National Institute for Health and Care Excellence

1

Version 2.0

Endometriosis: diagnosis and management

Appendix K

NICE guideline

Health Economics

September 2017

Final

Developed by the National Guidelines Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Appendix K:

K.1 Diagnosis and Treatment Model

K.1.1 Introduction

This section contains details of the review of the literature and subsequent health economic modelling relating to a variety of questions on the treatment effectiveness of different diagnostic strategies and treatment agents in the management of endometriosis.

This model is designed to provide health economic input on the following review questions:

- What is the accuracy of the following tests in diagnosing endometriosis:
  - Imaging
  - Biomarkers
  - Surgical diagnosis
  - Endometrial biopsy of nerve fibres
  - Peritoneal biopsy of suspected endometriosis?
- What is the effectiveness of the following treatments for endometriosis, including recurrent and asymptomatic endometriosis:
  - Analgesics
  - Neuro-modulators
  - Hormonal medical treatments
  - Ablation
  - Excision
  - Hysterectomy, with or without oophorectomy?
- Should a surgical diagnosis include histological confirmation?
- What is the effectiveness of pharmacological therapy before or after surgery compared with surgery alone?
- What is the effectiveness of non-medical therapies (for example acupuncture) for managing pain associated with endometriosis?

K.1.2 Review of the literature

A search of economic evidence relating to all treatments for endometriosis identified 438 papers. After screening titles and abstracts 73 full text articles were retrieved for further review. Of these 73 studies none were considered to be directly relevant to the review question as none considered possible diagnostic and treatment strategies together. Individual papers of relevance to specific subsections are considered in those sections.

K.1.3 Methods

No published health economic literature was identified that addressed the breadth of treatment alternatives included in the network meta-analysis for this guideline and it was therefore considered appropriate to develop a de Novo model which reflected this approach to synthesising clinical effectiveness data.

A Markov decision analytic model was developed in Microsoft Excel® to assess the cost-effectiveness of various combinations of diagnostic and treatment strategies across the lifetime of the woman.

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The model was run for four populations:

1. Women with endometriosis where pain (rather than infertility) is the main symptom
2. Women with endometriosis where infertility (rather than pain) is the main symptom
3. Women with endometriosis with both clinically significant pain and infertility
4. Women with asymptomatic endometriosis

To reflect uncertainty in model parameters, the results were assessed using probabilistic sensitivity analysis. The model aimed to follow the NICE Reference Case unless otherwise stated.

K.1.3.1 Basic model structure

Introduction to structure

The model can be considered as a form of agent-level Markov Chain Model. Each node in the model represents a health state that a woman could be in while receiving treatment for endometriosis, and progression through the matrix approximates a woman's journey through treatment (ending with menopause, and then eventually death). At each node, the woman receives some treatment (costing the NHS money but giving the woman some health benefit, measured in QALYs). The model then decides if the woman continues to a different node or remains in the same place, based on probabilities given by the literature and expert advice from the Committee. At the end of the woman's simulated 'life' we can look back over her lifetime costs and QALYs and determine if we would have been better off offering her a different combination of diagnosis and treatment. Over enough simulated lives, the model can determine the likely best course of treatment for different populations of women.

A Markov model involves the transition of a hypothetical patient across different 'health states' over time, divided into equally spaced cycles. Within each state costs and utilities are assigned according to the probabilities associated with the health state decision sub-tree (the various events and outcomes that occur within cycle). The health states in this model are:

- Endometriosis – Undiagnosed and Untreated
- Endometriosis – Undiagnosed and Treated (for example, empirical treatment with painkillers prior to diagnosis)
- Endometriosis – Diagnosed and Untreated
- Endometriosis – Diagnosed and Treated
- Menopause
- Death (which is known as an "absorbing state" as there can be no transition to an alternative state once this state is entered.)

Additionally, women could begin in an 'Endometriosis-like Symptoms' state. These women will accrue costs if they are misdiagnosed as having endometriosis (and hence treated for the wrong condition), but will otherwise not accrue health benefits or ever switch out of their health state, since they are out of scope.

In the base case, women's age of menopause and death are not fixed and are free to vary (constrained by values given in the literature). This means that in contrast to a typical Markov Chain Model the run-time of the model is not fixed. Since each cycle in this model represents three months a typical woman might develop endometriosis at age 20 (cycle 0), go through menopause at 50 (cycle 120) and die at 80 (cycle 240). However a woman who developed endometriosis at age 25 (cycle 0), went through menopause at age 55 (cycle 120) and died at 85 (cycle 240) would appear approximately the same from the point of view of the model, assuming their treatment outcomes were the same, since the model considers 'cycles' rather than chronological age.

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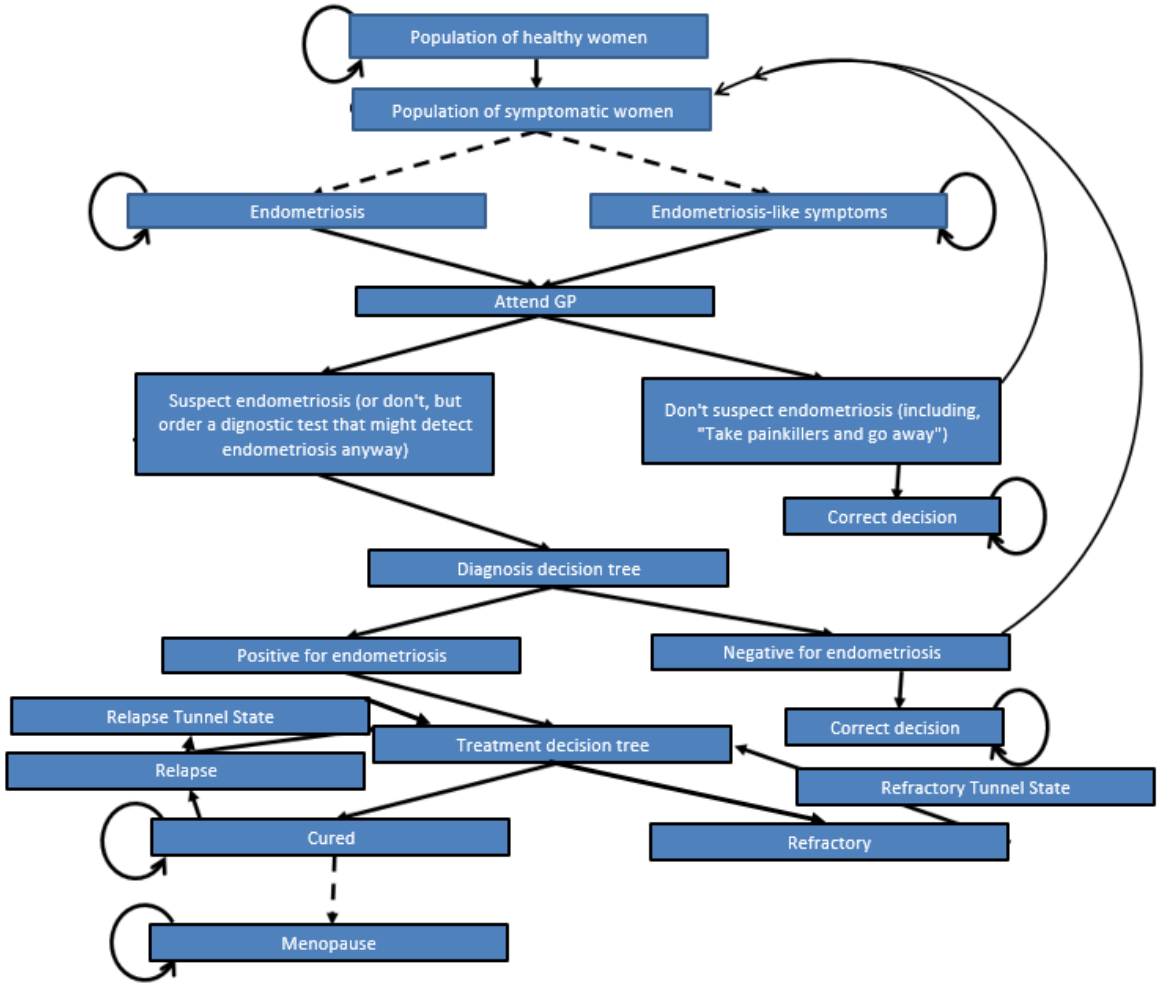
Transition between different states occurs at the end of cycles and is determined by transition probabilities derived from the literature, the network meta-analysis or assumption. No half-cycle correction was modelled because the cycle length was very short compared to the overall run time of the model. A schematic of the Markov model is shown in Figure 1. Costs and clinical states included in the model are described below.

Model diagram

A diagrammatic version of the model is reproduced below in Figure 1.

Figure 1: Schematic diagram of diagnosis and treatment model.



Source: Economic Model. Note that whether a woman has endometriosis, the age at which it occurs, the age of menopause and death are all determined at the start of the model and not redrawn again

Model description

The version of the model produced above can appear a little opaque. Below is a description of a typical patient pathway on the model.

1. All patients begin in the 'Population of healthy women' state at the top of the diagram. None of these women have endometriosis. After a certain length of time, all the women will move into 'Population of symptomatic women', and then from there immediately move into 'Endometriosis' or 'Endometriosis-like symptoms' (i.e. there is no 3-month cycle delay as there is elsewhere in the model, this happens instantly).

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2. Women may persist with symptoms for some time, or else seek treatment from a GP (or some other primary care provider)
3. The GP may either 'Suspect endometriosis' or 'Don't suspect endometriosis'. If they do suspect endometriosis, a diagnostic test is ordered (the test to consider in any particular model run is set before the model starts). If the GP does not suspect endometriosis then:
   a. If the patient really does have endometriosis, they return to the 'Endometriosis' state, where they will spend some time with the condition before reengaging their GP for treatment
   b. If the patient really does not have endometriosis, then they enter an artificial absorbing state called 'Correct decision' where they no longer accrue costs or QALYs relevant to the endometriosis decision problem
4. The diagnostic test may come back negative or positive for endometriosis. If the test comes back positive, treatment is ordered. As with diagnostic test, the treatment is set at the time of model initialisation. If it comes back negative:
   a. If the woman really does have endometriosis, the woman returns to the 'Population of symptomatic women' state (where she is instantly moved back into the correct 'Endometriosis' node).
   b. If the woman really does **not** have endometriosis, then she is either moved into the 'Correct decision' state (for some highly specific tests like laparoscopy) or back into the 'Population of symptomatic women' state (for less specific tests). This transition is set by the clinical characteristics of the test, and based on Committee opinion.
5. Treatment can either 'cure' the endometriosis or the disease can prove 'refractory' to treatment. A 'cure' doesn't mean a complete elimination of the disease (or even any physical change to the disease), but instead a response in symptom severity. 'Refractory' means no response in symptom severity. If the disease is 'refractory' then the patient enters a 'Refractory' state, then a 'Refractory tunnel state' three months later (an artificial state reflecting delays in retreatment following unsuccessful first-line therapy), before finally re-entering the 'Treatment' state for another attempt at therapy. If the treatment is successful the patient enters the 'cure' state.
6. When cured, the patient can either remain cured or relapse. A relapsing patient enters a 'Relapse' state, and then a 'Relapse tunnel state' state (much like a refractory patient enters a tunnel state when there condition does not respond to treatment). Much like the 'Refractory' state, this artificial tunnel node reflects the Committee's input that there is typically a 3-6 month delay between relapse and retreatment.
7. At any point, the woman can enter the 'menopause' state. The probability of entering the menopause state is greater the older the women gets, with most women entering the state at around 50 years old. Menopause is 'absorbing' in a practical sense, meaning that once a woman has passed through menopause there is no way for her endometriosis to recur and hence no more transitions for her to undergo – she will continue to accrue the same amount of QALYs as any other menopausal woman until her death.
8. At any point, the woman can enter the 'all-cause mortality' state (i.e. death). The probability of making this transition is greater the older the women gets, with most women entering the all-cause mortality state at around 75-85 years old. Death is absorbing in a technical sense (there are no transitions leading out of the death state) and so the model ceases to run once a woman has reached the death state.
9. At no point can a woman who isn't flagged to develop endometriosis go on to develop the disease. In contrast to real life, a woman who enters the 'no endometriosis' state can be assured that she will never develop endometriosis in the future. However the number of women who have endometriosis-like symptoms, which are not caused by endometriosis, who then go on to develop endometriosis is very small, so this simplifying assumption is unlikely to change outcomes significantly

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Model states

Table 1 below shows the corresponding health state for each node that a woman with endometriosis could find herself in. Women with endometriosis-like symptoms are always in the 'endometriosis-like symptoms' health state until they reach the 'correct decision' node, at which point the model ends.

Table 1: List of model nodes and corresponding health states.

Model node	Corresponding health state
Population of healthy women	N/A (Not a health state – women are only in this state when the model is determining the age of endometriosis onset and so accrue no relevant costs or benefits)
Population of symptomatic women	N/A (See above)
Endometriosis	Endometriosis – Undiagnosed and Untreated
Endometriosis-like symptoms	N/A (Can never be reached by woman who actually has endometriosis)
Attend GP	Endometriosis – Undiagnosed and Untreated
Suspect endometriosis	Endometriosis – Undiagnosed and Untreated
Don't suspect endometriosis	Endometriosis – Undiagnosed and Untreated
Correct decision	N/A (Can never be reached by woman who actually has endometriosis)
Diagnosis test	Endometriosis – Undiagnosed and Untreated
Positive for endometriosis	Endometriosis – Diagnosed and Untreated
Negative for endometriosis	Endometriosis – Undiagnosed and Untreated
Treatment	Endometriosis – Diagnosed and Untreated
Refractory (+ tunnel)	Endometriosis – Diagnosed and Untreated
Cure	Endometriosis – Diagnosed and Treated
Relapse (+ tunnel)	Endometriosis – Diagnosed and Untreated
Menopause	Menopause
Death	Death

Special transitions

A number of diagnosis and treatment options offer out-of-the ordinary transitions relative to the normal model. These transitions are listed below in Table 2:

Table 2: Special model transitions.

Criteria	Transition	Justification
Diagnostic test is 'Empirical Diagnosis'	Transition probability from 'Suspect endometriosis' to 'Treatment' is 100%, but disease remains 'undiagnosed' in all states	You can't physically give no test, so you would refer straight to treatment
Treatment is hysterectomy	Transition probability from 'Refractory' to 'Refractory' and from 'Relapse' to 'Relapse' is 100%. Additionally, age of menopause brought forward 4.1 years (Siddle, 1987)	You cannot give two hysterectomies, so if the treatment does not work or the patient relapses there are no other treatment options

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Criteria	Transition	Justification
Diagnostic test is laparoscopy	Diagnostic test adds QALYs as per treatment laparoscopy if the woman has endometriosis and transfers into 'treated' state if appropriate.	Committee opinion is that a 'diagnostic laparoscopy' is unlikely not to consent the woman to have minor surgery at the same time and therefore the two will almost always occur simultaneously

K.1.3.2 Time horizon

Endometriosis is not usually considered life-limiting, and treatment will usually be indicated throughout the fertile lifetime of the woman. The NICE Reference Case specifies that a lifetime time horizon is preferred if it is appropriate, and so consequently this model adopts a lifetime time horizon at the standard discount rate of 3.5% for both costs and benefits.

K.1.3.3 Interventions and comparisons

The model was designed to look at combinations of diagnostic strategy and treatment together. Consequently each run of the model selected a single diagnostic strategy from the list agreed in discussion with the Committee and combined it with a single treatment strategy from a different list.

The reason diagnosis and treatment must be considered together is that treatments for endometriosis span a range from very cheap (painkillers) to very expensive (surgery), and the cost-effectiveness of expensive treatments tends to be relatively higher when the specificity of the diagnostic test is high (because they are not being given to patients who will not benefit). Consequently selecting simply the 'best' diagnostic test without considering the treatment that is intended to be given as a result will unfairly bias the model against a certain kind of treatment. By considering diagnosis and treatment together as a 'bundle' we can be assured that each treatment is given the test which makes it appear most cost-effective, and so compare like with like.

Table 3 and Table 4 show which combinations of diagnostic strategy and treatment strategy were permitted for each population subgroup. Note that while every test could potentially be appropriate for every woman, some treatment strategies were not appropriate for women attempting to recover fertility; this could be because the treatment itself was not appropriate (for example hysterectomy) or because there was no evidence on the effectiveness of a given treatment at promoting fertility.

Table 3: Diagnostic tests considered for each population subgroup.

Treatment class	Pain only	Infertility only	Both	Asymptomatic
Empirical diagnosis, treat everyone	✓	✓	✓	✓
Transabdominal ultrasound[a]	✓	✓	✓	✓
Pelvic MRI	✓	✓	✓	✓
Peritoneal biopsy[b]	✓	✓	✓	✓
Nerve fibre biopsy	✓	✓	✓	✓
CA-125[c]	✓	✓	✓	✓

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Treatment class	Pain only	Infertility only	Both	Asymptomatic
Diagnostic laparoscopy[c]	✓	✓	✓	✓
Diagnostic laparotomy[c]	✓	✓	✓	✓

(a) The protocol additionally specifies transvaginal and transrectal ultrasound, but Committee opinion was that the techniques were broadly similar and would be selected on the basis of clinical appropriateness, so they have been grouped for health economic analysis
(b) Menaing a peritoneal biopsy of suspected endometriosis, not arbitrary tissue
(c) The protocol additional specifies HE-4, but no evidence was found for this biomarker and Committee opinion was that it was unlikely to be important to HE analysis unless its clinical relevance was demonstrated
(d) Cystoscopy, colonoscopy and sigmoidoscopy were specified in the protocol, but no evidence was found on the accuracy of these test
(e) Combinations of diagnostics were specified in the protocol, and these have been considered in sensitivity analysis

Table 4: Interventions considered for each population subgroup.

