognising policy development as evolutionary (e.g. a bill and a law on National Awareness Day were coded together). Recurring themes were identified, then mapped onto the WHO Health System's six core building blocks [107] (**Figure 4**). Unless specified, in the results 'n' refers to the number of countries where documents were identified, regardless of how many documents per country. This avoided inflation from countries with multiple policies and allowed for global representation, even when data came mainly from leading NGOs

Describing the policy narrative

Various approaches exist for defining the stages of policy development. The review has centred the policy narratives laid out by Heuristic Models, such as Jones[211], Howlett and Ramesh[212] and the descriptive stages outlined by the WHO[213]. Heuristic models such as Jones'[211] propose that policy development often occurs in stages:

1. Problem Identification / Problem Definition
2. Agenda setting
3. Policy formulation
4. Adoption/decision
5. Implementation
6. Evaluation

I based the policy development cycle used in this review on the stages outlined above, but iterative changes were necessary to enhance the clarity of what is included in each stage (**Table 26**). However, it is essential to recognise that policy development is not a

linear process, and not all countries will need to progress through each stage before a policy is implemented or evaluated.

Table 26: Iterations to the heuristic policy development model, targeting it to endometriosis policy development.

Stage	Original stages within typical Heuristic Policy Models	Adapted for the review	Justification for the iteration
1	Problem Identification/ Problem Definition	***Raising awareness for endometriosis as a national problem***	This stage was renamed to reflect the identified crucial first step in endometriosis policy development which was raising awareness of endometriosis and the challenges it causes.
2	Agenda setting	***Setting the Agenda for a National Endometriosis Strategy***	I decided to merge these two stages into one, that describes the various events before policy is adopted. This was due to there being significant overlap between the two stages. For example, a raised bill for an endometriosis law could be considered within both stages and if it was then rejected would it have to be moved back down a stage.
3	Policy formulation		
4	Adoption/decision	***Adopting Policies Towards a National Endometriosis Strategy***	The premise remained the same, but the term was amended to improve clarity.
5	Implementation	***Implementing and Evaluating a National Endometriosis Strategy***	I decided to merge the two groups as no country has truly completed their strategy and reached the evaluation stage. However, there are examples of countries evaluating and refining their strategies whilst still implementing their strategies.
6	Evaluation		

I developed a single question for each stage to assist with understanding of which stage in the policy development narrative the country should be categorised.

Stage 0: Policy Development Narrative: No information detected

Countries with no evidence of endometriosis policies were categorised as 'no information detected.' During the review, the critical role of endometriosis societies in raising awareness of endometriosis and advocating for policy reform became clear. In consultation with the authorship group, their presence was included as a marker of countries that were 'Raising awareness of Endometriosis as a National Problem,' even where policymakers had not yet made strategic efforts to address it.

Key question: Did the search identify any documents on national endometriosis policy or initiatives (including efforts by an endometriosis NGO)?

If not, the country remains in this stage; if so, it can be considered for the next stage.

Stage 1: Raising Awareness of Endometriosis as a National Problem

Key question: Did the search identify evidence that prominent NGOs or policymakers had begun raising awareness of endometriosis as a national problem?

If yes, the country remained in this stage or was considered for the next stage; if not, it was moved to the previous stage.

As previously discussed, this category primarily appreciates the crucial efforts of NGOs in raising awareness of endometriosis. Therefore, countries were included in this stage if an advocacy NGO with implemented initiatives was present. It also includes countries where policymakers have demonstrated awareness of the challenges of endometriosis in their nation but have not yet initiated the development of a strategic response.

Stage 2: Setting the Agenda for a National Endometriosis Strategy

Key question: Did the search identify evidence that policymakers were 'setting endometriosis on the political agenda', e.g., through interparliamentary discussions on endometriosis, political leaders' statements of intent for reform, passing *ad-hoc* initiatives or raising bills for an 'endometriosis law' or NAP?

If yes, the country remained in this stage or was considered for the next stage; if not, it was moved to the previous stage.

This stage primarily included countries where there was evidence that policymakers had begun considering or developing their political response to endometriosis. This could be as early as holding interparliamentary discussions on various aspects of endometriosis that they have determined need addressing and releasing statements of intent to raising bills and motions for a national policy. In instances where it was unclear if a strategic response had begun, it was decided that initiatives spanning two or more of the WHO healthcare building blocks were necessary to claim a strategic response had been

initiated. Although this stage was primarily reserved for countries with policymaker action, it was decided that countries with NGOs that had drafted and presented a national endometriosis action plan were also included in this group. This was to recognise the vital efforts of NGOs in devising action plans tailored to the country's needs, often in response to their work with patients. This is crucial information for policymakers to ensure their policies and initiatives have endometriosis patients at the centre.

Stage 3: Adopting Policies Towards a National Endometriosis Strategy

Key question: Did the search identify that the country had a national endometriosis strategy (including integrated NAPs) or law, or had passed a bill/motion for one?

If yes, the country remained in this stage or was considered for the next stage; if not, it was moved to the previous stage.

This stage is described when the policy has been adopted. However, there are variations depending on which policy development model is followed. Jones' model describes 'policy adoption' followed by 'policy implementation', whereas Howlett and Ramesh move through 'policy formation', 'decision making', and then 'policy implementation.' Moreover, the guidance from the WHO Director of Science, Information and Dissemination[214], combined 'decision making' into 'policy formation' and described this stage as where recommendations for policy are made and decided upon following the assessment of national data, consultation with stakeholders and identification of barriers. The Director then goes on to describe 'policy implementation' as the process of

deciding upon implementation strategies and plans, establishing timelines and deadlines, and allocating responsibilities. O' Toole's critical review[215] of policy implementation research also describes the implementation stage as what happens after the government's intention to act. However, in the context of endometriosis policy obtained from the included results, I believe this more accurately represents policy adoption (the process of passing national endometriosis laws, bills or creating endometriosis NAPs), and wanted the review to prioritise evidence of action over intention to avoid any misunderstanding based on assumptions (e.g., that passing a law meant policies had been implemented). Thus, the group was renamed to 'Passing Policies towards a National Endometriosis Strategy.'

Countries at this stage ideally had developed a comprehensive endometriosis strategy; however, I decided that even countries with modest initiatives within a policy framework would be included, in appreciation of the evolving nature of policy, which often begins small and develops over time.

Stage 4: Implementing and Evaluating a National Endometriosis Strategy

Key question: Did the search identify whether the country's endometriosis strategy had been implemented and/or evaluated? E.g., through the detection of a progress report.

If yes, the country remained in this stage; if not, it was moved to the previous stage.

This stage is renamed from the traditional 'evaluation of policy' as described by the WHO[214] to monitor progress, ensure accountability and evaluate the outcomes of the policy. The stage was reserved for countries where the search identified evidence that the country's national action plan had been implemented, for example, due to the release of a progress report that outlined the initiatives within the strategy that had been implemented. As highlighted in the results, the later evaluation stages include assessing the success of the strategy and its national impact.

Reporting the policy development narrative

The judgment of where a country was within the policy development cycle described was based on the highest available national data, wherever possible. However, if a country contained regions which had progressed into a higher stage, the country was assessed to determine whether there was sufficient evidence to suggest that other regions would follow. This was to appreciate that some countries have more provincial systems regarding health policy, e.g., Argentina and Italy. Moreover, to appreciate the evolving nature of development in these countries, which usually starts from a few provinces and expands nationally (likely influenced by each other). I presented my judgments visually on a map using MapChart.net. The phases of the policy development cycle were assigned different colours, and distinctions were made based on whether the judgment was based on national or regional data.

Stakeholder Consultation

As discussed, Levac et al.[202] recommended making stakeholder consultation mandatory in scoping reviews. To minimise the risk of missing data and to improve the contextual

understanding of the data I retrieved, I planned to release a survey to 'prominent' endometriosis advocacy groups and obstetric and gynaecological professional groups identified for each country. The email sent was based on whether evidence of the endometriosis policy had been found or not. In countries where no documents were identified, the following would be sent (option 1):

'As we have been unsuccessful in locating national documents within [insert region], we kindly request your cooperation in answering the following questions and sending the supporting documents.

1) Does your country have a national endometriosis policy/strategy/plan?

2) If your country does not have a national endometriosis policy, are you aware of any government/parliamentary discussions being conducted regarding endometriosis policy development?

3) Are you aware of any other endometriosis policy or guidance documents in your region (including any generated by your organisation)?

4) Is endometriosis care public or privately funded within your region?

5) Are specialist endometriosis centres available in your region? If so, how many? If not, how are those with endometriosis managed?

6) Are you aware of any documents supporting or describing the rights of those with endometriosis in your country?'

In countries where documents have been found, the following message would be amended appropriately based on the results. The emails were sent in English and their

primary language. If I receive no response in 2 weeks, the survey will be emailed again, after which I recorded 'no response.'

Unfortunately, I only received 8 responses from the initial 64 emails I sent, although these responses were reassuring that in regions that I had not identified endometriosis documents there in fact were no endometriosis policy. Nevertheless, we decided to take an alternative approach, which included consulting an international endometriosis health policy working group (International Committee Monitoring Assisted Reproductive Technologies Working Group). The working group included experts from 17 countries, which included representation from every continent (Australia, Brazil, New Zealand, France, United Kingdom, South Africa, United States / Puerto Rico, United States, India, China, Japan, Kenya, Italy, Netherlands, Turkey, Hungary, Belgium, Chile). The working group reviewed the results and provided contextual feedback and advice, which are discussed in the results.

Results

Included documents

A total of 12,127 documents were retrieved from the database search. Once the exclusion criteria were applied, only 34 documents were included, as the databases primarily held academic literature. In addition, 443 grey literature results were included, totalling 477 documents (**Figure 26**).

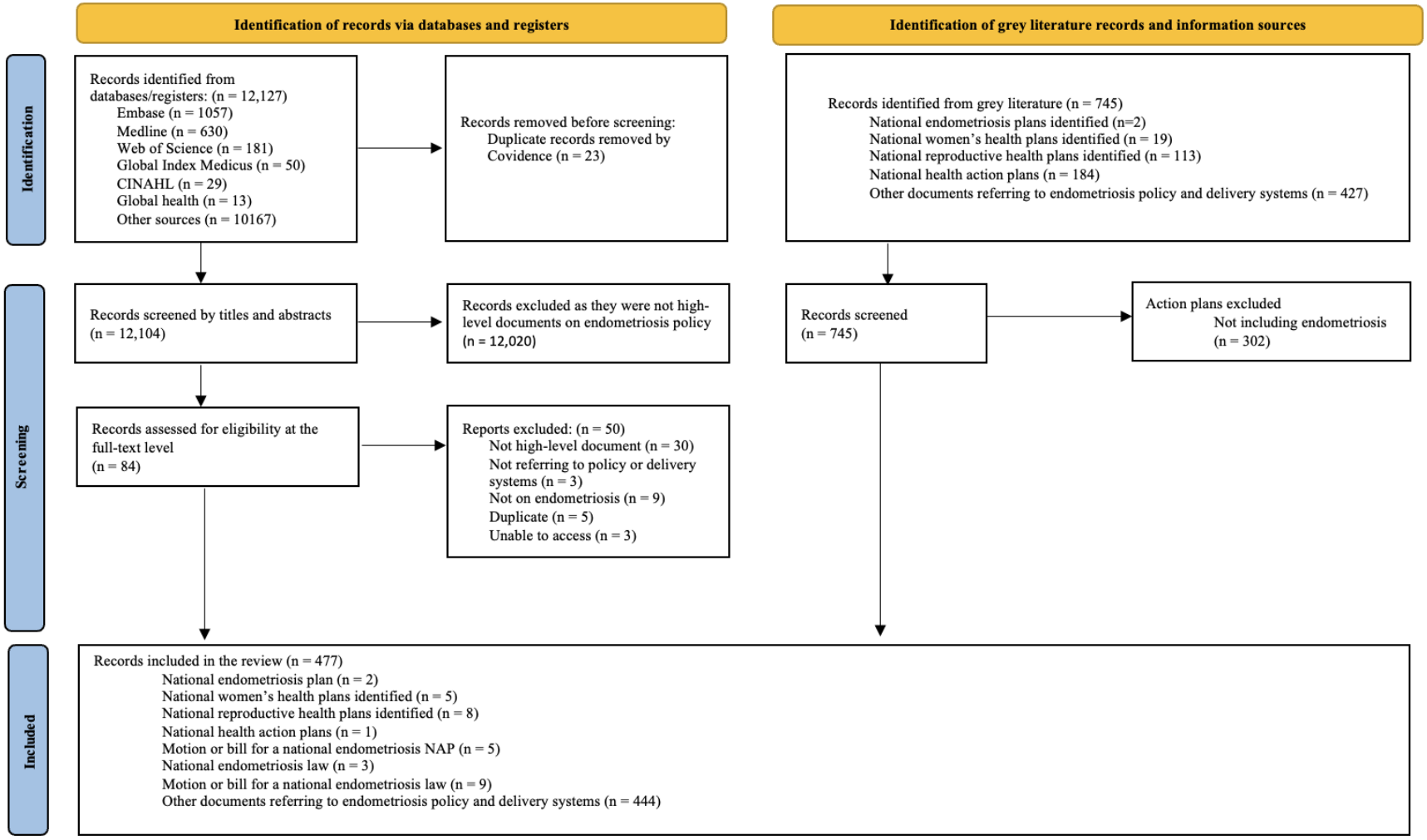


Figure 26: PRISMA-ScR[215] flow diagram summarising the process of record identification and selection.

N= number of documents

Results presented within the WHO Building Blocks

The Leadership and Governance Building Block

This building block discusses the strategic planning and oversight of health systems to ensure that policies and initiatives are implemented effectively and are accountable through monitoring practices.

The scoping review found four approaches used by countries to operationalise their endometriosis policies and initiatives, including the development of three strategic frameworks: 1) Stand-alone endometriosis NAPs, 2) Integrated endometriosis policies within other health NAPs, such as Women's Health NAPs, 3) Stand-alone endometriosis law (**Table 5**).

'Stand-alone' refers to a dedicated national document exclusively on endometriosis. Stand-alone laws and plans are key indicators used to monitor policy progression in the WHO Mental Health Atlas[199,200]. The final approach countries used was *ad hoc* initiatives. These initiatives existed outside of a strategic framework but were designed to address a specific area of concern, e.g. the development of an awareness campaign to improve endometriosis awareness.

Table 27:The availability, content and comparisons of global national endometriosis governance and leadership documents (e.g., laws and NAPs).