Treatment class	Pain only	Infertility only	Both	Asymptomatic
Codeine	No NMA	x	No NMA	✓
Tramadol	No NMA	x	No NMA	✓
'Generic' analgesia	✓	x	✓	✓
Combined oral contraceptive	✓	✓	✓	✓
Progestogen treatment	✓	✓	✓	✓
Danazol	✓	✓	✓	✓
GnRHa	✓	✓	✓	✓
Amitriptyline	No NMA	x	x	✓
Nortriptyline	No NMA	x	x	✓
Duloxetine	No NMA	x	x	✓
Venlafaxine	No NMA	x	x	✓
Capsaicin Patches	No NMA	x	x	✓
Gabapentin	No NMA	x	x	✓
Pregabalin	No NMA	✓	x	✓
Laparoscopic Treatment	✓	✓	✓	✓
Laparoscopy + Hormonal	✓	✓	✓	✓
Hysterectomy	No NMA	x	x	✓
Acupuncture	No NMA	No NMA	No NMA	✓
Chinese Herbal Medicine	No NMA	No NMA	No NMA	✓

(a) ✓ means that the intervention is included with NMA data, x means that the intervention is not included. 'No NMA' means that there is data on effectiveness, but that it did not link to any other effectiveness data in the network meta-analysis.

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K.1.3.4 Outcome modelling assumptions

A number of assumptions and simplifications were made in modelling the different clinical outcomes included in this model. These assumptions and their rationale is described below. The importance of some of these assumptions in driving model results was tested in sensitivity analyses.

Endometriosis-like symptoms

Some women in this model will not have endometriosis, but instead will have symptoms that might fit the diagnostic indications for endometriosis at first glance but in actual fact will be caused by something else. These symptoms could include chronic pelvic pain, dyspareunia or infertility. The purpose of including these women in the model is to better represent the decision problem facing primary care providers when they must select which diagnostic strategy to undertake with women presenting with something that might be endometriosis – they may not be able to jump straight to treatment because some treatments which might work for endometriosis may have no effect (or may exacerbate) other causes of chronic pelvic pain.

For the purpose of this model, these women accrue costs but not health benefits from treatment; the best that an endometriosis guideline can do for women without endometriosis is to exclude that diagnosis and send them for treatment elsewhere. To be explicit, the model assumes that there is no difference in outcomes between any possible treatment for women who do not have endometriosis but who nevertheless present with endometriosis-like symptoms.

This might affect our ordering of recommendations, for a variety of reasons:

- Since the initial visit to the GP (or other primary care provider) would happen regardless of how accurate GPs are at spotting endometriosis, this cannot truly be considered a cost of the endometriosis treatment pathway. If the woman in fact has dysmenorrhea, the cost of the initial appointment will already be accounted for in the health economic analysis of NICE CG44 (Heavy Menstrual Bleeding). Moreover, it is inconsistent to count the costs of misdiagnosing endometriosis as (for example) dysmenorrhea for the endometriosis guideline, but not then count the costs of misdiagnosing dysmenorrhea as endometriosis towards the dysmenorrhea guideline.
- Many diagnostic tests for endometriosis give at least some indication of what might be wrong with the woman, meaning that the value of an ‘inappropriate’ referral for a diagnostic test in a woman without endometriosis is not zero, as the model assumes. For example an MRI might reveal the presence of a malignant lump, which would help clinicians determine the best course of action for the woman even if that woman does not have endometriosis.
- Many treatments for endometriosis – especially first line treatments – are also relatively effective treatments for other conditions which might be mistaken for endometriosis. The model assumes these treatments have no value, but this is likely to underestimate their value in clinical practice.

Fully incorporating these concerns would be more important if the results were more equivocal. In actual fact, the base case gives us strong reason to suspect that this simplifying assumption does not matter to the overall ordering of the results, and in fact incorporating these assumptions would only strengthen our confidence in the results.

Progression

Endometriosis is thought to be a progressive disease in at least some women at least some of the time. For ethical reasons, however, there is extremely poor evidence on the prevalence, virulence or outcomes of such progressivity. An attempt has been made to

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synthesise the existing literature and expert clinical opinion on progressiveness in Section K.2, but the conclusions are quite speculative and unsuitable for inclusion in answering this question on the most appropriate diagnosis and treatment strategy. Consequently – for this question only – it is assumed that endometriosis does not progress appreciably in the average woman.

Menopause

The model assumes that all women post-menopause have the same quality of life (or rather, that their quality of life is always drawn from a distribution with the same mean and standard deviation). The Committee discussed how this did not fit with their experience of endometriosis, for at least two major reasons:

- There are biological effects of severe endometriosis (such as scarring of the bowel tissue) which can lead to long-term effects which persist beyond menopause. These effects are well documented but there is no evidence on their prevalence nor quality of life impact. Committee members said that these physiological effects were reasonably common in the case of severe disease.
- There may be some psychological effects of long-term endometriosis such as increased stress and anxiety. These effects are not documented in any quality of life related literature discovered in the HE search (even low quality or non-comparative studies), but Committee members were certain that these effects were clinically significant. Even if such a literature were discovered, the long-term effects of living with the stress of a diagnosis for as long as some women with endometriosis have done is likely to have deleterious effects on their postmenopausal QoL – for example a woman who had to give up work she enjoyed as a result of endometriosis-related stress.

Overall, the Committee disagreed with the assumption that postmenopausal QoL would be equivalent in women who have had and have not had endometriosis. However there was agreement that the topic was not well studied or understood, so it was difficult to assign placeholder values for the base case analysis. Consequently the Committee asked the Health Economist to perform robust sensitivity analysis in this area.

The only post-menopausal women who do have a lower quality of life which we can assign a known QoL decrement to are those who would have liked a child but were made infertile by endometriosis. This is not additional quality of life decrement relative to the decrement they had pre-menopause, but the same decrement continued until the end of the woman's life – this is to represent the fact that (unlike the clinical symptoms of endometriosis), childlessness will persist postmenopausally.

In the special case where hysterectomy is selected as the treatment, it is likely women will experience menopause a few years earlier than they would otherwise expect (Siddle, 1987). This could lead to an unexpected effect where women with endometriosis would benefit from a hysterectomy even if it did nothing for their symptoms – because postmenopausal women typically do not suffer from the symptoms of endometriosis, artificially inducing menopause will prevent symptoms or those few years. The Committee accepted that this was a possibility, but the results show that whether we could these earlier menopausal years as 'genuine' QALYs or not would not change our willingness to accept hysterectomy as a treatment at £20,000 / QALY so it was not thought to be a critical effect.

Fertility

The benefits of treating an infertile woman so that she becomes fertile are subject to a number of assumptions.

It is first assumed that there is no QALY loss from being infertile unless the woman is actively trying to conceive, and a live birth completely prevents the ongoing QALY loss of infertility.

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This is not really indicative of the state of mind of all women with severe endometriosis as in real life some women with severe disease will not even attempt to conceive as they are aware their chances of doing so are very low. However it would be a reasonable assumption that these women (if they desired a family) would also be made stressed and anxious by this decision, and so the model will report the correct results for these women even if the underlying assumption is a little simplistic. Additionally assuming women desire only one live birth is arbitrary, although there is no evidence on the schedule of QoL decrements by completing only a fraction of your preferred family size and such an addition to the model would be unlikely to change treatment recommendations.

It is assumed that the QALY loss of not having a child (if one is desired) persists throughout menopause, even though (by definition) no woman is fertile after menopause; the QALY loss is not having a child that is desired, not the clinical aspects of being infertile.

Ethical and moral arguments relating to the value of live births resulting from assisted reproduction are not addressed in the economic analysis because they go beyond the issues that can be addressed in a clinical guideline. The primary outcome considered in the economic models is a live birth and not a measure of life years. There is an important debate about whether the outputs of assisted reproduction can be incorporated into a measure than can be compared with other uses of the same resources. It is not logical to try to derive a quality-adjusted life-year QALY measure from live births arising from IVF because “QALYs are intended to capture improvements in health among patients. They are not appropriate for placing a value on additional lives. Additional lives are not improvements in health; preventing someone’s death is not the same as creating their life and it is not possible to improve the quality of life of someone who has not been conceived by conceiving them.” (Devlin, 2003)

Consequently this analysis considers only QALYs as they relate to the woman or couple seeking treatment. In keeping with NICE CG156 (Fertility), the infertile woman is assumed to be made somewhat anxious or depressed by her condition, and that this translates into a quality of life decrement which society may be willing to pay to rectify. The model assumes around 91% of women seeking fertility treatment have a partner who is equally concerned about her fertility and whose QALYs also count, which is based on ONS figures for the number of two-adult households in the UK but may be a misestimate as the mere fact two adults are cohabiting does not imply that both partners are equally concerned about having a child.

Fertility enhancement techniques such as IVF might be considered in tandem with fertility restoration techniques (i.e. treating the endometriosis). Consideration of the cost-effectiveness of such techniques in a subfertile population already exists in NICE CG156 (Fertility), so such considerations are out of the scope of this health economic model.

K.1.3.5 Treatment switching

In a conventional clinical setting, patients may wish to try a number of different therapies until they find one which is appropriate for their personal situation. This means that the expected result for a patient allowed access to all cost-effective treatments is likely higher than the average result for patients on the RCT demonstrating the effectiveness of that treatment; patients free to pick and choose therapies will probably not stick with a treatment which is not helping them, whereas patients enrolled in an RCT must (or if they do not, they are counted as having stuck with the treatment using statistical correction). Alternatively, however, a patient who does not improve on one treatment might be less likely to improve on a second treatment (because they have an especially pernicious variant of the disease, for example).

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This treatment-switching effect is not modelled in the economic analysis – there was no literature on the effectiveness of Intervention A following unsuccessful treatment with Intervention B, so no attempt to correct for this would be anything more than speculation.

A second complication is that treatment-switching can cause a re-ordering of economic priorities. Consider Table 5 as a demonstration of this. In conventional cost-effectiveness analysis we would mathematically eliminate Intervention B from consideration because (relative to Intervention A) it has an ICER of £16,667 whereas Intervention C (relative to A) has an ICER of £10,000. So any healthcare system prepared to pay £16,667 for a QALY (for Intervention B) must prefer to pay £10,000 / QALY for more QALYs (for Intervention C). This is known as extended domination. But if Intervention C is unsuitable for some reason (perhaps the patient does not like the intervention) then we would prefer not to have eliminated Intervention B from consideration - £16,667 / QALY is still cost-effective on conventional criteria.

Table 5: Demonstration of treatment-switching effect on extended domination.

	Cost	QALY
Intervention A	£1000	0.10
Intervention B	£1500	0.13
Intervention C	£2000	0.20

In order to correct for this effect, analysis will be re-run for each possible treatment switch (rather than performing the analysis mathematically by simple or extended domination, as preferred in the Reference Case) to ensure that any treatment-switching effects do not cause a previously dominated treatment to become preferred.

It is assumed that there will be no 'diagnosis switching', partly because most diagnostic strategies in the model are relatively sensitive and so likely to detect disease where it exists, and partly because the known side-effects of the diagnostic strategies are limited to uncomfortable but non-major outcomes such as localised pain (for example Querleu 1993).

K.1.3.6 Costs

Costs were based on an NHS and Personal Social Services perspective as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012). The model has a lifetime time horizon and therefore future costs and benefits were discounted at a rate of 3.5% in the base case analyses. The price year for costs was 2016.

Diagnostic costs

Table 6 gives the estimated costs for diagnostic strategies considered in the model

Table 6: Estimated costs for diagnostic tests included in the model.

Diagnostic Test	NHS Reference Cost Description	NHS Reference Cost Area	Cost
Empirical Diagnosis	N/A	N/A	£0
Transabdominal ultrasound[a]	N/A	N/A	£80.00
Pelvic MRI	Magnetic Resonance Imaging Scan of one area, without contrast, 19 years and over	Imaging	£146.00
Peritoneal biopsy[b]	Transvaginal Ultrasound with Biopsy	Outpatient, Gynaecology	£222.37

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Diagnostic Test	NHS Reference Cost Description	NHS Reference Cost Area	Cost
Nerve fibre biopsy	Transvaginal Ultrasound with Biopsy	Outpatient, Gynaecology	£222.37
CA-125[c]	Haematology	Direct Access Pathology Services	£3.10
Diagnostic laparoscopy	Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over	Day Case	£841.73
Diagnostic laparotomy	Intermediate Open Upper Genital Tract Procedures	Inpatient	£3,007.96

(a) The cost for a Transvaginal Ultrasound in an Outpatient Gynaecology setting was £149.61. Committee opinion was that this would be a significant overestimate in the case of endometriosis patients, as the currency code is possibly diluted with women receiving an ultrasound for pregnancy-related reasons. Consequently the figure of £80 was picked to better reflect the relative cost of Ultrasound vs MRI, according to the imaging expert on the Committee

(b) Meaning peritoneal biopsy of suspected endometriosis, not arbitrary tissue. As the cost for Transvaginal Ultrasound was lowered by the Committee, the cost for Ultrasound followed by biopsy has been lowered by the same amount to keep relative ranking the same

(c) Committee opinion is that this seemed too low, because the cost of explaining the results to the woman with endometriosis were not included. After discussion, the Committee agreed to keep the NHS Reference Costing as the price on the grounds that any reasonable change to the costing didn't change the fact that a CA-125 test would remain an order of magnitude below the next most expensive diagnostic test

(d) Source for all costs but Transvaginal Ultrasound is NHS Reference Costs (2016-17), https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016

In addition, patients will usually visit a primary care provider in order to be diagnosed (and again if symptoms recur after treatment). In this model, the cost of a primary care provider is modelled as the cost of a single GP appointment, given as £36 in the 2016 PSSRU Unit Cost of Health and Social Care. Although the Reference Case suggests that those who do not use their GP as their main primary care provider should be considered, in this case there is evidence that the majority of NHS-borne costs for the primary diagnosis and treatment of endometriosis is undertaken at GP surgeries (Wasiak, 2010) so the approximation was thought appropriate. Certain subgroups of patients may visit additional specialists, and these costs are accounted for in section K.2, time-in-state costs.

Treatment costs

Table 7 gives the estimated costs for treatments included in the model. As the Electronic Drug Tariff does not include some costs included in NICE CG 173 (for example increased GP visits), each Electronic Drug Tariff cost also includes the placebo-arm costs from NICE CG 173 Table F16 to account for these.

Table 7: Estimated costs for treatments included in the model.

Treatment	Cost	Notes	Source
Codeine	£145.79	Cost for 3 months	NICE CG 173[c]
Tramadol	£140.28	Cost for 3 months	NICE CG 173[c]
'Generic' analgesia[a]	£20.45	Cost for 3 months	Electronic Drug Tariff, January 2017
Combined oral contraceptive (as Ethinylestradiol / Gestodene tablet)	£19.31	Cost for 3 months[b]	Electronic Drug Tariff, January 2017

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Treatment	Cost	Notes	Source
Progestogen treatment (as Desogestrel)	£14.35	Cost for 3 months[b]	Electronic Drug Tariff, January 2017
Danazol	£86.63	Cost for 3 months[b]	Electronic Drug Tariff, January 2017
GnRHa (as Leuprorelin)	£236	Cost for 3 months[b]	Electronic Drug Tariff, January 2017
Amitriptyline	£58.80	Cost for 3 months	NICE CG 173[c]
Nortriptyline	£281.11	Cost for 3 months	NICE CG 173[c]
Duloxetine	£225.37	Cost for 3 months	NICE CG 173[c]
Venlafaxine	£99.21	Cost for 3 months	NICE CG 173[c]
Capsaicin Patches	£313.30	Cost for 3 months	NICE CG 173[c]
Gabapentin	£94.60	Cost for 3 months	NICE CG 173[c]
Pregabalin	£258.95	Cost for 3 months	NICE CG 173[c]
Topical lignocaine	£93.99	Cost for 3 months	Electronic Drug Tariff, January 2017
Laparoscopic Treatment	£1149.09	One-off procedure, procedure which can be repeated	NHS Ref Costs, Resection or Ablation Procedures for Intra-uterine Lesions (Daycase)
Laparoscopy + Hormonal	£1494.89	One-off procedure, procedure which can be repeated	Combined cost of Laparoscopic Treatment and one year of subsequent Danazol
Hysterectomy	£3202.86	One-off procedure, procedure which cannot be repeated	NHS Ref Costs, Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, with CC Score 0-1 (Elective Inpatient)
Acupuncture	£545	Cost for 3 months. Initial appointment typically more expensive, but assumed to average out over cost of woman's lifetime	NICE NG 23, based on data from http://www.ukacupuncture.co.uk
Chinese Herbal Medicine	£70.34	Cost for 3 months. Price includes shipping.	Source for dosing information is http://www.shen-nong.com/eng/herbal/danshen.html Source for cost is Amazon.com

(a) There is a lack of clarity in the evidence regarding exactly which analgesic was given to patients in a handful of trials – it appears to be simple NSAIDs, but to avoid confusion it is labelled in the model as 'generic' treatment and priced as Ibuprofen 400mg taken three times per day

(b) Hormonal treatment usually given cyclically (for example, six months on and six months off) so costs are for an average of this cycle

(c) Taken from Table F16 in Appendix F, inflated to 2016 costs.

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Time-in-state costs

As described in section K.1.3.1, there are seven possible health states a patient could be in for the purpose of accruing 'time in state' costs in the Markov model. These costs represent the background cost of living with endometriosis, for example additional GP visits or increased susceptibility to secondary conditions. These are listed in Table 8.

Table 8: Time-in-state costs.

State	Cost per year	Justification
Healthy	£2842.91	Base case from Fuldeore et al (2014)
Endometriosis – Undiagnosed and Untreated	£3908.40	Fuldeore et al (2014) average of annual prediagnosis spend
Endometriosis – Undiagnosed and Treated	£3908.40	Fuldeore et al (2014) average of annual prediagnosis spend
Endometriosis – Diagnosed and Untreated	£3994.61	Fuldeore et al (2014) average of annual postdiagnosis spend
Endometriosis – Diagnosed and Treated	£3994.61	Fuldeore et al (2014) average of annual postdiagnosis spend
Menopause	£2842.91	Assumes no long-lasting effects of endometriosis, so return to healthy state
Death	£0	Definition
Non-endometriosis	N/A	Definition

(a) Note that these values are simply 'time in state' costs – the cost of treatment or side-effects of the condition are accounted for elsewhere. This is especially relevant when Fuldeore (2014) finds that the first year postdiagnosis is significantly more expensive than any year before or previous, consistent with additional costs of diagnosis and treatment which are accounted for elsewhere in the model.

The values are calculated from Fuldeore, and are based on a longitudinal analysis of 37,570 matched pairs of women with and without endometriosis identified from the Health MarketScan claims database in America between 2000-2010. The costs have been uprated from their historic values and converted to GBP, but no correction has been made for the fact that American healthcare costs are typically more expensive than UK costs. This was not thought to affect the modelling results, as the critical value was the percentage increase from untreated to treated women (i.e. ~2.2%).

The cost reported is the difference between the average cost per year for the five years preceding a diagnosis of endometriosis and the average cost per year for the four years after the year in which a diagnosis of endometriosis was made. This is because a large amount of spending takes place in the year following a diagnosis of endometriosis (for example, diagnostic laparoscopy) and this is already included in the model; to include it twice would be double counting. There appears to be a slight trend towards costs increasing over time – this might be due to clinicians using increasingly expensive treatments if the woman's pain is not responding to conventional medicine or might be due to the general effect of older individuals requiring more healthcare generally. The effect is not pronounced, and so no consideration of this effect was given in the model.

The components of this increased cost are largely outpatient visits and A&E visits, which increase significantly once a diagnosis is made. Inpatient visits are not significantly affected by a diagnosis, although there appears to be a trend towards decreasing slightly after a diagnosis. One explanation for this slightly counterintuitive result is that an inpatient visit might disproportionately precede an incidental discovery of endometriosis, leading to the result observed by Fuldeore.

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K.1.3.7 Event probabilities

Transition probabilities

In the base case of the model, there are 19 nodes that a woman could be in. This implies that there are 361 possible transitions to consider in the matrix (for example the probability of a transition from node 3 to node 7). However, only a small fraction of these transitions will ever occur in reality in the model, and so in keeping with other descriptions of Markov Chain Models, only the transitions which are not certain to be zero are listed below, and transitions which result in 'remaining in a state' (for example a node 3 to node 3 transition) are not listed, but inferred from the fact the probabilities of the next transition must add up to 1. Table 9 lists these transitions.

Table 9: Transition probabilities in base case of Markov Chain.

Transition from…	Transition to…	Probability (base case)	Justification
Healthy	Symptomatic	See Table 10	
Symptomatic	Endometriosis	0.074	Zondervan, 2001
Symptomatic	Endometriosis-like symptoms	0.926	Zondervan, 2001
Endometriosis	GP	0.200	These numbers are not directly given, but calculated to give the same mean and SD for treatment delay as Hadfield (1996). Diagnosis delay was a key issue for patients and the public, so sensitivity around this parameter was considered especially important
Endometriosis-like symptoms	GP	0.200	
GP | Endometriosis[a]	Diagnosis	0.150	
GP | Endometriosis	Endometriosis	0.850	
GP | Endometriosis-like symptoms	Diagnosis	0.150	
GP | Endometriosis-like symptoms	Correct decision (i.e. non-endo absorbing state)	0.850	
Diagnosis	Positive for Endometriosis OR Negative for Endometriosis	N/A – Depends on the diagnostic test, see Table 11	
Negative for Endometriosis | Endometriosis	Endometriosis	1.00	This introduces a minimum delay between misdiagnosis and revisiting the GP
Negative for Endometriosis | Endometriosis-like symptoms	EITHER Correct decision (in the case of surgical diagnosis techniques) OR Endometriosis-like symptoms (all other tests)	1.00	Surgical techniques are viewed by the Committee as being the reference standard against which other diagnostic tests are viewed. Consequently it would be contradictory to return a woman with a surgical non-diagnosis to the general population.
Positive for Endometriosis	Treatment	1.00	Committee opinion is that almost no woman

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Transition from…	Transition to…	Probability (base case)	Justification
			would not want treatment for the condition if she was symptomatic enough to seek diagnosis
Treatment	Cured OR Refractory	N/A – Depends on the treatment, see Table 12	
Cured	Relapsed	N/A – Depends on the treatment, see Table 12	
Relapsed	Relapsed Tunnel State	1.00	These states introduce a delay between a relapsed / refractory condition and retreatment, in keeping with Committee opinion that retreatment takes around 3-6 months
Relapsed Tunnel State	Treatment	1.00	
Refractory	Refractory Tunnel State	1.00	
Refractory Tunnel State	Treatment	1.00	
Any state	Menopause	See Table 10	
Any state	Death	See Table 10	

(a) The straight vertical line notation is standard in conditional probability to denote an event conditioned on another event. For example, 'GP | Endometriosis' means the probability that you go and see the GP given that you do actually have endometriosis.

Three values in Table 9 – which relate to the age of endometriosis, menopause and death respectively – vary depending on the chronological age of the woman. In addition, a woman's fertility changes as she ages, affecting the probability of a live birth. From a technical point of view, this means these variables do not possess the 'Markov Property' (meaning that the probability of a particular transition is independent of all but the previous transition), which would ordinarily exclude them from a Markov-type analysis. Since the age of onset and menopause are critical for determining the most cost-effective treatment, and death and fertility important for quality of life outcomes, age correction for these parameters was included in the model. Table 10 gives these probabilities by 10-year increments, and the footnotes to this table give the underlying mathematics and references.

It is reasonable to argue that most transitions in this matrix do not strictly possess the 'Markov Property', since (for example) the probability of a treatment working after it has failed three times before is almost certainly lower than the probability of the treatment working for the first time. This will be considered in sensitivity analysis, but is an assumption typical to most Markov Chains in the published literature.

Table 10: Age-corrected transition probabilities per year.

Age	Endometriosis Onset[a]	Menopause Onset[b]	Death[c]	Live birth | Primary Infertility[d]
0	0.0061	0.0000	0.0035	N/A
10	0.0893	0.0000	0.0001	N/A
20	0.4272	0.0000	0.0002	0.3373
30	0.8359	0.0000	0.0004	0.0446
40	0.9838	0.0013	0.0010	0.0007
50	0.9995	0.5000	0.0025	0.0000

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Age	Endometriosis Onset[a]	Menopause Onset[b]	Death[c]	Live birth | Primary Infertility[d]
60	1.0000	0.9987	0.0061	0.0000
70	1.0000	1.0000	0.0160	0.0000
80	1.0000	1.0000	0.0533	0.0000
90	1.0000	1.0000	0.1437	0.0000
100	1.0000	1.0000	1.0000	0.0000

(a) Represents a normal distribution with mean 21.58 and SD 8.61 to match values in Hadfield (1996). The model assumes that onset of symptoms and onset of physical disease are synonymous, although in real life the physical disease can precede symptoms. This assumption is justified as the results show treating asymptomatic endometriosis is not cost-effective.
(b) Represents a normal distribution with mean 50 and SD 3.33 to match values in Hadfield Treloar (1981)
(c) ONS 2013 estimates
(d) NICE CG156, referencing Hunault (2004), plus an endometriosis-specific deflator to bring the equation in line with the endometriosis literature
(e) The model itself uses 3-month rather than 12-month cycles, and so corrects for this using standard formulae
(f) It is possible (but extremely unlikely) that a woman could die or go through menopause before the onset of endometriosis. The model handles these edge cases by reselecting the age-dependent parameters for that woman.

The figures for fertility are a little more complicated to calculate than those for the other three age-dependent parameters. They are generated with the following equation:

Equation 1 – Hunault Model

$$P = 100 * (1 - 0.181^{\exp(P1)})$$

Where P is the probability of a live birth in one year and P1 is a deflator based on specific characteristics of the couple:

Equation 2 – Hunault Model Deflator

$$\begin{aligned} P1 = \ & -0.03 * (Is\ woman\ younger\ than\ 31?) - 0.08 * (Is\ woman\ older\ than\ 31?) - 0.19 \\ & * (Duration\ of\ subfertility) + 0.008 \\ & * (Percentage\ of\ motile\ sperm\ in\ partner) - 0.58 \\ & * (Is\ the\ subfertility\ primary?) - 0.25 * (Is\ this\ a\ tertiary\ care\ couple?) \end{aligned}$$

Equation 3 – Hunault Model Deflator used in Endometriosis Guideline

$$\begin{aligned} P1 = \ & -0.03 * (Is\ woman\ younger\ than\ 31?) - 0.08 * (Is\ woman\ older\ than\ 31?) - 0.19 \\ & * (Duration\ of\ subfertility) - 0.35 \end{aligned}$$

Equation 3 is the actual model used in the guideline, since it is reasonable to assume the woman's partner has acceptable sperm motility of 60% (Irvine, 1996), that the infertility is primary and that the care is being delivered in a secondary setting.

Diagnostic effectiveness

The data on the effectiveness of the diagnostic tests are taken from the clinical reviews and summarised in Table 11. For more information please consult the relevant chapters in this Guideline.

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Table 11: Accuracy of diagnostic tests used in endometriosis.

Test	Sensitivity	Specificity	Notes
Empirical diagnosis	0.00	1.00	Treat everyone with symptoms that could be endometriosis, not 'treat indiscriminately'. Sensitivity and specificity given by fiat.
Transabdominal Ultrasound	0.57	0.97	Weighted average of Eskenazi 2001, Falco 2011, Ghezzi 2005, Holland 2010 and Said 2014.
Pelvic MRI	0.85	0.85	Weighted average of Arrive 1989, Ascher 1995, Ha 1994, Manganoro 2012a, Okada 1995, Stratton 2003, Sugimura 1993 and Thorneer 2014
Peritoneal Biopsy	0.98	0.79	De Almeida Filho 2008
Nerve fibre Biopsy	0.88	0.81	Weighted average of Al-Jefout 2007 & 2009, Bokor 2009, Elgafor el Sharkwy 2013, Leslie 2013, Makari 2012, Meibody 2011 and Yaday 2013
CA-125	0.36	0.94	Weighted average of 24 studies identified in evidence review
Laparoscopy	1.00	1.00	Reference standard, so sensitivity and specificity given by fiat

(a) All studies used in the economic model relate to the detection of pelvic endometriosis if multiple sites are given, which is the most common site. Different types of endometriosis have different associated accuracy; for example bowel endometriosis is easier to detect and bladder endometriosis harder in general.

Treatment effectiveness

The effectiveness of a treatment is defined as the change in pain VAS (in the pain group) or the odds ratio for a live birth (in the fertility group). These are given in Table 12, Table 13 and Table 14

Table 12: Treatment effectiveness of treatments modelled for pain subgroup (NMA results only).

Treatment	NMA Class	VAS score vs placebo (95% CI)	Estimated EQ-5D score vs placebo (95% CI)[b]
Codeine	N/A	N/A	N/A
Tramadol	N/A	N/A	N/A
'Generic' analgesia	N/A	N/A	N/A
Combined oral contraceptive	Progestogen and Oestrogen (oral)	-18.47 (-27.43, -9.48)	0.020 (0.010, 0.030)
Progestogen treatment	Progestogens (oral)	-12.29	0.013 (0.010, 0.016)

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Treatment	NMA Class	VAS score vs placebo (95% CI)	Estimated EQ-5D score vs placebo (95% CI)[b]
		(-15.16, -9.44)	
Danazol[a]	Danazol/ Gestrinone	-1.4 (-2.03, -0.76)	0.041 (0.012, 0.018)
GnRHa	GnRHa (intramuscular)	-10.82 (-18.04, -3.6)	0.012 (0.003, 0.020)
Amitriptyline	N/A	N/A	N/A
Nortriptyline	N/A	N/A	N/A
Duloxetine	N/A	N/A	N/A
Venlafaxine	N/A	N/A	N/A
Capsaicin Patches	N/A	N/A	N/A
Gabapentin	N/A	N/A	N/A
Pregabalin	N/A	N/A	N/A
Topical lignocaine	N/A	N/A	N/A
Laparoscopic Treatment	Laparoscopy	-26.05 (-44.05, -8.15)	0.030 (0.009 , 0.051)
Laparoscopy + Hormonal	Laparoscopy + Hormonal	-26.05 (-44.05, -8.15)	0.030 (0.009 , 0.051)
Hysterectomy	N/A	N/A	N/A
Acupuncture	Acupuncture	-5 (-6.79,-3.68)	0.006 (0.008, 0.004)
Chinese Herbal Medicine	Herbal Medicine	7.4 (-18.1, 32.9)	-0.008 (-0.037, 0.020)

(a) 0-3 Likkert scale, not 100-point VAS score like all others – this likely leads to substantial overestimate
(b) See below

The NMA data for pain considers only pain-related outcomes. In order to use these data in a health economic model, this VAS data must be converted into a form usable by standard HRQoL measures. To do this, a known EQ-5D score from the literature (Abbott (2004) which indicates the EQ-5D improvement of laparoscopic excision was around 0.03) was taken as a reference standard, and the rest of the scores scaled to the reference standard. For example, the VAS score for GnRHa was -10.82, which is 41% of the VAS score for laparoscopic excision, therefore the assumed EQ-5D score for GnRHa was 41% of 0.03, or 0.012.

This will be inaccurate compared to getting 'true' EQ-5D data; although the primary target of treatment in this group is control of pain, it is reasonable to assume that controlling pain might have positive effects on other areas of these women's lives, especially on the 'activities of daily living' and 'anxiety and depression' metrics. If certain treatments have an additional effect on 'activities of daily living' or 'anxiety and depression', the technique of scaling all scores to match the reference standard will overwrite this signal with noise. In practice this effect does not seem to be important; the values given by the NMA are similar to values in the literature.

Since some of the treatments specified in the protocol did not have NMA data associated with them, data from other sources were used to complete the table. Where possible, this was additional NMA data from NICE NG 173 on pain management, although data on confidence intervals was not available. If taken from NICE NG 173 then Table 9 (outputs of health economic model) was used. If not available from NICE CG 173, literature values were

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used, which, for the reasons described above, are likely to overestimate their effect relative to treatments which have received an NMA.

Table 13: Treatment effectiveness of treatments modelled for pain subgroup (combined results).

Treatment	Estimated EQ-5D improvement vs placebo (95% CI)	Source
Codeine	0.006 (0.006, 0.006)	NMA output of NICE CG 173
Tramadol	0.005 (0.005, 0.005)	NMA output of NICE CG 173
'Generic' analgesia	0.14 (0.003, 0.277)	Kauppila (1985)
Combined oral contraceptive	0.020 (0.010, 0.030)	NMA output of this guideline
Progestogen treatment	0.013 (0.010, 0.016)	NMA output of this guideline
Danazol[a]	0.041 (0.012, 0.018)	NMA output of this guideline
GnRHa	0.012 (0.003, 0.020)	NMA output of this guideline
Amitriptyline	0.018 (0.018, 0.018)	NMA output of NICE CG 173
Nortriptyline	0.023 (0.023, 0.023)	NMA output of NICE CG 173
Duloxetine	0.022 (0.022, 0.022)	NMA output of NICE CG 173
Venlafaxine	0.011 (0.011, 0.011)	NMA output of NICE CG 173
Capsaicin Patches	0.032 (0.032, 0.032)	NMA output of NICE CG 173
Gabapentin	0.022 (0.022, 0.022)	NMA output of NICE CG 173
Pregabalin	0.027 (0.027, 0.027)	NMA output of NICE CG 173
Topical lignocaine	0.140 (0.004, 0.254)	Wickstrom 2013
Laparoscopic Treatment	0.030 (0.009 , 0.051)	NMA output of this guideline
Laparoscopy + Hormonal	0.063 (0.028 , 0.098)	NMA output of this guideline
Hysterectomy	N/A[b]	Shakiba (2008)
Acupuncture	0.006 (0.008, 0.004)	NMA output of this guideline
Chinese Herbal Medicine	-0.008 (-0.037, 0.020)	NMA output of this guideline

(a) Danazol on separate scale in NMA, and therefore effect size likely overestimated
(b) It is expected that in all but exceptional cases a hysterectomy stops ongoing symptoms

As Table 13 demonstrates, 'Generic' analgesia, Hysterectomy and Lignocaine are based on substantially different sources of evidence to other treatments, and have results that are inconsistent with clinical practice and common sense (with the exception of Hysterectomy, which is consistent with clinical practice and common sense but is nevertheless from an unusual source). For consistency, these treatments will be excluded from the main analysis of results.

There is also a suggestion in the data that NICE CG 173 overestimates the effectiveness of treatments relative to the output of the endometriosis NMA. This is because – for example – we might expect hormonal treatments (which actually affect the cause of pain) to be more effective than analgesia (which only masks a symptom), whereas Table 13 suggests that many neuro-modulators are slightly better than most hormonal treatment. It is perhaps unsurprising that the two sets of results do not quite mesh, as NICE CG 173 is on the topic of neuropathic pain which will have very different symptoms and treatments to endometriosis. As the results from NICE CG 173 are within the realms of plausibility, and no better data source exists, it was decided to retain these values in the economic model. However the results should be interpreted in the light of uncertainty about the face validity of the neuromodulators results; this would make surgery look more cost-effective in women who cannot tolerate hormonal treatment as we can be more certain neuro-modulators and analgesia will not lie on the cost-effectiveness envelope.

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Table 14: Treatment effectiveness of treatments modelled for fertility subgroup (NMA results only).