Endometriosis Strategies		National Endometriosis Plan		Women's Health Plan				Reproductive Health Plan					General Health NAP	Endometriosis Law				
Countries with Endometriosis Documents		**Australia**[216]	**France**[217,218]	**Australia**[219]	**France**[220]	**UK**[221–223]	**Ireland**[224]	**Finland**[225]	**France**[226]	**Italy**[227]	**Maldives**[228]	**Mauritius**[229]	**Italy**[230]	**Argentina**[231–237] **(combined regional)**	**Colombia**[238]	**Italy** [239–248] **(combined regional)**	**Panama**[249]	**Peru**[250]
Endometriosis Initiatives Identified Within Core Healthcare Building Blocks																		
Service Delivery	**Establishment of clinical pathways**	x	x	x	x	x				x				x	x	x		x
	Policies to improve access to care	x	x	x	x	x					x			x	x	x	x	x
	Provision of clinical guidelines	x		x		x				x				x	x	x		
	Develop multidisciplinary teams	x	x												x	x		
	Diagnostic and treatment innovation	x	x	x	x										x	x		
	Promotion of specialist endometriosis centres	x	x		x	x	x			x				x	x	x		x

Health System Financing	**Minimising financial barriers to care**	x	x	x		x								x	x	x		x
	Recognition of chronic or disabling symptoms especially in the context of financial protection	x		x										x	x	x		
Health Workforce	**Healthcare staff training**	x	x	x						x				x	x	x	x	x
Health Information Systems: awareness	**Awareness campaigns**	x	x	x	x	x				x	x			x	x	x	x	
	Education initiatives	x	x	x		x				x	x			x	x	x	x	
	Improving access of educational resources	x	x	x		x									x	x		
	Development of patient registries	x (research)	x											x	x	x	x	x
	Improvements to workplace support	x	x	x		x									x	x		
Health Information Systems: Research	**Clinical trials network or programmes**	x	x	x	x										x	x	x	
	Biorepository	x																

	Epidemiological databases	x	x										x			x	x
	Research funds	x	x	x		x			x				x	x	x	x	
	Patient engagement in research	x													x		
	Research on pathophysiology	x	x	x													x
	Research on environmental triggers							x									
	Research on/to reduce disease burden	x	x													x	x
	Research on associated infertility	x										x					

NAPs that did not include initiatives and only made reference to endometriosis were not included in the table but are referenced in the main text. Note, England, Northern Ireland and Scotland are included under the United Kingdom as per the WHO member list, thus, a total of 1 WHO-recognised country.

Leadership and Governance Building Block: Stand-alone Endometriosis NAPs

Two of the 194 WHO member countries, Australia and France, had stand-alone endometriosis NAPs. The 2018 Australian National Action Plan for Endometriosis (NAPE)[216] was the first to be developed. Its generation was inspired by "passionate patients and parliamentarians", called parliamentary friends of endometriosis awareness.[251] The NAPE's three main priorities were raising awareness, maximising access to clinical management and promoting research. A flagship initiative was the development of the National Endometriosis Clinical and Scientific Trials (NECST) Network,[252] comprising of clinicians, scientists and patients committed to filling gaps in endometriosis research. To reduce the risk of discrimination and barriers to health of at-risk groups, the NAPE highlighted that care provided should be culturally and linguistically tailored.[216] The Endometriosis Advisory Group ensured accountability to drive the implementation of the plan's actions. Progress updates were scheduled for review at 1, 3 and 5 years. A 2024 progress report [253] highlighted various project-specific investments totalling 87.2 million Australian Dollars. The efforts included endometriosis research grants, support for EndoZone [254] (an educational digital platform for patients), and the Periods, Pain and Endometriosis Programmes [255] (teaching students about unusual menstruation). The report stated that all the planned projects have been initiated, with estimated completion dates provided up to 2026. The next phase will be to complete and evaluate the initiative's effectiveness.

The French endometriosis NAP[218] followed in 2020. Similarly to the Australian NAPE, the French NAP was developed in consultation with nearly "200 experts, patient associations, health professionals and researchers". Both NAPs shared the same three priorities: raising

endometriosis awareness, improving access to quality care and supporting research. Its flagship initiative is to develop the world's largest endometriosis epidemiological database using six French cohort studies to generate accurate epidemiological data on endometriosis. The NAP recognised the presence of populations and regions with unequal access to care. It stipulated that these should be targeted in future regional health projects (PRS) with the assistance of patient associations and regional health observatories. Accountability was ensured through the oversight of various ministries, which have developed roadmaps to achieve the NAP targets. In 2023, the NAPs steering committee, made up of various ministries including the Minister of Higher Education and Research, the Minister of Health and Prevention, and the Minister for Equality between Women and Men, declared that 85% of NAPs initiatives have been implemented or completed.[256] For example, to ensure patients receive a timely diagnosis and quality care nationwide, the NAP planned the establishment of dedicated endometriosis units in each geographic region. Supported by €4.5 million annually from the Regional Intervention Fund, five regions have already completed setup, and the Health Minister stated that the remaining units must be set up by the end of 2023.

In six countries, policymakers have raised motions for an endometriosis NAP, including Sweden in 2019, Austria, Canada, Germany, Spain (regional) in 2022 and Portugal in 2023.

Leadership and Governance Building Block: Endometriosis Policy Integrated Within Women's Health NAPs

Nineteen of the 194 WHO member countries were found to have Women's Health NAPs (see **Appendix 8**). Only four countries had government-led Women's Health NAPs with

endometriosis initiatives integrated: Australia and France (in addition to their NAPs), Ireland, and two in the UK.

Scotland's Women's Health NAP of 2021-2024 [221] was guided by the Endometriosis All-Party Parliamentary Group (APPG) Inquiry,[257,258] which included the insights of 10,783 people with endometriosis. The NAP aimed to reduce the diagnosis delay from 8 years to 12 months. Similarly to the stand-alone endometriosis NAPs, initiatives to raise awareness, improve access to quality care and support research were discussed. A fundamental goal was to empower women with consistent information on their health throughout their life course. The NAP addressed gender inequalities in healthcare by aligning its policies with the European Convention on Human Rights and the Convention on the Elimination of Discrimination Against Women. The Women's Health Plan Implementation Programme Board ensured accountability and that the plans were implemented appropriately. A 2023 progress report [222] highlighted completed initiatives being implemented to achieve the NAPs aims. For example, to support the NAPs aim of developing care pathways, NHS Scotland has approved a standardised Integrated Endometriosis Referral Care Pathway as part of the Modernising Patient Pathways Programme (MPPP) to outline how patients with suspected or confirmed endometriosis should be referred and managed. Moreover, to support the NAPs intentions to commission research, in December 2022, £250,000 was allocated to research projects developing improvements in endometriosis treatment and management.

The second NAP in the UK that integrated endometriosis policy is England's 10-year Women's Health Strategy 2022[223] , that responded to the gender inequality in healthcare and a call for evidence from women and expert stakeholders. Similarly to the other NAPs discussed,

England's NAP initiatives aimed to raise endometriosis awareness, improve access to clinical care and support research. A cross-government delivery system is overseeing the implementation of the NAP, and an implementation framework has been provided to demonstrate how the NAP will be implemented and refined, with a progress report expected in 2025.

The Irish Women's Health NAP 2022 – 2023[224] aimed to improve endometriosis clinical care. The 2023 progress report highlighted the establishment of two supra-regional specialist centres and additional funding to develop a regional network for endometriosis.

Leadership and Governance Building Block: Endometriosis Policy Integrated Within Reproductive Health NAPs

113 out of 194 WHO member countries were found to have reproductive (including sexual or fertility) health plans; only 31 were current as of 2024. NAPs of only 8 countries referred to endometriosis, including 5 that outlined government initiatives (Finland, France, Italy, the Maldives, and Mauritius). See the **Appendix 8**, for the identified NAPs.

The Maldives' 2020-2025[228] National Reproductive Health Action Plan (RMNCAH), a collaborative effort of various stakeholders, including the Ministry of Health, NGOs and UN agencies, aimed to increase endometriosis awareness, access to care (including services for complex cases), and endometriosis research. The NAP highlighted that the unknown national prevalence of endometriosis, limited awareness, and insurance providers' disease classifications were current barriers to care, which could be overcome through national research. This would support the advocacy for endometriosis care to be included in national

health insurance packages. Accountability was ensured by assigning each intervention a responsible group and developing annual targets, for example, the gradual increase in tertiary hospitals offering endometriosis care from 75% in 2020 to 100% in 2025.

Three reproductive health NAPs included a single endometriosis initiative, most centring around education and research. Italy's 2014 fertility NAP [227] focused on teaching healthcare professionals factors that affect fertility and strategies to assist with the early diagnosis of endometriosis. Finland's sexual and reproductive NAP 2014–2020[259] wished to investigate the effects of environmental toxicants on diseases such as endometriosis. Whilst Mauritius' 2022-27 NAP [229] set research priorities of data gathering for an endometriosis "severity and infertility" survey.

Cabo Verde's 2008-2012 NAP highlighted endometriosis as a frequent cause of consultations. Whilst Chile and Malawi referred to the use of oral contraceptives for endometriosis.

Leadership and Governance Building Block: Endometriosis Policy Integrated Within General Health NAPs

General Health NAPs typically outline the nation's health priorities and could indicate how far endometriosis was considered a national priority. National health plans were identified in 184 countries, but only 106 were current in 2024 (found within the **Appendix 8**). Only Italy included endometriosis, to support endometriosis research, including the study of national incidence.

Leadership and Governance Building Block: Stand-alone 'Endometriosis laws'

Ten countries (Argentina, Brazil, Chile, Costa Rica, Dominican Republic, Italy, Mexico, Portugal, Uruguay and the USA) have taken an alternative approach to developing an endometriosis policy by raising bills for a national 'endometriosis law.'

'Endometriosis laws' have been passed in 5 countries: Panama, Colombia and Peru nationally, Italy and Argentina regionally. These bills and laws often provide a comprehensive framework and legislative obligation for policymakers to develop and implement strategies for endometriosis. Initiatives included in the Endometriosis NAPS and 'Laws' share many similarities, as explored in the policy comparison **Table 27**. All of the 'laws' promoted initiatives to improve access to care, train healthcare staff, promote research, and develop patient registries.

In April 2021, Panama passed the endometriosis bill (440) into 'Law 213'.[249] This law assigned the Ministry of Health the responsibility of developing strategic initiatives to raise awareness, provide training for groups such as healthcare workers, improve access to care, and promote research. NGOs such as patient groups were encouraged to participate in the development of initiatives that followed from the law. Furthermore, an interinstitutional commission would be developed to empower endometriosis patients with information and support. To promote labour rights, the law recognised endometriosis as a chronic disease under Panama's Labour Law 59 of 2005. Finally, in Law 213, budgetary and oversight responsibilities were stipulated to ensure accountability. The search did not locate information on the implemented initiatives.

Two ‘endometriosis laws’ were passed in South America in 2023. Peru passed Law 31868[250] encouraged initiatives to improve health worker training, creating specialised service units, a patient registry, and progressively implementing programs to assist with fertility preservation. Two months later the president of Colombia sanctioned ‘Law 2338,’[238] which allocated the Ministry of Health one year to implement a comprehensive endometriosis public policy. Both Peru and Columbia’s law actively encouraged citizen and NGO participation in the development of initiatives. Similar to Australia, France, Scotland, England and the Maldives’ NAPs and Panama’s law, Colombia’s law proposed initiatives to raise awareness, improve clinical care services and pathways, health worker training and research programs. A key initiative was the promotion of flexible working arrangements for those with endometriosis. Accountability was encouraged with the requirement of an annual report to the Colombian Congress. However, the report was not identified in the search.

In addition to the bills for a national endometriosis law, Italy (2012-2021) and Argentina (2019-2023), both with strong provincial healthcare regulations, passed numerous regional laws with similar objectives to the national laws (**Table 27** global policy comparisons). For instance, in 2016, the Italian Chamber of Deputies approved a motion[260] that called on the Italian government to adopt initiatives recognising endometriosis as a disability, reducing healthcare costs, improving workplace support, and enhancing research and awareness, including the establishment of a national register. In response, several Italian regional councils and governments have introduced regional laws[239–248] that reflect many of these objectives.

Leadership and Governance Building Block: Ad hoc initiatives

Even in the absence of organised policy frameworks, such as NAPs and Laws, fragmented *ad hoc* initiatives for endometriosis exist. However, they often fail to demonstrate the nation's strategic vision for endometriosis as clearly as policy frameworks and often do not offer the same level of accountability.

Ad hoc initiatives were analysed and aggregated alongside the NAPs and Laws and described within the remaining 5 WHO Healthcare Building Blocks. The full list of initiatives for each country, along with the building blocks they serve, can be found in the **Appendix 8**.

Initiatives Within the 'Service Delivery', 'Health Workforce', and 'Access to Essential Medicines' Building Blocks

46 countries described initiatives within the clinical care building blocks. Governments often began by commissioning working groups to provide clinical recommendations. The most common initiatives within this theme included the development of accredited specialist services (n=25) usually to address specific needs of those with severe disease, refinement of training for healthcare staff (n=18), cohesive care networks (n=15) and the development of structured care pathways (Argentina, Australia, France, Ireland, Italy, Spain, USA, and the UK). Endometriosis clinical care guidelines were another common initiative.[173] and were complemented by twelve documents on international clinical consensus statements from clinical experts such as the World Endometriosis Society (WES) and the EndoKey Group.[261,262]

Initiatives Within the 'Financing' Building Block

Sixteen countries demonstrated initiatives to alleviate some of the financial burden associated with endometriosis (**Table 28**).

Table 28: Notable examples of initiatives raised to reduce the economic burden of endometriosis.

Country	Year	Initiative
Slovakia	2004	Act No. 777/2004 Coll in 2004 was an early example of policy reform entitling those with endometriosis three cycles of assisted reproduction procedures up to the age of 39.[263]
Kenya	2019	In 2019, endometriosis medical treatments including Danazol, Dienogest, Goserelin and the Levonorgestrel-releasing Intrauterine systems were introduced within Kenya's Essential Medicines List (KEML).[264] Inclusion of endometriosis treatments in the KEML supports access to care by ensuring they are prioritised in public financing. As the KEML shapes Universal Health Coverage benefit packages, this step also contributes to reducing out-of-pocket costs.
Iceland	2020-2022	In 2020, the government announced ISK 20 million in subsidies for hormonal IUDs for women requiring them for clinical reasons, such as endometriosis.[265] Subsequently, the Ministry of Health entered a formal agreement in 2022 with private clinics to fund endometriosis surgeries, aiming to reduce waiting times, improve access to care and provide financial protection.[266]
Spain	2023	Spain introduced several key measures to provide financial support individuals with endometriosis. The 2023 approved State Budget Law[267] allocated €3 million for egg preservation for those with endometriosis. Moreover, the 2023 Law 1/2023 [268] amended Law 2/2010 on sexual and reproductive health and provided sick leave (menstrual leave) entitlements by recognising endometriosis as a temporary disability to increase support in the workspace.