Treatment	NMA Class	Clinical pregnancy odds ratio, vs placebo[b]
Codeine	N/A	N/A
Tramadol	N/A	N/A
'Generic' analgesia	N/A	N/A
Combined oral contraceptive	Laparoscopy+ Progestogen and Oestrogen (oral)[a]	0.73 (0.67 , 0.79)
Progestogen treatment	Progestogens (oral)	1.41 (0.43, 4.84)
Danazol	Danazol/ Gestrinone	0.48 (0.27, 0.83)
GnRHa	GnRHa (intramuscular)	3.89 (0.76, 31.76)
Amitriptyline	N/A	X
Nortriptyline	N/A	X
Duloxetine	N/A	X
Venlafaxine	N/A	X
Capsaicin Patches	N/A	X
Gabapentin	N/A	X
Pregabalin	N/A	X
Topical lignocaine	N/A	N/A
Laparoscopic Treatment	Laparoscopy	1.91 (1.26, 2.91)
Laparoscopy + Hormonal	Laparoscopy + Hormonal	1.84 (0.77, 3.53)
Hysterectomy	N/A	X
Acupuncture	Acupuncture	N/A
Chinese Herbal Medicine	Herbal Medicine	0.87 (0.40, 1.83)

(a) No data on Progestogen and Oestrogen alone, so comparison is against Laparoscopy alone
(b) An odds ratio of N/A means no data, whereas an odds ratio of X means the treatment cannot be given to a woman attempting to become pregnant, according to Committee opinion

As it seems unlikely Codeine, Tramadol or NSAIDs would have a noticeable effect on fertility, it is thought the NMA provides all the information required to model treatment effects on fertility.

Relapse probabilities

After treatment, a patient may find her symptoms are under control. Committee opinion is that this is typically a temporary control. In the case of surgery the endometriosis can come back if it is incompletely excised (and possibly if it is completely excised – the biology is uncertain) and in the case of pain management drugs such as analgesia and neuromodulators there is a wide literature suggesting that discontinuation frequently occurs because of intolerable side effects. There is also some evidence these drugs fall off in effectiveness over time, but this effect is not modelled. It is not expected that hormonal treatment or non-pharmacological treatment like acupuncture or herbal medicine will relapse. Table 15 gives these probabilities and their associated sources.

Table 15: Relapse probabilities used in the economic model

Treatment	Probability Relapse	Source
Codeine (as Morphine)	0.52 (0.07, 1.00)	NICE CG 173 Table F5
Tramadol	0.45 (0.17,0.86)	NICE CG 173 Table F5
'Generic' analgesia	N/A	NICE CG 173 Table F5

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Treatment	Probability Relapse	Source
Amitriptyline	0.24 (0.12, 0.41)	NICE CG 173 Table F5
Nortriptyline	0.28 (0.03, 0.92)	NICE CG 173 Table F5
Duloxetine	0.24 (0.13,0.40)	NICE CG 173 Table F5
Venlafaxine	0.24 (0.08, 0.54)	NICE CG 173 Table F5
Capsaicin Patches	0.11 (0.03, 0.27)	NICE CG 173 Table F5
Gabapentin	0.18 (0.10, 0.29)	NICE CG 173 Table F5
Pregabalin	0.19 (0.13, 0.26)	NICE CG 173 Table F5
Topical lignocaine	0.04 (0.00, 0.12)	Assumption based on Wickstrom 2013
Laparoscopic Treatment	0.30	Committee Opinion
Laparoscopy + Hormonal	0.30	Committee Opinion
Hysterectomy	0.02 (0.00, 0.05)	Falcone 2008

K.1.3.8 Health state utilities

Time in state utilities

The qualities of life associated with different health states depend on which subgroup women are in. Those women who have endometriosis-associated infertility are further subdivided into a pre-birth and post-birth cohort; it is assumed that post-birth all infertility issues are resolved and QoL reverts to either population baseline health (in the infertility only group) or equivalent to the pain subgroup (in the 'both' subgroup). These are given in Table 16, Table 17, Table 18 and Table 19. The values from Table 12, Table 13 and Table 14 are added to the 'symptomatic' EQ-5D scores to produce the mean effect for if a woman is 'cured', which may give fewer QALYs than if the woman was healthy. The 'cured' score is bounded to the 'healthy' score, which means no woman in the model can ever have a quality of life higher than 0.91 (plus or minus a standard deviation given in the table.

In conventional cost-effectiveness analysis it is usually assumed that the maximum utility someone can achieve is 1.00. That would be inappropriate in the case of this model, as it (could) imply that women with treated endometriosis are better off than those with no disease at all, which would lack face validity. Consequently the maximum utility someone with endometriosis can achieve is that of a healthy person, which is 0.91 in most subgroups.

The QoL score for women with undiagnosed endometriosis is 0.68, which is taken from Abbott 2004. It is assumed the QoL for women with diagnosed but untreated endometriosis is the same, which is likely to be false for two reasons. First, women who are diagnosed may feel more comfortable accessing resources to help them live with endometriosis such as online discussion groups. Second, the Abbott 2004 paper contains the possibility that women report higher quality of life following a diagnostic laparoscopy with no intervention compared to prior to the laparoscopy. This could be due to pure placebo effect, or a more complex effect mediated through reversion to the mean. It is also possible the knowledge that treatment was likely to be forthcoming led to a genuine improvement in QoL, or the natural history of endometriosis means that leaving the symptoms without intervention for six months will cause them to subside anyway. If these latter two explainations (or similar) are the case, there is a strong argument that the QoL for diagnosed endometriosis should be higher, possibly as high as 0.74 (the maximum increase that would be possible to attribute to this effect). Committee opinion is that it is likely to actually be somewhere between 0.68 and 0.74. As there is no good reason to pick any one value over another, 0.68 has been selected for the base case, but this effect has been investigated in sensitivity analysis.

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Table 16: Time-in-state utilities (pain subgroup).

State	QoL (SD)	Source
Healthy	0.91 (0.15)	Abbott (2004) control arm[a]
Menopause	0.91 (0.15)	Abbott (2004) control arm, assuming no ongoing effects of endometriosis (see section K.1.3.4)
Undiagnosed Endometriosis	0.68 (0.28)	Abbott (2004) treatment arm, assuming no disutility from having symptoms of an unknown source
Diagnosed Endometriosis	0.68 (0.28)	Abbott (2004) treatment arm
Endometriosis-like symptoms	N/A	QALYs not included in model

(a) EQ-5D population norm for women <45 is 0.87 (Kind, 1999), so Abbott paper finds fractionally higher baseline score in women matched with women with endometriosis. Abbott paper preferred for this source because it more accurately captures the QoL of women who have contact with the endometriosis system, but don't themselves have endometriosis

Table 17: Time-in-state utilities (fertility subgroup).

	Prior to birth QoL (SD)	Following birth QoL (SD)	Source
Healthy	0.91 (0.15)	0.91 (0.15)	Abbott (2004) control arm[a]
Menopause	0.84 (0.28)	0.91 (0.15)	Loss of 0.07 for no birth, equivalent to value in CG 156
Undiagnosed Endometriosis	0.84 (0.28)	0.91 (0.15)	Loss of 0.07 for no birth, equivalent to value in CG 156
Diagnosed Endometriosis	0.84 (0.28)	0.91 (0.15)	Loss of 0.07 for no birth, equivalent to value in CG 156
Endometriosis-like symptoms	N/A	N/A	QALYs not included in model

(a) EQ-5D population norm for women <45 is 0.87, so Abbott paper finds fractionally higher baseline score in women matched with women with endometriosis. Abbott paper preferred for this source because it more accurately captures the QoL of women who have contact with the endometriosis system, but don't themselves have endometriosis

Table 18: Time-in-state utilities (both subgroup).

	Prior to birth QoL (SD)	Following birth QoL (SD)	Source
Healthy	0.91 (0.15)	0.91 (0.15)	Abbott (2004) control arm[a]
Menopause	0.84 (0.28)	0.91 (0.15)	QALY loss from both groups summed
Undiagnosed Endometriosis	0.61 (0.28)	0.68 (0.28)	QALY loss from both groups summed
Diagnosed Endometriosis	0.61 (0.28)	0.68 (0.28)	QALY loss from both groups summed

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	Prior to birth QoL (SD)	Following birth QoL (SD)	Source
Endometriosis-like symptoms	N/A	N/A	QALYs not included in model

(b) EQ-5D population norm for women <45 is 0.87, so Abbott paper finds fractionally higher baseline score in women matched with women with endometriosis. Abbott paper preferred for this source because it more accurately captures the QoL of women who have contact with the endometriosis system, but don't themselves have endometriosis

Table 19: Time-in-state utilities (asymptomatic subgroup).

	QoL	Source
Healthy	0.87	EQ-5D population norm
Menopause	0.87	Asymptomatic endometriosis equivalent to healthy
Undiagnosed Endometriosis	0.87	Asymptomatic endometriosis equivalent to healthy
Diagnosed Endometriosis	0.87	Asymptomatic endometriosis equivalent to healthy
Endometriosis-like symptoms	N/A	QALYs not included in model

(a) Note these figures cannot be parameterised as they are from a different source

K.1.3.9 Sensitivity Analysis

The model included some deterministic inputs, such as costs based on published prices for example. Health state utilities were also deterministic inputs in the model as, given the way they were estimated, it was difficult to define a meaningful distribution from which to sample. However, to address this limitation in the model, extensive one way sensitivity analysis was undertaken on those variables influencing QALY gain to assess the extent to which cost-effectiveness was influenced by changes to these inputs.

All model analyses presented in section K.1.4 are based on probabilistic modelling to reflect uncertainty in parameter estimates. However, for some variables there is parameter uncertainty other than that accounted for by sampling variability. Therefore, a number of sensitivity analyses were undertaken whereby a deterministic input is changed before running the probabilistic sensitivity analysis. These can help assess how sensitive the model is to changes in particular parameters especially where simplifying assumptions were used. Furthermore, these sensitivity analyses can also be used to validate the model by checking that the model changes in a predictable way in response to its inputs.

For each analysis at least 1000 patients were simulated, and each analysis which contained fertility as an outcome had at least 2500 patients simulated.

K.1.4 Results

K.1.4.1 Women with pain as the primary symptom

Base case - Pain

The results of the base case analysis are presented in Figure 2. All possible diagnosis and treatment options are presented. A cluster of obvious outliers are highlighted, which relate to the following three treatments (and their corresponding diagnostic strategies) described in Table 13 as being based on evidence sufficiently uncertain as to justify their exclusion:

- Hysterectomy
- Perturbation with lignocaine

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- NSAIDs

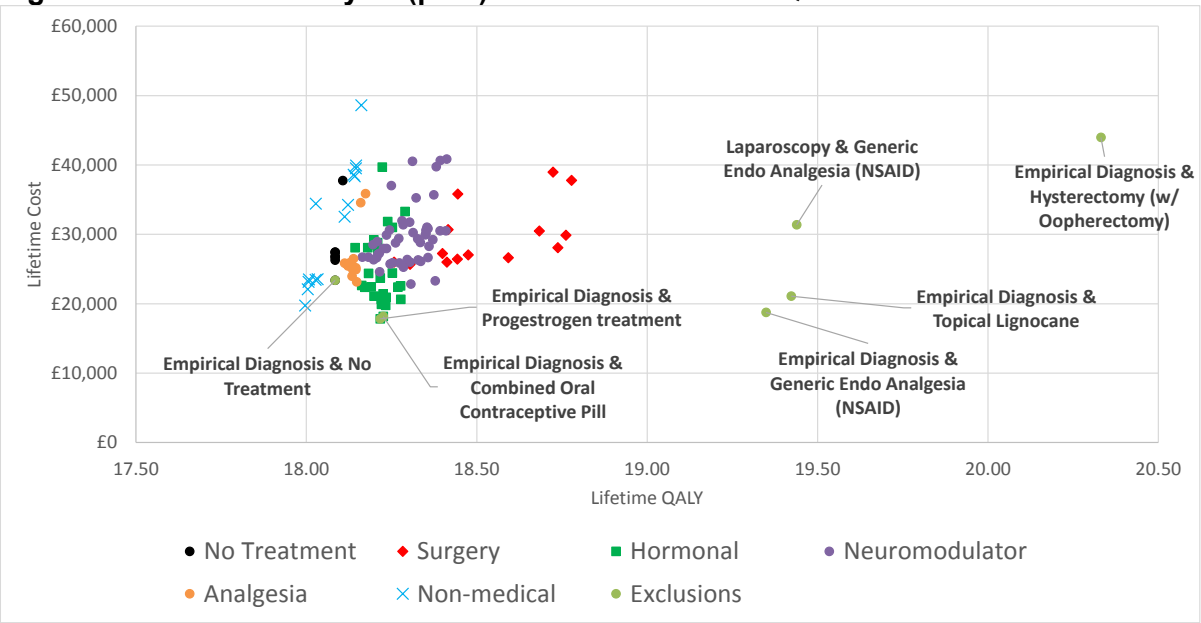
All three of these treatments have extremely poor underlying data, which may explain why their results are so counterintuitive. However in the case of hysterectomy magnitude of the effectiveness is likely correct - the procedure itself is a 'one off' which produces lifelong benefits from the point of view of the management of endometriosis. This notwithstanding, the fact that hysterectomy permanently and irrevocably ceases fertility is reason to prefer more conservative management strategies first.

Committee opinion is that NSAIDs are also likely to have a disproportionately cost-effective impact on treatment, although they concluded that – while likely highly cost-effective relative to most other treatments – they were unlikely to be as effective as the data suggested.

The quality of data was thought so poor that these three treatments are removed from all further graphical depictions of the results, such as Figure 3.

Owing to the number of comparisons, not all treatments have been labelled if doing so would obscure a comparison with a possibility of being cost-effective (or with some other health economic reason to pick out).

Figure 2: Base case analysis (pain) – lifetime costs and QALYs.



Source: Economic model

Figure 3 depicts what we might regard as the 'main schedule' of results. It shows increasing cost and increasing effectiveness as a move through hormonal treatments, neuromodulators and surgery respectively. Non-medical interventions, analgesics and no treatment are dominated in general, although owing to the structure of the model it is certainly possible to locate specific pairings of diagnostic and non-medical strategies that would be preferred to a specific pairing with some other treatment option.

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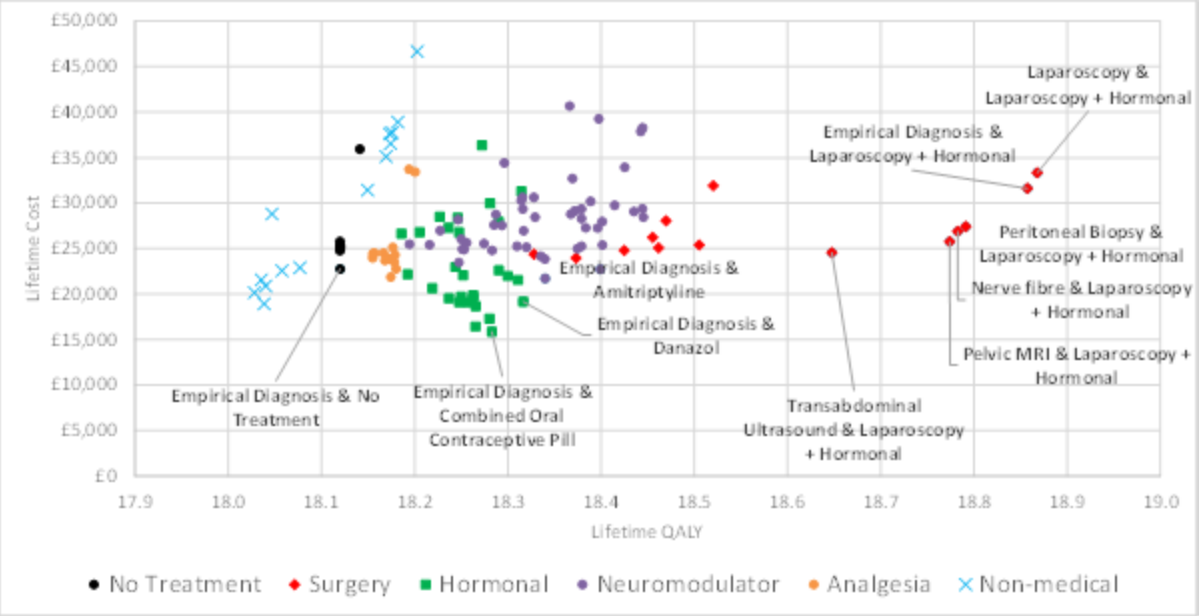
Figure 3: Base case analysis (pain) – Costs and QALYs, no outliers.



Source: Economic model

Table 20 demonstrates that despite the large number of treatment possibilities displayed in Figure 3, the dominance of oral contraceptives over non-medical, analgesic and non-intervention strategies means that only two treatments are likely to be worth considering on average. This supports the literature, in the sense that there is very little clinical disagreement that oral contraceptives represent the most cost-effective way of treating endometriosis in cases where it is appropriate to treat a woman with these drugs, but that the addition of surgery is likely to generate benefits on top of simple hormonal treatment. Additionally, by considering the 'probability cost-effective vs no treatment' columns, we can see that there is a very high chance that the 'Laparoscopy & Laparoscopy + Hormonal' strategy is cost-effective at £20,000 / QALY relative to no treatment. Similarly there is a good probability that some neuromodulators might be cost-effective relative to no treatment (although every neuromodulator is extendedly dominated by surgery on average, so this finding is not as important). A specific breakdown of the treatment strategies for such women is given in Table 21.

Table 20: Base case analysis (pain) – ICERs (showing only non-dominated results and no intervention).