As per the protocol, countries without NAPs or national laws (which have already been discussed) were prioritised to provide a wider scope of global initiatives.

Progressive trajectories for financial protection exist, starting with reimbursing specific medical treatments, progressing to providing universal coverage for care and advancing to providing fertility services, such as cryopreservation.

Initiatives Within the 'Information Health Systems' Building Block

Three key types of information health systems are being implemented for endometriosis: information systems to raise awareness, provide education and promote research.

Initiatives by multiple stakeholder levels have been implemented to raise awareness and education of endometriosis (n=52). Initial efforts by policymakers include publishing educational articles on their websites (n=13), with more advanced efforts including declaring a national Endometriosis Awareness Day/Week/Month in March (n=12). Argentina (regional), Italy, Canada (regional), Croatia, Brazil, and Portugal have in fact passed laws or acts establishing an Endometriosis Awareness Day. Awareness efforts not only improve the societal understanding and appreciation of endometriosis but can even stimulate policy reform as seen in the EndoMarch Global Movement, which involved over 100 organisations, and has contributed to political initiatives such as the bipartisan bill for endometriosis research funding in the United States.[269]

Education is another crucial information system, especially in adolescents, when endometriosis symptoms often develop. Numerous countries have made efforts to develop educational campaigns in schools to enhance understanding of what symptoms are abnormal (n=14) (**Table 29**). Promotion of school educational campaigns establishment can be found in various commissioned reports, drafted or actioned endometriosis bills, laws NAPs and even guidelines (e.g. South Africa).

*Table 29: **Notable examples of implemented initiatives identified to raise awareness and education of endometriosis, especially among the young***

Country	Year	Initiative
New Zealand	1998-2024	The What about me® programme[270], developed by Endometriosis New Zealand, is one of the most successful and evidence-based school initiatives globally for menstrual and endometriosis education. Launched in 1998, it reached over 300,000 students and significantly improved early recognition of endometriosis, with the proportion of under-20s seeking help rising from 12% in 2001 to 62% in 2015. The programme combines WHO-endorsed health education practices with accessible, inclusive content and has received international recognition and awards. Now available as a free national e-learning platform, it serves as a global model for empowering adolescents to understand menstrual health and seek timely care.
Barbados	2014-2019	A progress report[271] by was published by the United Nations Economic Commission for Latin America and the Caribbean to track the progress Barbados had made between 2014-2019 in advancing gender equality and empowering women and girls, specifically in relation to the Beijing Platform for Action, an international agreement established at the Fourth World Conference on Women in 1995. The review highlighted the important work of the Barbados Association of Endometriosis and PCOS who had launched educational initiatives such as visiting schools and speaking to students and sharing a book they published a book, with UNFPA's to schools but also governmental agencies. Moreover, the association has created various culturally grounded toolkits to support Caribbean and Afro-Caribbean individuals affected by endometriosis.
Argentina (Tucumán region)	2019	Tucumán was the first Argentine province to pass an endometriosis law in 2019 which guaranteed comprehensive, free access to diagnosis, treatment, and follow-up for endometriosis patients. A key initiative was the "Aula Amarilla" (Yellow Classroom)[272] within a hospital, that served as a space for community-based educational and psychosocial support. Workshops are held in this classroom led by nutritionists, psychologists, and physical activity specialists, along with recreational sessions and public education talks.

As per the protocol, countries without NAPs or national laws (which have already been discussed) were prioritised to provide a wider scope of global initiatives.

Finally, promotion of research is a vital information system implemented by many countries (n=18), primarily through funding endometriosis research projects (n=9) (**Table 30**).

Table 30: Notable initiatives identified in the search to fund endometriosis research.

Country	Year	Initiative
Canada	2018-2020	The Canadian Institutes of Health Research (CIHR), a government federal funding agency for health research, has supported various notable endometriosis research initiatives. For example, The CIHR Early Career Investigators in Maternal, Reproductive, Child and Youth Health Grant, was awarded to an endometriosis project in 2018.[273] Moreover, a Women's Health Clinical Mentorship Grant[274] supported the "next generation of women's health clinician-researchers" in fields such as endometriosis. In 2020, the programme awarded a maximum of CAD 50,000 for one year to each of the selected 12 mentorships. Two grants were provided to endometriosis mentorships. Finally, the CIHR Canada Research Chairs Program which invests over CAD $300 million to "achieve research excellence" included the appointment of a national chair for endometriosis research.[275]
US	2022 - 2023	In 2020, the US House of representatives approved an amendment to double the funds for endometriosis research from $13 million in 2019 to $26 million for the fiscal year beginning Oct. 1, 2020.[276] Subsequently, the US congress introduced the HR 7974 Coverage, Awareness, Research, and Education (CARE) Act[277] of 2022 which required the Department of Health and Human Services to address endometriosis through various initiatives such as those to increase awareness and research. No results were found on its enactment status. The 2022 HR 2617 bill however has been passed and enacted by US Congress. It aimed to provide funds for endometriosis research programmes to assess endometriosis causes, treatments and potential cures. Later, in 2023 the first White House initiative was launched to fund research in conditions such as endometriosis affecting women.

As per the protocol, countries without NAPs or national laws (which have already been discussed) were prioritised to provide a wider scope of global initiatives.

Information systems, including awareness, education, and research efforts, are crucial to ensuring patients are empowered with the information they need for clinical autonomy and for ensuring policies receive societal acceptance.

Analysing the Policy Development Narrative

Analysing the results, a policy development narrative emerged that fit with the recognised 5-stage policy development cycle (stage and justification for each country can be found in the (**Appendix 8**). The ultimate goal is to develop a comprehensive, stand-alone policy that encompasses various elements of the healthcare building blocks, with measurable outcomes, to evaluate and refine the infrastructure based on the evolving requirements of its population.

Not only would this be beneficial for individual countries to track their progress, but it would also enable the establishment of global programs, such as the WHO Mental Health Atlas, for endometriosis.