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£22,752.60	18.120	Base Case	100.0%	100.0%
Empirical Diagnosis & Combined Oral Contraceptive Pill	£15,845.16	18.283	-£42,434.80	96.7%	96.7%

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Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & Danazol	£19,158.84	18.316	Extendedly Dominated	92.3%	93.4%
Empirical Diagnosis & Amitriptyline	£21,702.24	18.340	Extendedly Dominated	92.3%	95.6%
Empirical Diagnosis & Gabapentin	£22,734.50	18.399	Extendedly Dominated	94.5%	95.6%
Transabdominal Ultrasound & Laparoscopy + Hormonal	£24,562.05	18.648	Extendedly Dominated	85.7%	87.9%
Pelvic MRI & Laparoscopy + Hormonal	£25,772.03	18.774	£20,210.26	93.4%	96.7%
Nerve fibre & Laparoscopy + Hormonal	£26,875.57	18.783	Extendedly Dominated	92.3%	94.5%
Peritoneal Biopsy & Laparoscopy + Hormonal	£27,422.18	18.791	Extendedly Dominated	94.5%	96.7%
Empirical Diagnosis & Laparoscopy + Hormonal	£31,626.43	18.857	£70,170.78	95.6%	97.8%
Laparoscopy & Laparoscopy + Hormonal	£33,344.74	18.868	£164,710.65	97.8%	100.0%

A particular subgroup of interest is women who cannot tolerate oral contraceptives, either because of a genuine intolerance to the drug or because they are considering having a baby (but do not have endometriosis-associated infertility, which is covered in K.1.4.2). Table 21 suggests that the best treatment for these women is either an empirical diagnosis with amitriptyline to treat, or a pelvic MRI followed by conventional surgical treatment if a slightly higher cost per QALY threshold is acceptable.

As with the main schedule of results, surgical treatment is unlikely to be cost-effective at £20,000 / QALY if the woman is responding to treatment with conventional analgesia, but is more likely than not to be cost-effective relative to no treatment, and so could be considered if other treatments were inappropriate or the patient did not respond to them. This is important to note as Committee opinion is that in most cases where oral contraceptives are not prescribed, neuromodulators are likely to be inappropriate as well, which would change the ICER of surgical treatment to around £14,000 – this is below the standard NICE cost/QALY threshold indicating that if neuromodulators are contraindicated that surgery can be performed in a cost-effective manner..

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Table 21: Base case analysis (pain) – ICERs in women who cannot tolerate oral contraceptives (showing only non-dominated results and no intervention).

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£22,752.60	18.120	Base Case	100.0%	100.0%
Empirical Diagnosis & Herbal Medicine	£18,925.51	18.038	£1,049.17	29.7%	36.3%
Pelvic MRI & Herbal Medicine	£20,873.45	18.040	Extendedly Dominated	27.5%	36.3%
Empirical Diagnosis & Amitriptyline	£21,702.24	18.340	£9,207.08	92.3%	95.6%
Empirical Diagnosis & Gabapentin	£22,734.50	18.399	Extendedly Dominated	94.5%	95.6%
Peritoneal Biopsy & Laparoscopic Treatment	£24,783.78	18.425	Extendedly Dominated	86.8%	89.0%
Pelvic MRI & Laparoscopic Treatment	£25,079.29	18.462	£27,746.50	89.0%	93.4%
Empirical Diagnosis & Laparoscopic Treatment	£28,052.06	18.470	Extendedly Dominated	90.1%	94.5%
Laparoscopy & Laparoscopic Treatment	£31,899.07	18.520	£116,358.58	92.3%	94.5%

Sensitivity Analysis 1 – Diagnosis valuable in itself

Patient and lay members of the Committee suggested that there is a difference in quality of life between a person with undiagnosed but symptomatic endometriosis and a person with a diagnosis. Specifically, it is expected that a diagnosis is psychologically reassuring (since it demonstrates the NHS is taking the symptoms seriously) and might create a feeling of optimism (since it is possible for the symptoms to be tackled now that they are known). Additionally, women might be able to join support groups (either online or in person) which we might expect to have a positive effect on their quality of life.

In this sensitivity analysis, we assume that relative to the base case, being 'diagnosed' carries 0.05 extra QALYs and being 'undiagnosed' carries 0.05 less.

The results in Figure 4 demonstrate that there is a general decrease in overall lifetime QALYs if diagnosis is valuable in itself – because it takes such a long time for women to be

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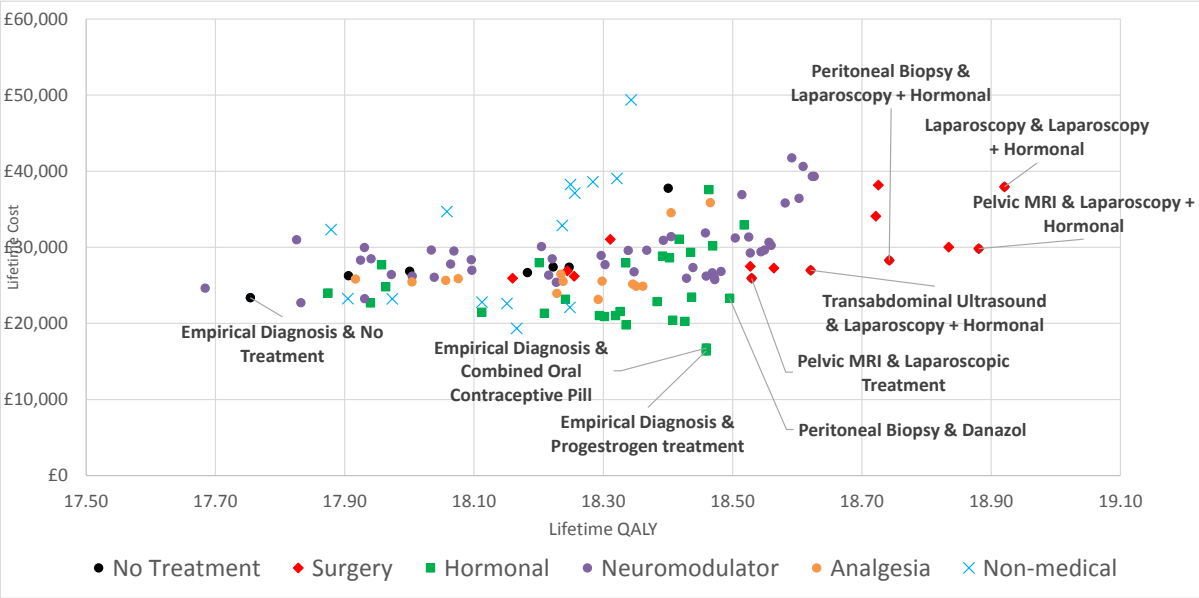
diagnosed and treated, making 'undiagnosed' more costly in terms of QALYs has a disproportionate impact on the overall outcome. However the rank ordering of diagnostic strategies does not change significantly, as demonstrated in Figure 5 – MRI followed by surgery remains the most preferred option from a QoL perspective, with empirical diagnosis followed by contraceptive hormonal treatment still on the cost-effectiveness frontier.

Figure 4: Sensitivity Analysis 1.1.1 – Diagnosis valuable at 0.1 QALY.



Source: Economic model

Table 22: ICERs in women who receive some benefit from a definitive diagnosis (showing only non-dominated results and no intervention)

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£23,386.07	17.754	Base Case	N/A	N/A
Empirical Diagnosis & Progestogen treatment	£16,379.62	18.459	-£9,938.98	100%	100%
Empirical Diagnosis & Combined Oral Contraceptive Pill	£16,765.95	18.459	Extendedly Dominated	98%	99%
Peritoneal Biopsy & Danazol	£23,317.99	18.495	Extendedly Dominated	93%	96%
Pelvic MRI & Laparoscopic Treatment	£25,948.88	18.529	Extendedly Dominated	90%	92%

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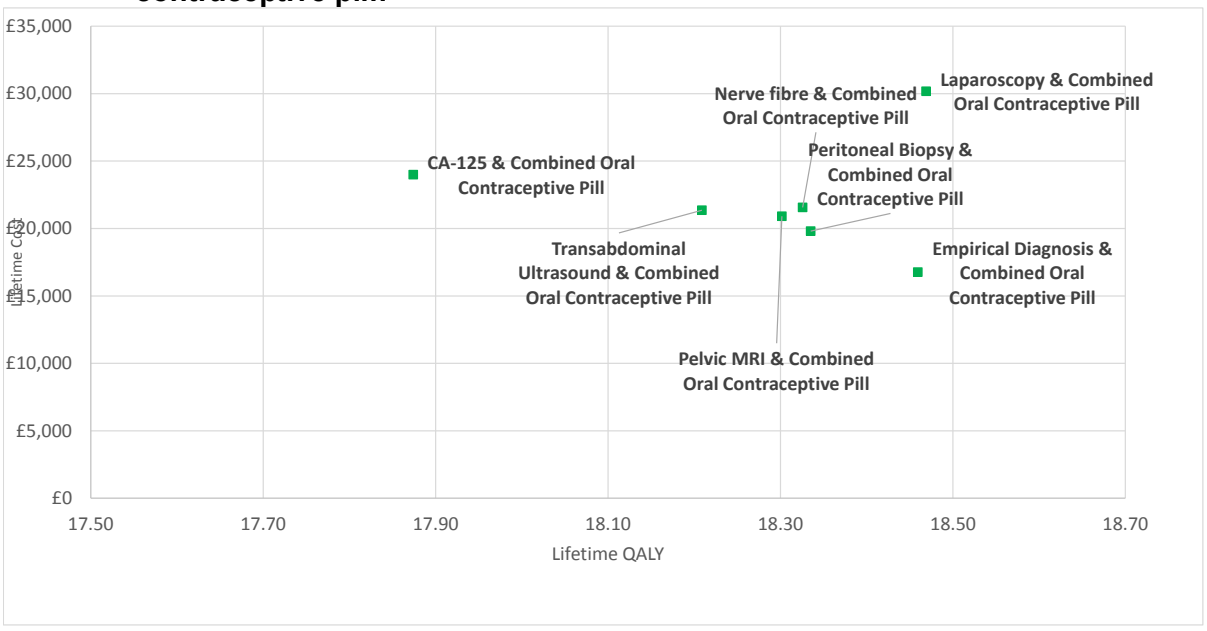
Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Transabdominal Ultrasound & Laparoscopy + Hormonal	£26,988.51	18.621	Extendedly Dominated	81%	84%
Peritoneal Biopsy & Laparoscopy + Hormonal	£28,296.36	18.742	Extendedly Dominated	89%	94%
Pelvic MRI & Laparoscopy + Hormonal	£29,818.36	18.881	£10,890.84	96%	97%
Laparoscopy & Laparoscopy + Hormonal	£37,936.87	18.921	£203,479.04	92%	95%

Figure 5: Sensitivity Analysis 1.1.2 – Rank ordering of diagnostic strategies for contraceptive pill.



Source: Economic model

Sensitivity Analysis 2 – Effectiveness of surgery

We may also be interested in how our recommendations on treatment change depending on the availability of good surgeons. A concern raised by the Committee was that the trials the model are based on tend to be carried out in the highest centres of excellence and treatment by a non-specialist might be harmful to women. Recommendations in the specialist services model explicitly consider that possibility for women with complex endometriosis, but we might want to consider it for women with less complex endometriosis.

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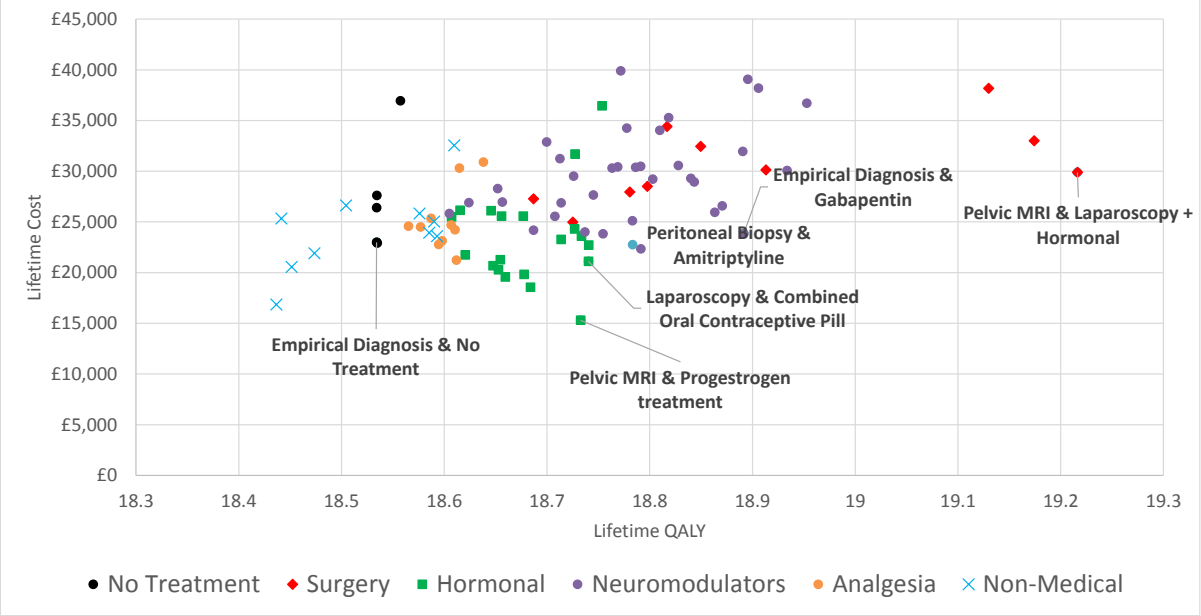
Figure 6 depicts the results when only the lower quartile of outcome scores from the surgical results of the NMA are considered for use in the model, effectively making use only of the least effective 25% of surgeons relative to the NMA predictions. This is potentially statistically unsound as it breaks the correlation between the surgical and hormonal NMA results, but is intended to be only illustrative and for sensitivity analysis purposes. Table 23 tabulates the same results.

Figure 6 shows that surgery is likely to be cost-effective if the woman cannot tolerate hormonal or neuromodulator treatment (likely to coincide, as these treatments are inappropriate for women who are trying to conceive). It also demonstrates that surgical treatment is unlikely to be cost-effective relative to neuromodulators in the lowest quartile of surgical outcomes. This is a marginal decision, as the result only just lies outside the conventional upper bound for NICE cost-effectiveness thresholds (£30,000). Since – in general – women cannot know whether they have a highly skilled or unskilled surgeon, this reaffirms the cost-effectiveness justification of the Committee recommendation to begin with a treatment of hormonal contraceptives.

Given the size of the dataset attempting this sensitivity analysis with fractions of the overall result less than around a quarter means outliers begin to start to dominate and so might not be a valid. Note that while it is entirely possible for every endometriosis surgeon to be extremely well qualified in an absolute sense, or even relative to peers in other countries, it is not possible for every surgeon to have good outcomes relative to other surgeons in the same field; exactly one quarter of surgeons must lie in the lowest quartile (although it is an unjustified assumption that the skill of the surgeon is directly related to postoperative QoL, when it may not be).

Figure 6: Sensitivity Analysis 1.2.1 – Showing only least skilled quartile of surgeons.



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Source: Economic model

Table 23: ICERs in women who receive treatment where effects are drawn from the bottom 25% of the NMA results (showing only non-dominated results and no intervention)

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£22,997.46	18.534	Base Case	N/A	N/A
Pelvic MRI & Progestogen treatment	£15,294.10	18.733	-£38,766.44	97%	98%
Laparoscopy & Combined Oral Contraceptive Pill	£21,104.88	18.740	Extendedly Dominated	94%	94%
Peritoneal Biopsy & Amitriptyline	£22,744.42	18.783	Extendedly Dominated	98%	98%
Empirical Diagnosis & Gabapentin	£23,840.67	18.892	Extendedly Dominated	87%	93%
Pelvic MRI & Laparoscopy + Hormonal	£29,882.57	19.216	£30,176.33	85%	90%

Sensitivity Analysis 3 – Postmenopausal QoL

A key concern of the Committee is whether the assumption of good postmenopausal QoL made a difference to recommendations. To test this, a variant of the model was run with the assumption that any postmenopausal QALYs are equal to zero – in other words that the quality of postmenopausal life with endometriosis is entirely terrible, only barely better than being dead. This is an absurd assumption, but Figure 7 demonstrates that it does not have unexpected effects on the outcomes; we would clearly rather live in a world where women have healthy postmenopausal lives, but given a world where postmenopausal QALYs do not exist we would still want to treat women in the same way to ensure their premenopausal years were as pleasant as possible.

It is possible that – given a hard threshold of £20,000 / QALY - the NHS might choose not to offer surgical treatment to women with endometriosis and poor postmenopausal QoL outcomes. However Table 24 demonstrates that relative to no treatment it is highly likely that surgery is cost-effective and so the Committee's recommendations are likely to be cost-effective even if postmenopausal QALY was near zero.

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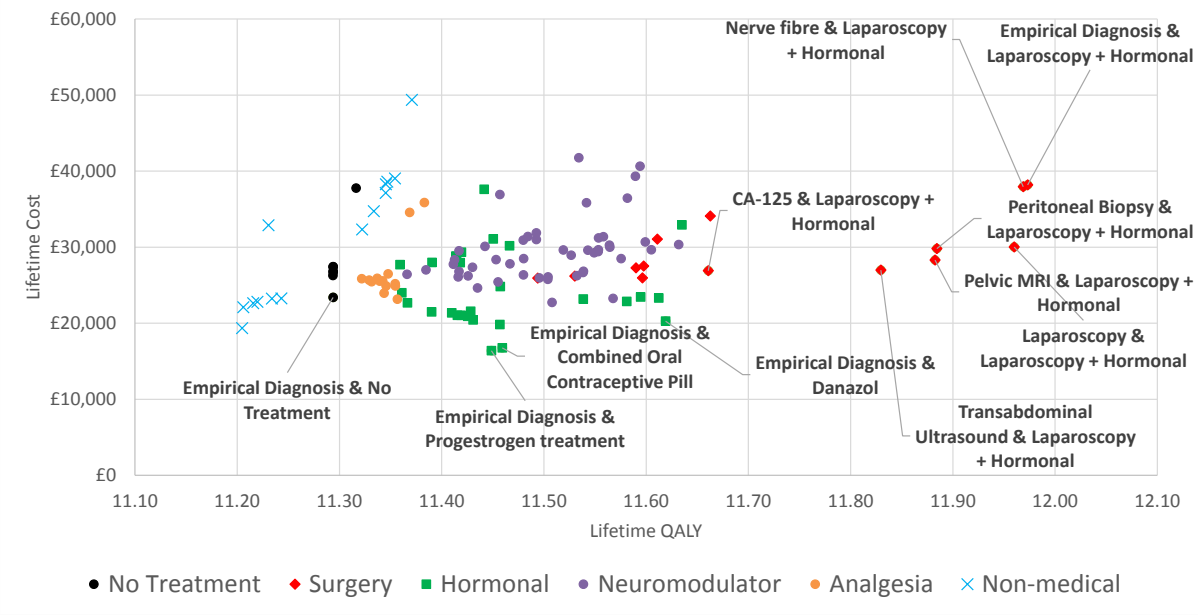
Figure 7: Sensitivity Analysis 1.3.1 – Assume zero postmenopausal QoL.



Source: Economic model

Table 24: ICERs in women who have zero postmenopausal QoL (showing only non-dominated results and no intervention)

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£23,386.07	11.294	Base Case	100%	100%
Empirical Diagnosis & Progestogen treatment	£16,379.62	11.449	-£45,270.79	97%	98%
Empirical Diagnosis & Combined Oral Contraceptive Pill	£16,765.95	11.459	Extendedly Dominated	94%	94%
Empirical Diagnosis & Danazol	£20,277.31	11.619	Extendedly Dominated	98%	98%
CA-125 & Laparoscopy + Hormonal	£26,896.93	11.661	Extendedly Dominated	69%	73%
Transabdominal Ultrasound & Laparoscopy + Hormonal	£26,988.51	11.830	Extendedly Dominated	90%	92%

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Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Pelvic MRI & Laparoscopy + Hormonal	£28,296.36	11.883	Extendedly Dominated	91%	94%
Peritoneal Biopsy & Laparoscopy + Hormonal	£29,818.36	11.884	Extendedly Dominated	95%	98%
Laparoscopy & Laparoscopy + Hormonal	£30,019.87	11.960	£26,697.32	95%	97%
Nerve fibre & Laparoscopy + Hormonal	£37,936.87	11.969	Extendedly Dominated	91%	93%
Empirical Diagnosis & Laparoscopy + Hormonal	£38,173.09	11.973	£610,891.69	93%	95%

The difference between the two scenarios is around 7 QALYs per woman, which has a social value of at least £140,000. This does not account for the potential that in real life whatever condition was causing such a dramatic decline in women's postmenopausal QoL would likely involve a high cost to the NHS. This may have implications for clinicians trying to prevent conditions thought to cause postmenopausal distress in women with endometriosis if further work is done estimating the impact of these conditions.

Sensitivity Analysis 4 – Laparoscopy Imperfect

The assumption that laparoscopy alone is perfectly discriminant at identifying endometriosis is potentially incorrect, especially given the evidence review suggesting that histological confirmation is important. Nevertheless the underlying model can only fairly compare diagtnostic strategies against a 'gold standard' which is assumed (on Committee advice) to be laparoscopic diagnosis. A sensitivity analysis was conducted to suggest whether laparoscopic diagnosis would remain cost-effective if inputs for this strategy were taken from the literature, rather than by rather than taken to be perfect as a modelling assumption.

Figure 8 and Table 25 show that while MRI and laparoscopic treatment remains borderline cost-effective, the ICER for laparoscopic diagnosis is considerably higher. As the ICER for laparoscopic diagnosis was outside the conventional 'borderline' of cost-effective in the base case, this did not substantially alter the Committee's thinking; they contended there were significant benefits to a laparoscopic diagnosis such as identifying endometriosis, and the fact that decreasing the power of the diagnostic test made it only less cost-effective (rather than dominated by some other treatment) was sufficient to justify this recommendation made on the basis of the main health economic model.

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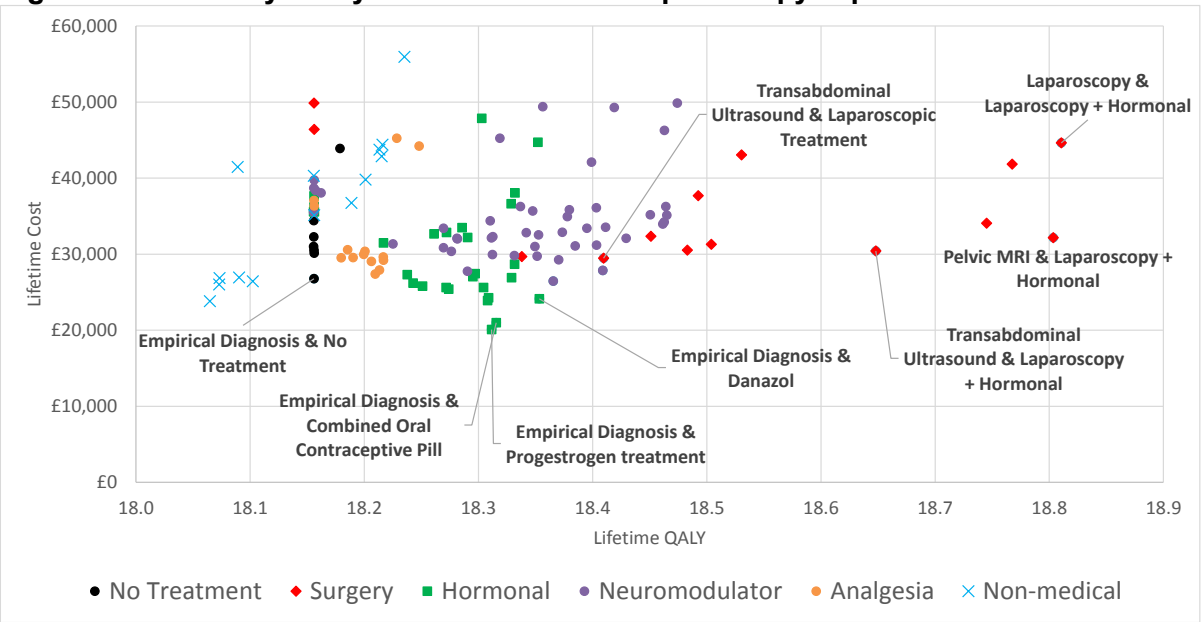
Figure 8: Sensitivity Analysis 1.4.1 – Assume laparoscopy imperfect



Source: Economic model

Table 25: ICERs in women who have 'imperfect' laparoscopy (showing only non-dominated results and no intervention)

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£26,778.25	18.156	Base Case	100.0%	100.0%
Empirical Diagnosis & Progestogen treatment	£20,080.72	18.312	-£43,027.39	96.7%	96.7%
Empirical Diagnosis & Combined Oral Contraceptive Pill	£20,973.66	18.316	Extendedly Dominated	90.0%	90.0%
Empirical Diagnosis & Danazol	£24,114.72	18.353	Extendedly Dominated	91.7%	93.3%
Empirical Diagnosis & Amitriptyline	£26,439.46	18.365	Extendedly Dominated	90.0%	96.7%
Empirical Diagnosis & Gabapentin	£27,843.13	18.409	Extendedly Dominated	86.7%	93.3%
Transabdominal Ultrasound	£29,452.04	18.409	Extendedly Dominated	78.3%	81.7%

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Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
& Laparoscopic Treatment					
Transabdominal Ultrasound & Laparoscopy + Hormonal	£30,406.98	18.648	Extendedly Dominated	86.7%	91.7%
Pelvic MRI & Laparoscopy + Hormonal	£32,145.88	18.804	£24,523.91	91.7%	93.3%
Laparoscopy & Laparoscopy + Hormonal	£44,631.25	18.810	£1,795,893.83	91.7%	93.3%

K.1.4.2 Women with infertility as the primary symptom

In this group of women the principle problem is to do with infertility. As described above, these women may either not be being caused discomfort from their endometriosis or the pain from endometriosis may be irrelevant to them compared to the importance of having a child. These women are therefore assumed to be totally 'cured' (in the sense that their endometriosis no longer causes a QALY decrement) following a live birth.

Base case – Infertility

The results of the base case analysis are presented in Figure 9 and Figure 10. The three treatments excluded from the main analysis of the pain subgroup have not been excluded here, although the assumption is that lignocaine and NSAIDs have no effect on fertility and hysterectomy immediately and permanently destroys fertility, so none of these treatments are in a position to be selected. In addition, progestogen treatments have been excluded from all analysis subsequent to **Error! Reference source not found.** owing to Committee concern hat the NMA shows a mean effect of progestogen treatments improving fertility when the Committee argued that this could only be an error with one or more of the studies as progestogen treatment is a contraceptive.

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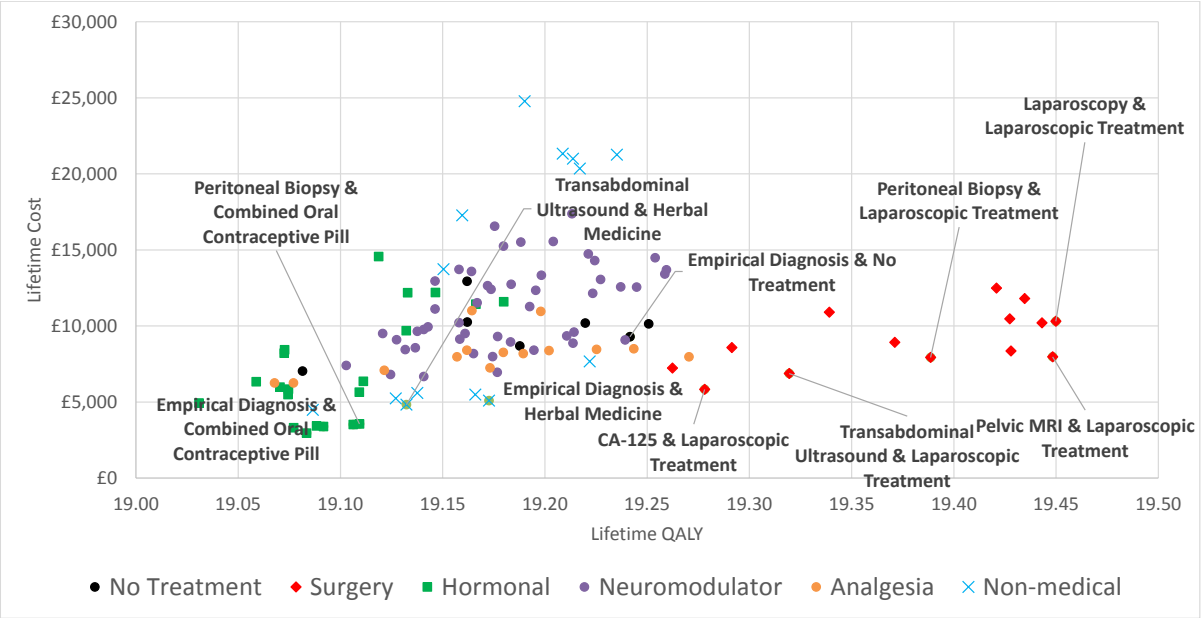
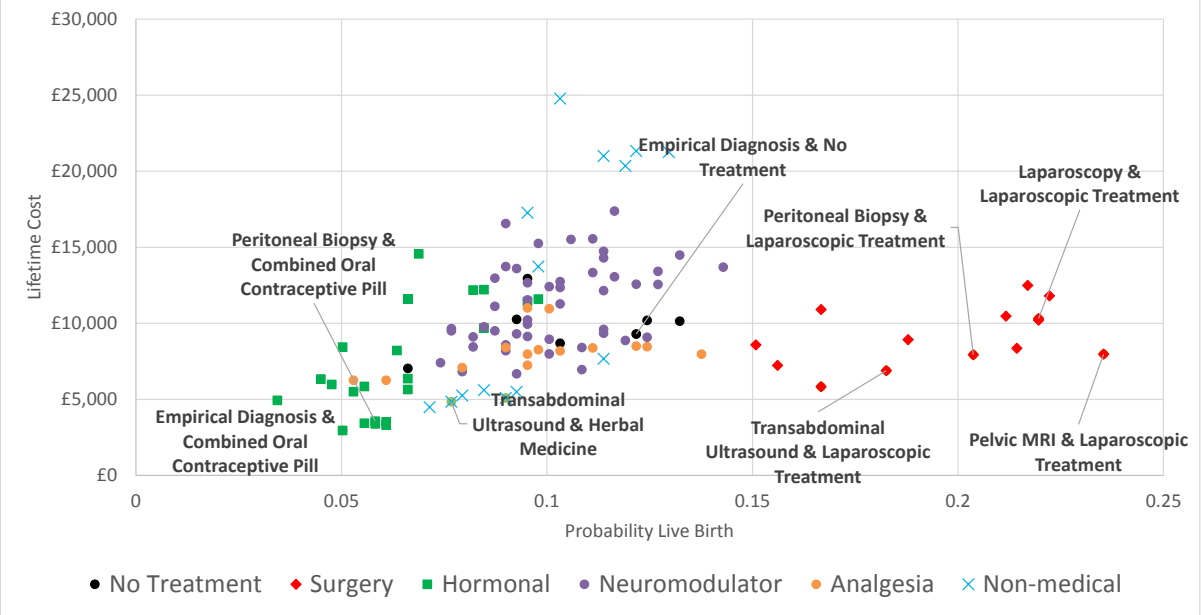
Figure 9: Base case analysis (fertility) – lifetime costs and QALYs (progestogen treatment excluded).



Source: Economic model

Figure 10: Base case analysis (fertility) – lifetime costs and live births (progestogen treatment excluded).



Source: Economic model

Clinical consensus is that surgery offers the best chance of conception for a woman with endometriosis-related subfertility. This is borne out by economic modelling, as demonstrated in Table 26 where every treatment more effective than the base case of doing nothing is a surgical technique – either laparoscopic excision on its own or laparoscopic excision plus hormonal therapy.

A significant economic issue is that the model assumes that any treatment – even treatments which harm fertility – are likely to reduce overall costs to the NHS. This might be true in real

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life (because women will likely visit their doctor less if they believe they are being treated) but would be a clear ethical breach for a doctor prescribing harmful drugs in order to make use of the placebo effect. Consequently the high price of 'no treatment' should not be taken to imply that prescribing hormonal contraception is a good idea in the case of women seeking better fertility.

Table 26: Base case analysis (fertility) – ICERs (progestogen treatment excluded).

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£9,287.14	19.242	Base Case	100%	100%
Empirical Diagnosis & Combined Oral Contraceptive Pill	£2,951.71	19.083	Extendedly Dominated	100%	100%
Transabdominal Ultrasound & Combined Oral Contraceptive Pill	£3,382.11	19.092	Extendedly Dominated	100%	100%
Nerve fibre & Combined Oral Contraceptive Pill	£3,512.64	19.106	Extendedly Dominated	100%	100%
Peritoneal Biopsy & Combined Oral Contraceptive Pill	£3,555.55	19.109	Extendedly Dominated	99%	100%
Transabdominal Ultrasound & Herbal Medicine	£4,829.00	19.132	Extendedly Dominated	100%	100%
Empirical Diagnosis & Herbal Medicine	£5,089.31	19.173	Extendedly Dominated	100%	100%
Transabdominal Ultrasound & Laparoscopic Treatment	£5,832.58	19.278	-£94,477.49	100%	100%
CA-125 & Laparoscopic Treatment	£6,876.99	19.319	Extendedly Dominated	100%	100%

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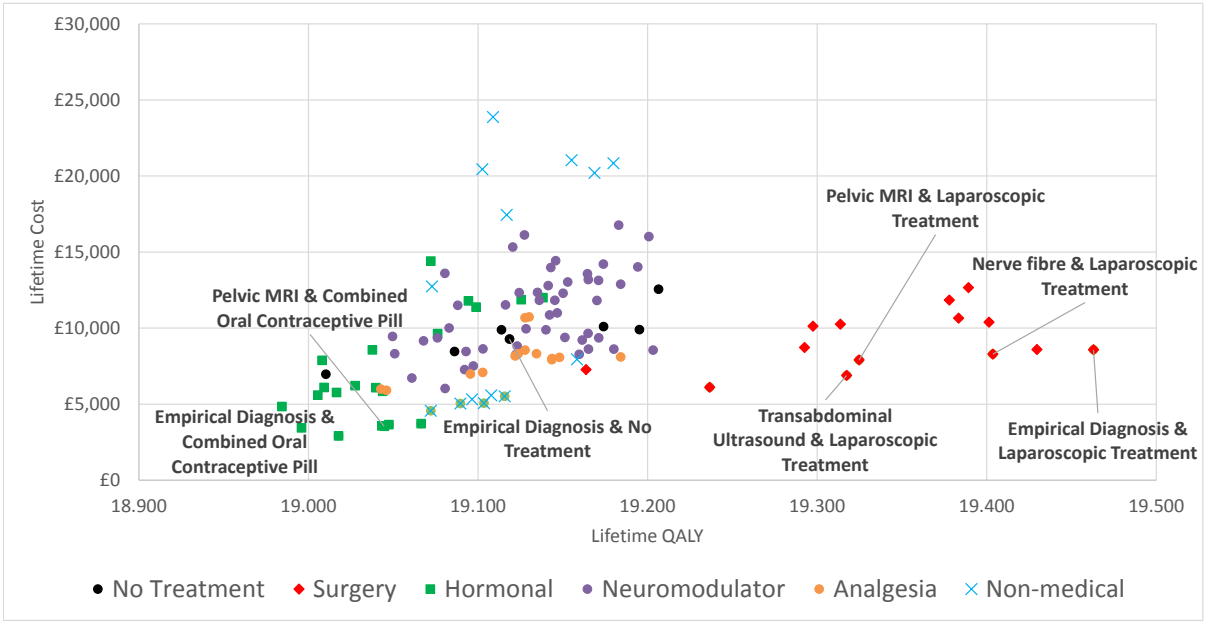
Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Peritoneal Biopsy & Laparoscopic Treatment	£7,930.55	19.389	Extendedly Dominated	100%	100%
Pelvic MRI & Laparoscopic Treatment	£7,966.94	19.448	£12,544.08	100%	100%
Laparoscopy & Laparoscopic Treatment	£10,307.01	19.450	£1,471,769.45	100%	100%

Sensitivity Analysis 1 – Secondary (rather than primary) infertility

Committee members pointed out that the model assumes all women are targeting one birth, whereas in fact many women have families of multiple children. Although the model was not well set up to consider women desiring larger families (it is based on Hunault's calculations, which do not consider more than one birth), one way we could approximate this is by considering women with secondary, rather than primary infertility. In secondary infertility, the woman has already had one child and desires another. In Hunault's model, the switch is handled by a simple deflator, so we know that this analysis will not change recommendations, but it might be useful for the Committee in forming recommendations based on the change in absolute probability and QALY.