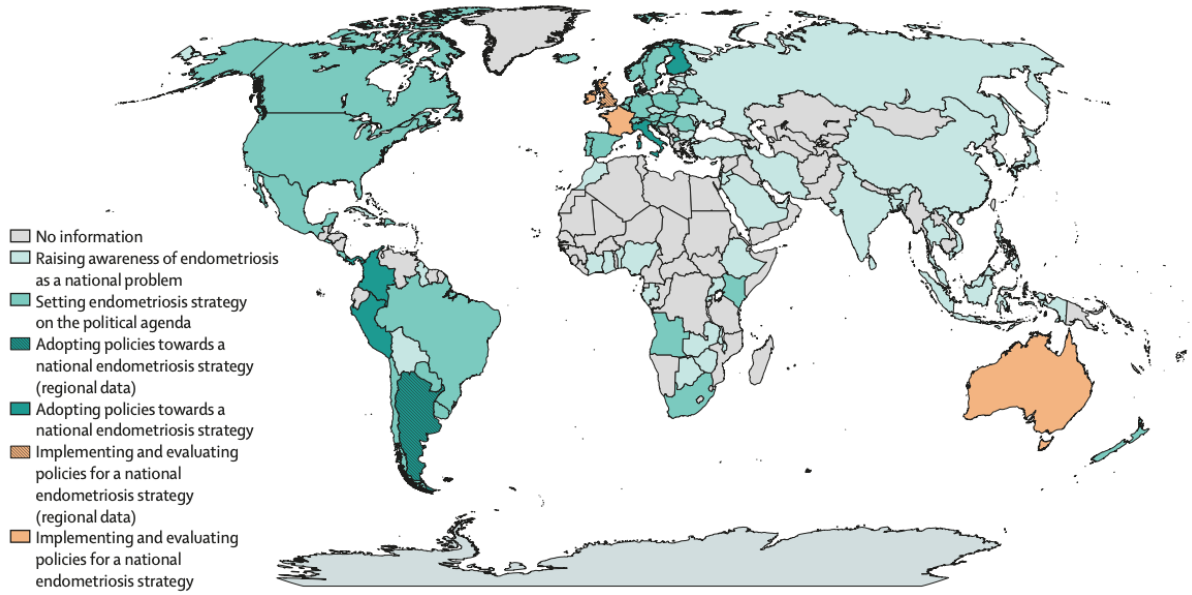


Figure 27: Policy development cycle map.

The global map representing how far countries are within the policy development cycle. Created using MapChart.net.

Policy Development Narrative: No Information Detected (98 countries)

Recognising endometriosis advocacy groups as a fundamental driver in developing endometriosis policy, countries without detectable endometriosis policy documents, initiatives or an endometriosis society were classified as 'no information detected'. This term reflects the plausibility of missing data due to the challenges of obtaining international policy documents. This classification was given to 98/194 countries (classifications for each country are within the **Appendix 8).** 80 countries were classified as low to middle-income countries.[278] These regions may represent the countries in greatest need of endometriosis advocacy.

Raising awareness of Endometriosis as a National Problem (48 countries)

This initial stage of policy development involves stakeholders recognising endometriosis as a national problem and taking steps to raise awareness. The classification was often given due to the crucial representation of prominent advocacy groups and NGOs. It also included cases such as in Botswana, where the Minister of Health identified endometriosis as a public health concern, but among available resources, life-threatening diseases were prioritised over endometriosis.

Setting the Agenda for a National Endometriosis Strategy (36 countries)

Agenda setting ranged from policymakers declaring their intent to develop reforms to introducing bills for an endometriosis strategy. Moreover, it included countries such as Croatia, Denmark, Romania, Luxembourg, Slovenia, and South Africa, where NGOs had developed draft strategies for endometriosis, which had been presented to political leaders. Although notable initiatives were identified, they lacked a strategic policy framework.

Adopting Policies Towards a National Endometriosis Strategy (8 countries)

8 countries had adopted endometriosis policies within a strategic framework, e.g. comprehensive laws or NAPs, allowing for the development of a structured and accountable response to the nation's endometriosis challenges. However, this group is limited by evidence of the implementation of the described policies.

Implementing and Evaluating a National Endometriosis Strategy (4 countries)

Australia, France, the UK (Scotland) and Ireland demonstrated the development of endometriosis strategies and provided evidence of their implementation in progress reports. The stand-alone NAPs were the most comprehensive, but all had initiatives for clinical care, awareness and research, except for Ireland, which had clinical care initiatives. Progress reports are the initial stages of the evaluation process. The later stages are assessed by evaluating the impact of the NAP on its population, which no country has yet conducted. Australia is the furthest along, with the 2024 progress report demonstrating that the initiatives are in the final stages, with the evaluation and refinement of the NAPE to commence.[253]

Results of the stakeholder consultation

The stakeholder consultation exercise was performed to enrich the contextual understanding of the manuscript and to highlight any missing data. Overall, the stakeholders believed the results accurately represented the availability of data in their country. However, it was noted that there was missing data in terms of representing the countries delivery system. For example, a stakeholder from Hungary noted that endometriosis care, including surgery and IVF treatments, is fully free within the public health system, tax relief is available post-surgery, and there are unique therapies such as medicinal water treatments. Additionally, that a national guideline was signed in 2024, and efforts are underway to reduce diagnostic delays, define care standards, establish research infrastructure, and integrate endometriosis into education. Unfortunately, this data was not identified in the search, likely as the financials of healthcare is not often made publicly available. Moreover, guidelines were not specifically searched due to the complementary scoping review on global endometriosis guidance

discussed in **Chapter 2.** In addition, a stakeholder from Italy noted that some regional policy documents were missing. This was due to the search not being region-specific, as searching was limited to WHO member states. Thus, territories and regions within states were not specifically searched, which may be a limitation in countries with strong provincial regulation. To assess the impact of this, a regional search was conducted in Italy, given its largely regionally governed healthcare system. The search without region-specific terms had already identified 10 regional endometriosis laws. The remaining 10 regions were searched, revealing 2 missing regional laws that did not affect the overall conclusions of the review.

Discussion

Availability and maturity of endometriosis policies and delivery systems

This scoping review has highlighted a notable worldwide inadequate representation of endometriosis policies, especially if compared to the results of the WHO Mental Health Atlas previously discussed. Only 1% of countries have a stand-alone plan for endometriosis (compared with 75% for mental health), and only 4% have an endometriosis law (57% for mental health)[200]. Endometriosis policy can also be found integrated within other health NAPs or as stand-alone initiatives, but these often lack the comprehensive approach, goals and accountability of a stand-alone plan. However, various *ad hoc* initiatives do exist and often fall within the WHO health system building blocks. In terms of maturity, policies on endometriosis are globally in the early stages of development, with a concerning number of countries not having identified endometriosis as a problem, and no country having reached the crucial evaluation and refinement process.

Drivers of endometriosis policy

Countries in the later stages of policy development have all attributed success to the collaborative engagement of stakeholders, including with patients, advocacy groups—often founded by patients—clinicians, researchers, and political leaders. NGOs ensure the voices of endometriosis patients are heard and that reforms are tailored to their population's needs. However, policymakers can allocate resources based on their country's resource availability and ensure accountability through the implementation of steering groups and progress analytics.

Collaborative NGO networks such as South America's UNIENDO share advances in their legal frameworks to build on each other's successes.[279,280] The World Endometriosis Organisations is another example of international collaborative efforts aimed at improving awareness.[281] Further, the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) developed tools for global research collaboration.[120,125,126,282,283]

Barriers and Challenges to Endometriosis Policy

A lack of societal awareness of endometriosis, particularly among policymakers, is a significant initial barrier to effective endometriosis policy. In addition, policies often require significant funding, which is especially limited in low to middle-income countries, which often must prioritise life-threatening conditions. However, even after endometriosis has been prioritised, operational barriers exist. For example, in the province of Jujuy (Argentina), a 2023 endometriosis law that was expected to improve endometriosis research, clinical care and awareness, was vetoed three months after passing due to insufficient funds. Moreover, in

Sardinia (Italy), it took eight years after the regional endometriosis law was passed for a commission to be developed to act on the law.

A crucial challenge in developing endometriosis policy is addressing the varying disease impact. Whilst some people are severely affected, others have mild to no symptoms. Thus, policy development must be nuanced to recognise these differences so resources can be allocated appropriately.