Figure 11 gives the result of this analysis

Figure 11: Sensitivity Analysis 2.1.1 – Secondary (rather than primary) infertility – lifetime QALYs.



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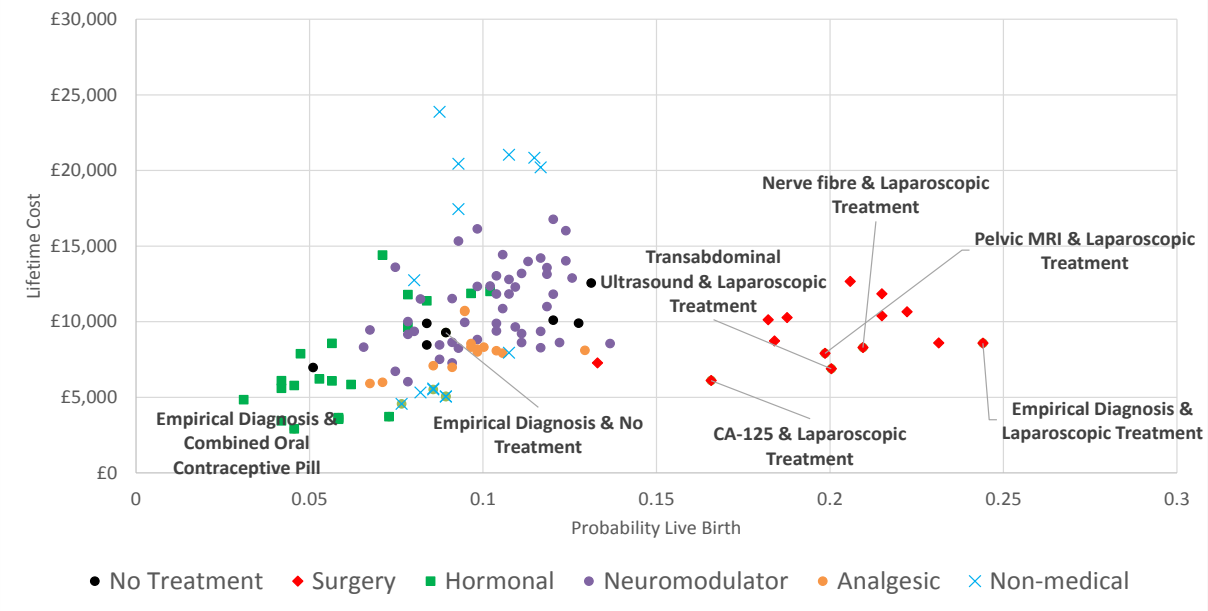
Source: Economic model

Figure 12: Sensitivity Analysis 2.1.2 – Secondary (rather than primary) infertility – probability live birth.



Source: Economic model

Sensitivity Analysis 3 – Consider child's QALYs

NICE guidelines involving fertility do not usually consider the QALYs of 'hypothetical' children who might be conceived as a result of fertility treatment. This is because of a philosophical judgement that the purpose of cost-effectiveness analysis is to maximise QALYs for those currently living, rather than maximising QALYs for those who might one day come to live. However as part of sensitivity analysis we might want to relax this assumption and assume that a live birth produces a child who will accrue over their lifetime around 25 (discounted) QALYs. This will make treatment appear considerably more urgent, as the opportunity cost of not treating is the mother's QALYs added to the hypothetical child's QALYs. The extent to which this is true dominates all other considerations; compared to no treatment the optimal treatment of laparoscopy followed by laparoscopic treatment costs only £857 / QALY. This philosophical consideration does not therefore significantly change treatment recommendations unless the cost/QALY threshold is lowered below £14,000 / QALY, but very greatly raises the importance and certainty with which we recommend surgical treatment. Figure 13 gives the results of this sensitivity analysis.

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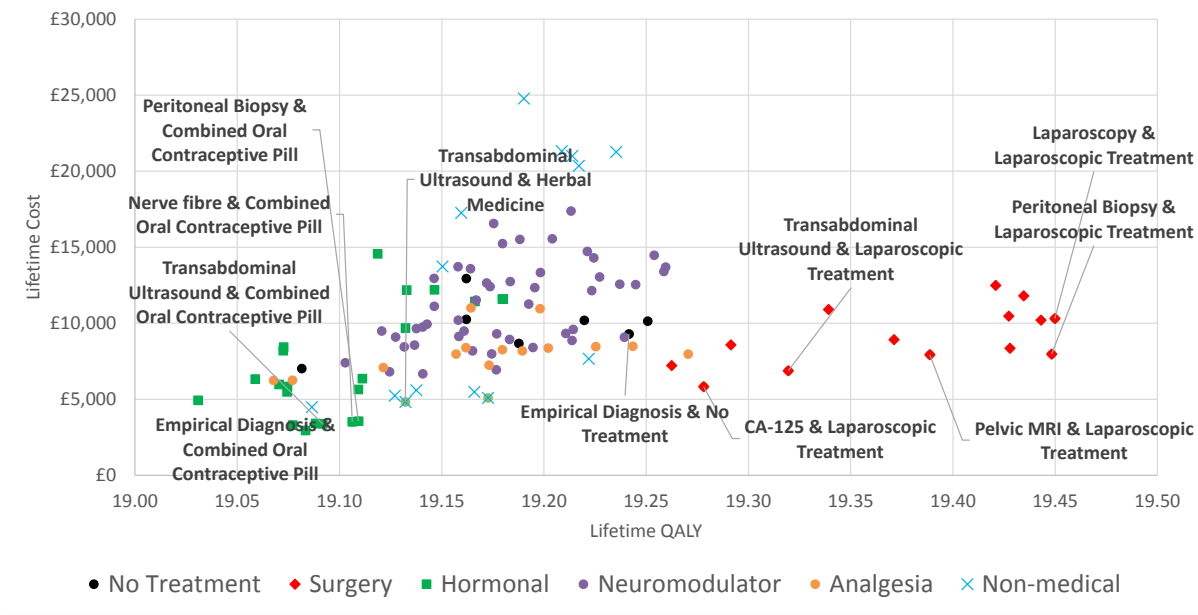
Figure 13: Sensitivity Analysis 2.2.1 – Adding hypothetical child's QALYs.



Source: Economic model

Table 27:– ICERs in women who receive fertility treatment if the QALY of their unconceived child is accounted for conventionally (showing only non-dominated results and no intervention) (progestogen treatment excluded).

Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Empirical Diagnosis & No Treatment	£9,287.14	19.242	Base Case	N/A	N/A
Empirical Diagnosis & Combined Oral Contraceptive Pill	£2,951.71	19.083	Extendedly Dominated	100%	100%
Transabdominal Ultrasound & Combined Oral Contraceptive Pill	£3,382.11	19.092	Extendedly Dominated	100%	100%
Nerve fibre & Combined Oral Contraceptive Pill	£3,512.64	19.106	Extendedly Dominated	100%	100%
Peritoneal Biopsy & Combined Oral	£3,555.55	19.109	Extendedly Dominated	99%	100%

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Treatment	Cost	QALY	ICER	Probability cost-effective vs no treatment (£20,000 / QALY)	Probability cost-effective vs no treatment (£30,000 / QALY)
Contraceptive Pill					
Transabdominal Ultrasound & Herbal Medicine	£4,829.00	19.132	Extendedly Dominated	100%	100%
Empirical Diagnosis & Herbal Medicine	£5,089.31	19.173	Extendedly Dominated	100%	100%
Transabdominal Ultrasound & Laparoscopic Treatment	£5,832.58	19.278	-£94,477.49	100%	100%
CA-125 & Laparoscopic Treatment	£6,876.99	19.319	Extendedly Dominated	100%	100%
Peritoneal Biopsy & Laparoscopic Treatment	£7,930.55	19.389	Extendedly Dominated	100%	100%
Pelvic MRI & Laparoscopic Treatment	£7,966.94	19.448	£12,544.08	100%	100%
Laparoscopy & Laparoscopic Treatment	£10,307.01	19.450	£1,471,769.45	100%	100%

K.1.4.3 Women with both pain and infertility as important symptoms

Base case – Both

In this group of women endometriosis causes both pain and infertility. This is a highly artificial group, as women will tend to weight considerations of pain and infertility differently (both different women rating the importance of these two concerns differently and the same women rating their importance differently at different times in their own life). In these women a live birth is a significant positive effect, but the impact of endometriosis is felt until menopause. Figure 11 and Table 28 give the results for this group.

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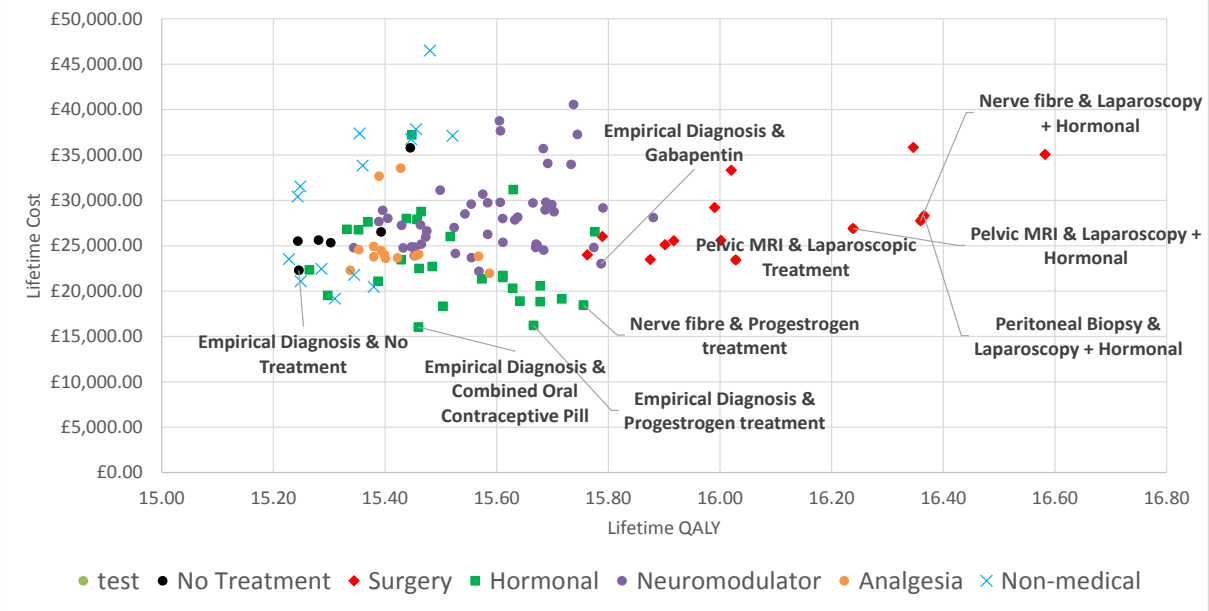
Figure 14: Base case analysis (Both) – lifetime costs and QALYs.



Source: Economic Model

Table 28: Base case analysis (both) – ICERs (progestogen treatment excluded).

Treatment	Cost	QALY	ICER	Pr. cost-effective vs no treatment (£20k / QALY)	Pr. cost-effective vs no treatment (£30k / QALY)
Empirical Diagnosis & No Treatment	£22,295.00	15.245	Base Case	100%	100%
Empirical Diagnosis & Combined Oral Contraceptive Pill	£16,034.76	15.460	-£29,222.45	95%	96%
Empirical Diagnosis & Progestogen treatment	£16,212.57	15.666	£863.13	98%	98%
Nerve fibre & Progestogen treatment	£18,445.40	15.755	Extendedly Dominated	96%	98%
Empirical Diagnosis & Gabapentin	£23,014.34	15.787	Extendedly Dominated	96%	96%
Pelvic MRI & Laparoscopic Treatment	£23,436.47	16.028	Extendedly Dominated	96%	96%

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Treatment	Cost	QALY	ICER	Pr. cost-effective vs no treatment (£20k / QALY)	Pr. cost-effective vs no treatment (£30k / QALY)
Pelvic MRI & Laparoscopy + Hormonal	£26,880.44	16.238	Extendedly Dominated	95%	96%
Nerve fibre & Laparoscopy + Hormonal	£27,751.54	16.359	£13,027.58	97%	99%
Peritoneal Biopsy & Laparoscopy + Hormonal	£28,303.03	16.366	Extendedly Dominated	96%	98%
Laparoscopy & Laparoscopy + Hormonal	£35,060.20	16.582	£32,775.59	95%	97%

As the results for women with both pain and infertility are so dominated by the results for women with pain alone, and they represent a high 'artificial' subset of women (moreso than other modelling variants) no sensitivity analysis has been undertaken.

It is likely that the pain dimension dominated because fertility is quite a low-probability event (especially amongst a low-fertility group like women with endometriosis), whereas pain is an unfortunate fact of life for many women. Therefore small changes to pain management can deliver a stream of QALYs for a long time in the future, whereas small changes to fertility merely change the probability of a low-probability event, and therefore only generate a stream of QALYs after a considerable delay. This is likely to be the case in reality, but this observation should be significantly moderated with a discussion of a woman's individual circumstances; if – for example – a woman makes it a high priority to finish her family by a certain age and believes the pain to be manageable until that age clinicians should not attempt contraceptives as a first line treatment.

K.1.4.4 Asymptomatic women

Base Case - Asymptomatic

This variation on the base case represents the fact that many women – possibly even a majority – do not suffer any symptoms of their endometriosis and only have the disease discovered incidentally (and presumably, some women never have the disease identified at all). Assuming this represents a cohort of women who are genuinely asymptomatic (i.e. it is not just that they have a different baseline expectation of how much pain is 'normal' for menstruation), it is a potential clinical challenge knowing how to treat these women; the two most important questions are whether these women should be more frequently identified, and - given that a diagnosis has been made – whether they should be treated with any conventional endometriosis therapies.

In this model, represented in Figure 15, having endometriosis causes no decline in fertility or health-related quality-of-life, but is otherwise unchanged from the standard model. Note that the scale is extremely 'zoomed in' compared to the other models

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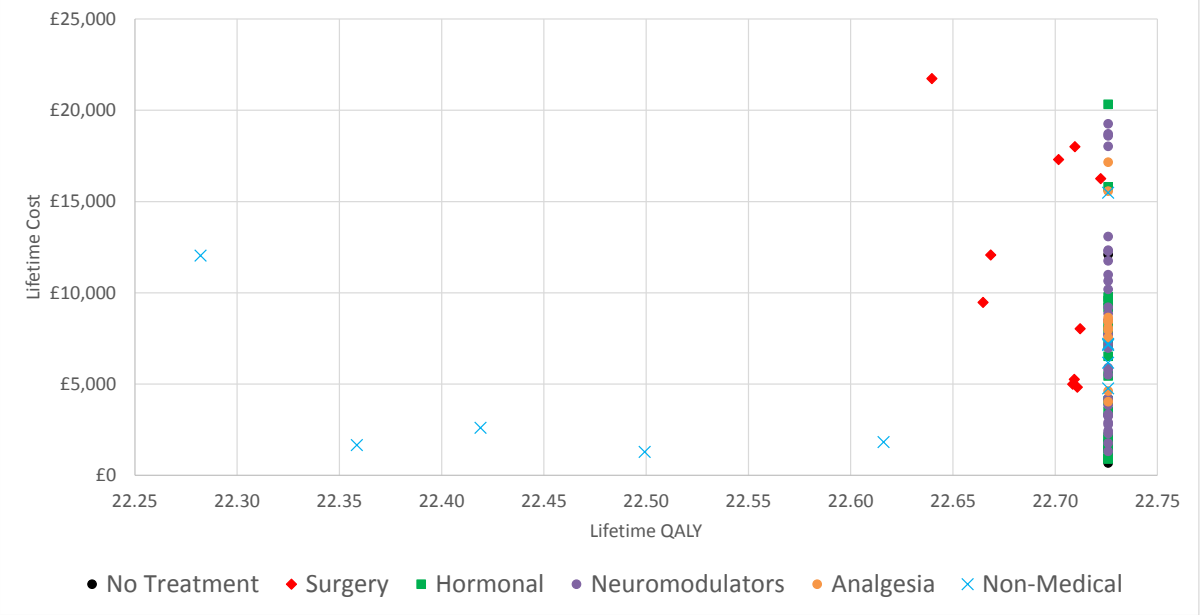
Figure 15: Base case analysis (Asymptomatic) – lifetime costs and QALYs.



Source: Economic model

The base case analysis strongly confirms that asymptomatic women are best left untreated unless there is reason to believe their disease is progressive.