Future outlook – Progressive realisation

Societal consciousness of the importance of endometriosis policies has increased in recent years, instilling a promising outlook for the future. The presence of stand-alone mental health NAPs in 75% of countries demonstrates it is achievable and that the NAP must be country and resource-specific. Australia and France have demonstrated that the NAPs enable the country's strategic vision to be publicly visualised, hold governments accountable and allow for progress to be tracked and refined. Until a stand-alone NAP is achieved, integrating endometriosis within existing NAPs (e.g. reproductive health NAPs, which exist in 58% of countries) still ensures accountability. The Maldives' reproductive health NAP, for example, assigned quantitative yearly targets and responsible groups for each of its endometriosis initiatives. Numerous countries were found to have already implemented *ad hoc* initiatives which could form the foundation of their 'stand-alone' or integrated endometriosis NAPs. As highlighted by Australia's 2024 progress report, after implementing a NAP, a structured evaluation of the effects of the initiatives on affected individuals' lives, with dynamic adaptations, is crucial.

Strengths and weaknesses of the review

A strength of this scoping review is that it presents, for the first time, a comprehensive search of all WHO-recognised countries to encompass a global understanding of the availability and maturity of endometriosis policy. This resource may be used to support the establishment and development of national endometriosis policy by demonstrating positive examples (most often to improve access to clinical care, raising awareness and promoting research) and the various forms that policy can take (plans, laws or *ad hoc* initiatives). It crucially demonstrated critical factors that must be considered whilst designing endometriosis national policy, including healthcare frameworks such as the WHO Building Blocks and human rights frameworks such as the PANEL approach. Finally, using the healthcare policy development cycle, the importance of country-specific objectives, action timeframes, adequate funding allocation and accountability measures such as steering groups and progress reports were demonstrated.

A crucial strength of the paper is the success of a comprehensive systematic grey literature search strategy that identified pivotal policies and initiatives, overcoming the limitation of the database search, which identified only 34 documents due to the nature of policy document archiving and databases that typically publish academic works. The reliance on grey literature does increase the risk of bias from individual agendas. This was minimised by limiting inclusion to documents from prominent NGOs and policymakers. Despite the comprehensive language-tailored search strategy, there is a risk of missing eligible documents due to the nature of policy searching. Parliamentary discussions, for example, are not always published publicly. Additionally, country-tailored search methods may have limited effectiveness in policy identification. Google search algorithms limit results based on location, and despite efforts to

overcome language barriers by using translated terms, Google Translate has known limitations, especially for medical terms.[284]

Conclusion

The scoping review described in this chapter concludes that, regardless of a country's economic status, the availability of endometriosis policies is sparse. Even when policies are available, countries are only beginning to shape their responses to endometriosis. However, the future holds promise, demonstrated by a marked surge in recent policy initiatives and an enhanced societal and state consciousness regarding endometriosis, often driven by patients and their advocacy groups. Policy makers hold the potential to formulate and implement refinable, tailored policies within the nation's resource capacity. Encouraging progress is being made through the development of comprehensive frameworks that serve as reference points for other countries seeking to expand their infrastructure (e.g. stand-alone endometriosis NAPs, integrated NAPs and stand-alone 'endometriosis laws'. Once a country has selected a framework to use, an initial step can be expanding their *ad hoc* initiatives into the framework, then utilising existing NGOs to support the development of an endometriosis strategy that meets the evolving needs of their population.

Contributions

I would like to recognise my excellent research team's contribution to this project: Devon Evans, Becky Skidmore, Christian M Becker, Stacey A Missmer, Linda C Giudice, G David Adamson and Krina T Zondervan, and the Endometriosis Global Policy (ICMART) Working

Group. KTZ, SAM, GDA, LCG, and CMB contributed to conceptualisation and supervision of the project. BS is the senior information specialist referenced to in the methods who assisting with developing and performing the comprehensive database search. DE performed the second screening of the database results and provided a vital source of motivation and intellectual support by engaging in critical discussions, sharing and developing ideas throughout the duration of the project.

Thesis discussion

Concluding Remarks and Clinical Significance

This thesis examined the diagnostic, treatment and policy frameworks that guide the way those with endometriosis are supported.

To begin, a mixed methods survey completed by over 1,000 respondents provided a clearer understanding of the experiences and barriers that individuals with endometriosis face while seeking a diagnosis. In addition to diagnostic delays, respondents reported negative experiences with the investigative techniques we use to diagnose endometriosis.

TVUS, our first-line non-invasive method, can be painful and is often perceived as a 'tick box' exercise that can prolong diagnostic delays, due to deficits in streamlined referral pathways, healthcare professional training, and patient education. This is compounded by the inherent diagnostic limitations of TVUS. Conversely, laparoscopy, while being invasive was found to have the highest satisfaction scores, partly due to providing a definitive diagnosis after the 'fight' many patients experience to have their symptoms legitimised.

A stepwise diagnostic approach from least to most invasive investigative technique remains reasonable. However, its effectiveness depends on a healthcare framework that equips clinicians to support and inform their patients throughout their journey. This

includes transparent communication on the limitations of imaging, concurrent treatment approaches and counselling through the known uncertainties the current diagnostic pathway creates. Increased healthcare staff training to provide advanced TVUS could improve the accuracy of TVUS, which was raised as a significant concern by survey respondents. Given the waiting times to see a gynaecologist, improving diagnostic accuracy before a gynaecology appointment could reduce diagnostic and treatment delays, improve satisfaction, and even streamline referrals for those with positive ultrasound findings to an endometriosis specialist.

The limitations in non-invasive diagnostic methods, poor satisfaction and recognised diagnostic delays highlight the need for the development of novel diagnostic tests. The DETECT study demonstrated that Maraciclatide holds potential for diagnosing extra-pelvic and pelvic endometriosis and may support us moving away from a surgical diagnostic model as supported in international guidelines such as ESHRE.[57] In fact, Maraciclatide exceeded the requirements as a SPiN triage test for SPE, marking the first research study to achieve this for SPE beyond the pouch of Douglas.

A Phase 3 study is planned to provide powered diagnostic performance metrics for Maraciclatide. If similar diagnostic accuracy can be achieved, this approach could be integrated into the existing diagnostic pathway prior to surgery in cases where SPE is suspected, such as in patients presenting with endometriosis symptoms where no visible disease can be found on ultrasound and/or MRI. Incorporating a Maraciclatide scan at this stage has the potential to reduce diagnostic uncertainty, provide a diagnosis

of endometriosis without the need for surgery, shorten diagnostic delays, and enable patients to make informed decisions about their health, endometriosis care and lives.

Furthermore, the insights into the pathogenesis of endometriosis from the DETECT study, specifically regarding angiogenically 'active' and 'inactive' lesions, opens new possibilities in terms of tracking lesion progression and treatment response. The development of novel metrics for assessing treatment effectiveness, such as angiogenic activity, could facilitate a shift from generalised to more personalised treatment approaches by enabling more targeted evaluation of both existing and emerging therapies.

Despite the wide range of treatments available for endometriosis, current treatment frameworks are limited in their ability to predict individual treatment response, often necessitating a trial-and-error approach. This is particularly challenging in resource-limited settings, where repeated treatment attempts may not be feasible and where a clearer understanding of treatment effectiveness is essential to support efficient resource allocation. The NMA conducted in this thesis sought to address this gap by providing a comparative ranking of treatment effectiveness, which may inform the development of more standardised guidance, particularly in countries where endometriosis specific guidelines are lacking. The scoping review identified this as a particular concern in low- and middle-income countries.

Finally, the thesis examined how leading stakeholders, including policymakers, are addressing the gaps within their endometriosis frameworks by developing initiatives, policies, and laws.

Although globally, we are still in the infancy of national policy development, various policy frameworks exist that policymakers could adapt to suit their particular country or region. The hope the review will serve as an informational but also a motivational tool for the expansion of endometriosis policy by demonstrating what others are achieving and what each country could do to strengthen their support for those with endometriosis. For example, some countries may choose to introduce an endometriosis policy slowly within their existing reproductive health policies. Some countries may wish to use this as an opportunity to develop their first women's health policy, including conditions such as endometriosis, acknowledging that their consequences are not confined to reproductive health but encompass wider systemic and societal effects. Some countries may want to develop policies within a legislative framework, such as an endometriosis law, or they may be able to develop a comprehensive national action plan, as seen in Australia and France. Frameworks exist, such as the PANEL framework, which can ensure these policies are developed with a human rights-based approach. By providing this data, advocates and policymakers can begin to develop country-tailored initiatives or plans to address the needs of their endometriosis population within their available resources.

By critically examining the existing frameworks that shape the experiences of those with endometriosis, this thesis has highlighted persistent infrastructural gaps within healthcare frameworks that hinder timely diagnosis, standardised care, and societal

awareness and support. While progress and advances have been made, it is evident that substantial work remains for patients, advocates, researchers, clinicians, and policymakers to identify and dismantle barriers, as well as strengthen the clinical care infrastructure. Addressing gaps will require coordinated efforts in terms of education, standardisation, improved research quality and patient-centred policies. Only by committing to systemic reform can we replace a legacy of delay and dismissal with a future defined by healthcare frameworks that provide timely, effective care and social frameworks that ensure recognition and support for those living with endometriosis.

Future work

Within the diagnostic framework, future research will include the development of a phase 3 study to confirm the results of the phase 2 DETECT study. The Phase 3 study will be a multi-centre study with a larger sample size, allowing for the calculation of powered diagnostic accuracy metrics. Based on the data of this study, the Food and Drug Administration has granted Fast Track Designation[285] to Maraciclatide for the detection of SPE, given its recognised potential to address a critical unmet need. This will facilitate the accelerated prioritisation of regulatory approvals to reduce the administrative delay before the scan can be clinically utilised if the Phase 3 studies are to replicate the findings of the DETECT study. The hope is that Maraciclatide will be made available as a diagnostic test for those with a suspicion of endometriosis (particularly SPE) but negative imaging, to support a non-invasive diagnosis of endometriosis, and hopefully reduce the recognised diagnostic delay.

Within the management framework, the NMA model will first be updated with data up to 2025 and then will be developed into a living NMA, allowing for the continued incorporation of new endometriosis research. With increased funding for endometriosis research and standardisation efforts, it is hoped that future incorporated research will be of higher quality and at a lower risk of bias, allowing for a model based on low-risk bias studies. It is hoped that with this data, a ranking of endometriosis treatments will become visible, supporting the development of endometriosis guidelines. When paired with costing calculations, it will enable regions with limited resources to develop guidelines tailored to their country's specific needs, healthcare infrastructure, and resource availability.

Both global scoping reviews on endometriosis guidance and policies will lay the foundations for a repository of documents, enabling the advocacy of guideline and policy development in regions without existing guidelines and policies. By presenting examples of guidelines and policies, it is hoped that other countries will be able to use the data to develop country or region-tailored documents. As demonstrated by the WHO Mind Atlas, which has been tracking the development of mental health policies (NAPs and laws), 75% of the 194 WHO member countries in 2021 have a stand-alone policy or plan for mental health (an increase from 68% in 2014) and 57% had a mental health law (an increase from 51% in 2014). This demonstrates that policy development is possible despite resource limitations for conditions that are considered non-deadly but also traditionally highly stigmatised. As such, these scoping reviews present the first efforts to map the global advancement of policies and guidelines related to endometriosis. Future work will continue to track the development of policies and guidelines and will continue to advocate for their development as a crucial

commitment to establishing robust infrastructures that support the evolving needs of the global endometriosis community.

Thesis publications

1. Gibbons T et al. **DETECTing endometriosis angiogenesis with a novel 10-minute 99mTc-maraciclatide imaging scan.** Accepted by the Lancet Obstetrics and Gynaecology 2025.

2. Gibbons T et al. **Endometriosis policy and delivery systems: a comprehensive global scoping review.** Accepted by the Lancet Obstetrics and Gynaecology 2025.

3. Evans D, Gibbons T et al. **Availability of region-specific endometriosis care guidance: a global scoping review.** Accepted by the Lancet Obstetrics and Gynaecology 2025.

4. Gibbons T et al. **Safety, biodistribution and radiation dosimetry of the Arg-Gly-Asp peptide 99mTc-maraciclatide in healthy volunteers.** Nucl Med Commun. 2024;45(4):295–303. doi:10.1097/MNM.0000000000001814.

5. Gibbons T et al. **Crimson clues: advancing endometriosis detection and management with novel blood biomarkers.** *Fertil Steril*. 2024;121(2):145–163. doi:10.1016/j.fertnstert.2023.12.018.

Other Publications Completed During the DPhil

1. Grammatis AL, Gibbons T et al. **Progesterone receptor modulators for endometriosis.** Cochrane Database of Systematic Reviews Issue 7. Art. No.: CD009881. Accepted 2025.

2. Gibbons et al. **Timed intercourse for couples trying to conceive**. Cochrane Database of Systematic Reviews 2023, Issue 9. Art. No.: CD011345. DOI: 10.1002/14651858.CD011345.pub3

3. Gibbons et al. **Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery**. Cochrane Database Syst Rev. 2021 Dec 20;12(12):CD005072. doi: 10.1002/14651858.CD005072.pub4. PMID: 34928503; PMCID: PMC8686684.

4. Leonardi M, Armour M, Gibbons T, et al. **Surgical interventions for the management of chronic pelvic pain in women.** Cochrane Database of Systematic Reviews 2021, Issue 12. Art. No.: CD008212. DOI: 10.1002/14651858.CD008212.pub2.

5. Book contribution: **Endo Smart: A Guide to Understanding and Managing Your Health**

Conference Presentations

1. World Endometriosis Congress 2025, Sydney. **DETECTion of Endometriosis (Including SPE) with 99Tc-Maraciclatide Imaging, nominated for the Rodolphe Maheux Award (oral)**

2. Society of Endometriosis and Uterine Disorders Congress 2024, Geneva. **A ranking of interventions for endometriosis (oral)**

3. Society for Reproductive Investigation 2024, Vancouver. **Potential to diagnose endometriosis using 99mTc-maraciclatide**

4. European Endometriosis League 2024, Bucharest. **SPECT-CT detection of endometriosis and its subtypes (poster)**

5. Royal College of Obstetrics and Gynaecology Annual Conference 2023, London. **Diagnostic experiences and preferences of individuals with suspected or confirmed endometriosis – national survey results (poster)**

6. European Society of Human Reproduction and Embryology, 2022 Milan. **Timed intercourse for couples trying to conceive: A Cochrane systematic review (oral).**

7. World Endometriosis Conference 2023, Scotland. **Novel diagnosis of endometriosis using 99mTc-maraciclatide and SPECT-CT (oral)**

8. World Endometriosis Conference 2023, Scotland. **The availability of global endometriosis policies, delivery systems and rights: An ICMART and WHO scoping review. Awarded - Highly commended for the 'Best Oral Presentation'**

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