The analysis especially recommends against therapeutic surgery or herbal medicine in this group – since surgery carries a small risk of side effects and 'no treatment' results in optimal health anyway, 'no treatment' is clearly preferable. All other treatments and diagnostic strategies appear to lead to no detriment to lifetime QALYs, but are more expensive than no treatment, meaning we would never prefer these treatments to 'no treatment' under any willingness to pay threshold.

Sensitivity Analysis 1 – Small QoL Decrement

In this sensitivity analysis variation, having asymptomatic endometriosis causes a tiny decrease to a woman's quality of life. This is intended to represent the fact that some women may have endometriosis that is not truly 'asymptomatic', but is nevertheless sufficiently asymptomatic that they may not wish to bother their doctor. The decrement to quality of life is fixed at 0.01, which is a decrement too small for most people to notice and around 5% of the decrement indicated in the main economic model.

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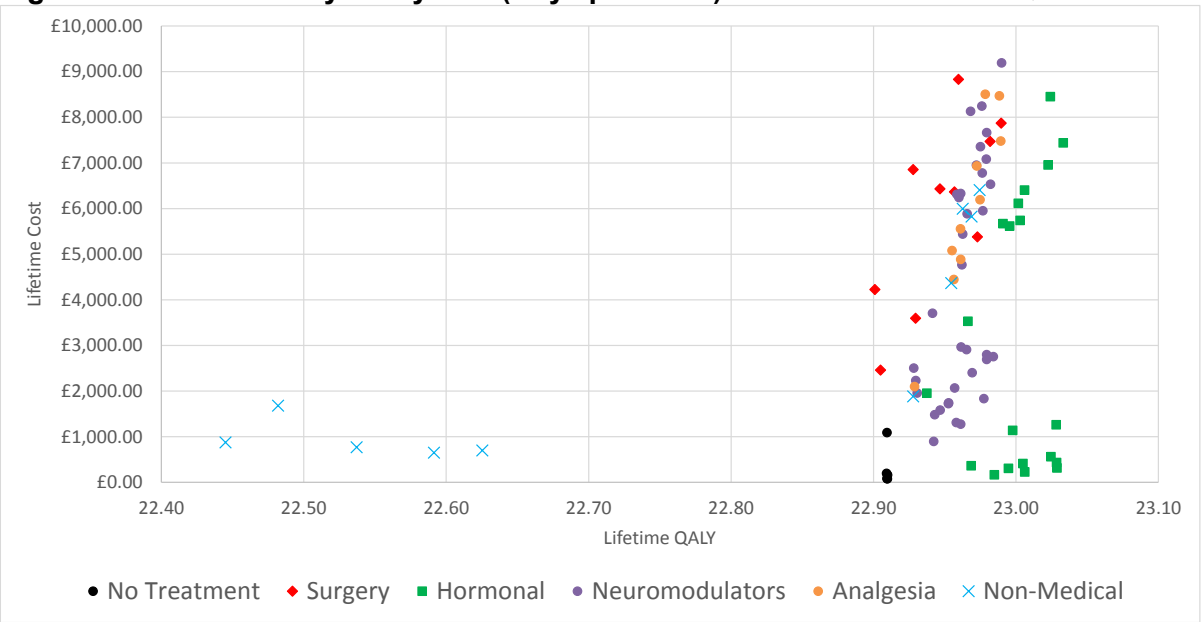
Figure 16: Sensitivity Analysis 1 (Asymptomatic) – lifetime costs and QALYs.



Source: Economic Model

Perhaps unsurprisingly, adding a small QoL decrement to living with untreated endometriosis tends to make treating endometriosis appear more effective. Relative to 'empirical diagnosis, no treatment' the most cost-effective strategy of 'empirical diagnosis, combined oral contraceptive pill' adds 0.1 QALYs over a woman's lifetime. At £20,000 / QALY society would be willing to pay around £2000 to acquire those QALYs, or roughly £50 / year for every year a fertile woman lives with asymptomatic endometriosis. At extremely high willingness to pay thresholds it may be appropriate to offer women a diagnostic laparoscopy before beginning treatment. This affirms the wisdom of the recommendation to offer oral contraceptives immediately while investigating possible endometriosis; even if it the endometriosis turns out to be completely benign, the possibility that it might be fractionally QoL decreasing is all that is required for this treatment course to be cost-effective.

K.1.5 Discussion

Overall, the economic model strongly supports existing practice of offering oral contraceptives to women suffering from endometriosis-related pain and only escalating to surgical treatment in the case of women who do not benefit from these contraceptives or who cannot take them for other reasons. It confirms that all treatments for endometriosis are likely to be cost-effective relative to no treatment in the pain group.

In the infertile group, surgery is strongly recommended on cost-effectiveness grounds. Certain hormonal treatments appear to improve fertility (for example progestogen treatment and surgery followed by hormonal treatment). This is unexplained by the Committee – there may be an extremely subtle effect at work or it may be an issue with the underlying data. Either way, even if the health economic analysis would recommend prescribing contraceptive hormonal treatment to women who are trying to get pregnant, common sense would dictate not to do this.

The mixed group is simply the combination of the pain and infertility group. In the main analysis pain dominates in terms of QALYs (suggesting that clinicians should prioritise controlling pain over promoting fertility), but in real practice women might have different priorities at different times in their life. Clinicians should take these priorities and the relative

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cost-effectiveness of treatment options into account when considering treatment for this group.

The model confirms that treating asymptomatic endometriosis is at best wasteful of NHS resources and at worse harmful to patients. If a woman is 'asymptotic' in the sense of having a QoL decrement she cannot recognise but which nonetheless is likely to exist at a low level, cheap treatments such as oral contraceptives might be considered.

Although the model approximately represents the real-world delivery of treatment for endometriosis, there are a number of limitations. Key amongst them is the assumption that quality of life after menopause is comparable in women with and without endometriosis, and various assumptions about fertility that are made for consistency with other NICE Guidelines. The source of effectiveness for many treatments are taken from a variety of sources not designed to be compared with each other, but basing the model on the results of an NMA goes some way to reducing the bias of these assumptions.

The model is not built to resolve fine distinctions between treatments within a class. For example, if a pain specialist believes gabapentin is more appropriate than codeine for a particular women, it is likely that the specialist has information that the model does not, and therefore should supersede the economics. However the model is quite clear on distinctions between classes; for example patients who are tolerating oral contraceptives well almost certainly do not need adjunct acupuncture.

K.2 Timing of Interventions Model

K.2.1 Introduction

This section contains details of the review of the literature and subsequent health economic modelling relating to the review on the timing of interventions. Specifically, it models costs and outcomes to answer the question "Does early laparoscopy and treatment improve outcomes?"

K.2.2 Review of the literature

A search of economic evidence relating to all treatments for endometriosis identified 438 papers. After screening titles and abstracts 73 full text articles were retrieved for further review. Of these 73 studies none were considered to be directly relevant to the review question.

K.2.3 Methods

A patient-level semi-Markov decision analytic model was developed in Microsoft Excel® to assess the cost-effectiveness of deliberate and unintended delays to diagnosis and treatment in a mixed population of women with progressive endometriosis, with nonprogressive endometriosis and without endometriosis (but still displaying endometriosis-like symptoms). The model considered lifetime cost and QALY differences arising from different levels of delay.

To reflect uncertainty in model parameters, the results were assessed using a mixture of probabilistic and deterministic sensitivity analysis. The model aimed to follow the NICE Reference Case unless otherwise stated.

The model was created by adding parameters relating to the progressiveness of the disease to the existing model described in Chapter K.1.

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K.2.3.1 Basic model structure

The model testing the importance of early vs late intervention might be considered a kind of 'enhanced' sensitivity analysis of the diagnosis and treatment model described in section K.1.3.1. The model testing the importance of early vs late intervention uses the same basic structure, but varies the probability with which the primary care provider refers a patient for investigation (see section K.2.3.4). In addition, women with endometriosis might have that endometriosis progress, making its removal more difficult and costly (see section K.2.3.3). Other than these two changes, the models are identical.

K.2.3.2 Time horizon

The NICE Reference Case specifies that a lifetime time horizon is preferred if it is appropriate. As this model relates to progressiveness of a disease over longer than a five year timeframe, a lifetime time horizon is both appropriate and preferred. In keeping with the NICE Reference Case, a discount rate of 3.5% has been adopted for both costs and benefits.

K.2.3.3 Clinical states included in the model

Early treatment of endometriosis carries a number of benefits. It prevents people living with endometriosis unnecessarily, it can make a women fertile during years she wishes to reproduce and it can prevent progression of the endometriosis to a more difficult-to-treat form. Early treatment is also identified as something which women with endometriosis find particularly important, and might contribute to reducing the psychological burden of the disease.

However, early treatment carries some costs. There are risks and costs associated with aggressively over-treating all diseases which look like endometriosis (especially surgically treating / investigating), treatment might not have any meaningful impact and the principle of discounting means that we would prefer to bear costs in the future if at all possible.

In general, the Committee thought the biggest risk of delaying diagnosis / treatment was the risk of progressive endometriosis. Although endometriosis is progressive on a continuum, after discussion with the Committee, the five following discrete clinical outcomes were agreed:

- No endometriosis at all (but symptoms similar to endometriosis and therefore outside the scope of the guideline)
- Superficial endometriosis (defined as endometriotic lesions anywhere in the pelvis other than the bowel or adnexus)
- Adnexal endometriosis (defined as endometrial involvement of the ovaries and / or fallopian tubes), including ovarian endometrioma
- Deep endometriosis (defined as any endometriotic lesions found on the bowel; for example a recto-vaginal nodule of 2 cm that does not invade beyond the serosa of the bowel)
- Complex deep endometriosis (defined as more extensive endometriotic lesions than just 'deep' endometriosis; for example bowel stricture and ureteric involvement)

A sixth form of endometriosis – endometriotic lesions outside the pelvis – could potentially have been included but is extremely rare and would be outside the scope of the Guideline.

Progressing to a more serious form of endometriosis is known to have costs associated with its treatment, and is thought to have an impact on quality of life and incidental healthcare utilisation costs. Progression can introduce new symptoms, for example infertility or constipation.

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The model considers the health state after menopause to be alike for all five clinical states. This is recognised to be an oversimplification, since more seriously progressed endometriosis can – for example – leave scarring on the bowel which causes symptoms even after the symptoms of superficial endometriosis have ceased due to menopause. However in the absence of evidence on this topic it was thought most appropriate to treat 'no difference' as the default as described in Section K.1.3.4.

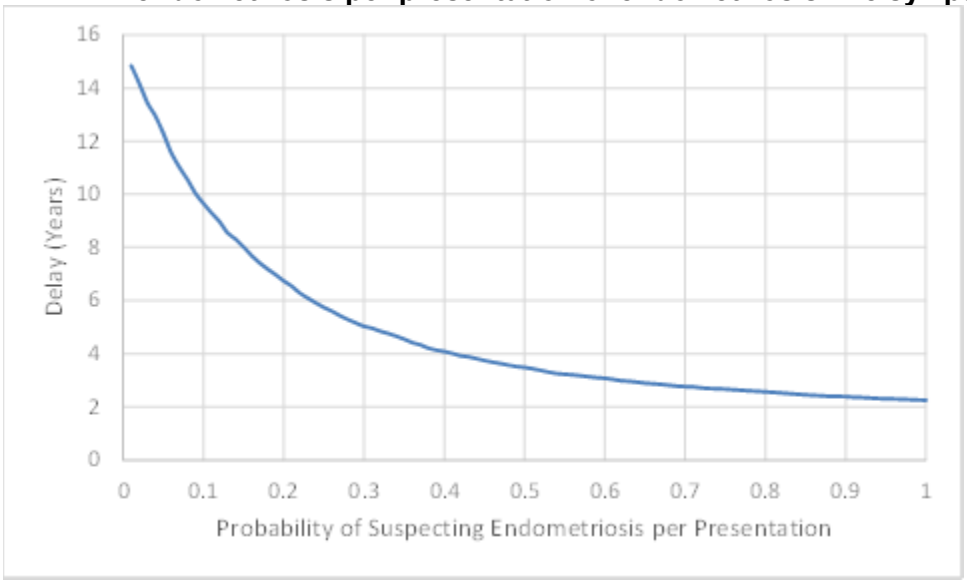
K.2.3.4 Interventions and comparisons

The model was set up to look at the effect of a delay on treatment. Consequently each run of the model adopted only one treatment strategy, with comparator strategies being the same treatment given with a different delay.

The delay itself was introduced by changing the probability that a primary care provider would suspect endometriosis given a patient presenting with endometriosis-like symptoms. This was further modified by introducing a class of patients without endometriosis, but with symptoms sufficiently similar to endometriosis that it could provoke a misdiagnosis. The principle behind the model was that altering the probability that the primary care provider made a Type II error would change the average delay a woman with endometriosis faced for treatment, and that this delay would introduce costs and QoL concerns which could be compared against each other.

The delay this strategy introduces is not linear – because patients who are incorrectly diagnosed can attend the primary care provider multiple times, over the course of a patient lifetime even very low chances of diagnosis on any one occasion would usually result in at least one episode of treatment. Consequently more attention was focussed on the area around a diagnosis chance of 0.15, which produced the delay of around 7-8 years known from the literature. In addition, results are presented with 'delay' on the x-axis (rather than 'probability of misdiagnosis'), since these results are more intuitively understandable. Figure 17 demonstrates the relationship between the probability of suspecting endometriosis per presentation and the average expected delay in receiving treatment in the base case of the model. Note that at a 0% probability the average delay is infinite (and not shown in this figure) while at a 100% probability there is still an average two-year delay, constituting – for example - surgical waiting lists, delays in seeking diagnosis, errors in diagnostic tests leading to diagnosis etc.

Figure 17: Expected delay in treatment given different probabilities of suspecting endometriosis per presentation of endometriosis-like symptoms.



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Source: Economic Model

In the base case, the diagnosis delay factor was 0.15 for both endometriosis and non-endometriosis, and the treatment selected was laparoscopic excision. These assumptions were varied in sensitivity analysis.

K.2.3.5 Outcome modelling assumptions

The assumptions underpinning the diagnosis and treatment model from section K.1 also hold for this timing of intervention model. However there are also three additional major modelling assumptions made to simplify the modelling of complex surgery for more serious forms of endometriosis:

Treatment failure

The primary purpose of operations to prevent or reverse highly-infiltrated endometriosis is the removal of visible lesions. It is hoped that this will also control pain, or return fertility. The model assumes that treatment failure in the form of failing to remove visible endometriosis is negligibly rare, although treatment failure in the sense of failing to control pain or returning fertility is quite frequent. It is unknown whether this assumption is realistic; Clinical Committee members were fairly certain it was true in their own tertiary / specialist experience, but Lay Members discussed how it was not their experience of care in secondary centres. Given Committee recommendations on the provision of specialist services, it was thought this assumption was sound for the purpose of modelling.

Regressive endometriosis

In the literature, endometriosis is divided into 'progressive' (meaning it gets more infiltrated over time), 'stable' (meaning it does not alter over time) and 'regressive' (meaning it gets *less* infiltrated over time. As a modelling approach, 'regressive' endometriosis is modelled as superficial endometriosis, 'stable' endometriosis can take any level of progressivity (but will never get worse over time) and 'progressive' endometriosis will always start at a 'superficial' level and then progress towards complex bowel infiltration over time. Committee opinion is that this is a clear simplification of the complexities of endometriosis progression in real life, but will probably capture the essence of the clinical problem – that a subset of women need constant reoperation to prevent heavy bowel infiltration.

Progression and Quality of Life

It is assumed that there is no difference in quality of life between a woman with superficial endometriosis and complex deep endometriosis. Committee opinion is that more infiltrated endometriosis probably causes differences in quality of life, and almost certainly is more likely to cause side-effects that persist post-menopause (such as bowel scarring). However, as there was no literature on this topic the Committee agreed that 'no change' would represent a reasonable base case.

K.2.3.6 Costs

Costs were based on an NHS and Personal Social Services perspective as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012). The model has a lifetime time horizon and therefore future costs and benefits were discounted at a rate of 3.5% in the base case analyses. The price year for costs was 2016.

Treatment costs

In the base case of the model, treatment was always given by surgical excision / ablation of the endometriosis sites. The complexity of the infiltration varied the cost of the surgery, and

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there is no published comparative data on how this complexity affects costs. Descriptions of the main cost factors were provided by surgeons on the Committee, and these are reproduced below in Table 29:

Table 29: Resource usage associated with various complexities of endometriosis.

	Operating Time (not including theatre prep)	Specialists Required	Risk of complication [c]	Estimated bed-days following surgery
Superficial Endometriosis[a]	32.35 mins[b]	Gynaecological Surgeon	0.3%	0.5
Adnexal	1.5 hours	Gynaecological Surgeon, and possibly involvement from urological surgeon and reproductive specialist	0.7%	1.5
Deep	2.5 hours	Expert endometriosis gynaecological surgeon	0.9%	1.5
Complex Deep	4.0 hours	Expert endometriosis gynaecological surgeon leading operation, plus involvement from at least colorectal surgeon and urological surgeon	7.3%	2.5 (if no ileostomy) 5.5 (if ileostomy)

(a) Non-endometriosis as per superficial endometriosis
(b) Lalchandani (2005)
(c) Based on Kent (2015) and Committee opinion
(d) All other values Committee opinion

The diagnosis and treatment model gives the cost of a Daycase 'NHS Ref Costs, Intermediate Female Pelvic Peritoneum Adhesion Procedures' (a proxy for a superficial excision) as £1494.89. The costs of treatment for deep and complex deep endometriosis are certain to be higher, since they involve excision / ablation of all superficial endometriosis and additional excision of material on the bowel. There is no relevant literature on the surgical costs associated with deep infiltrating endometriosis, however the NHS Classifications Services National Clinical Classifications Helpdesk did publish suggested costing codes for endometriosis in 2012 (https://bsge-online.org.uk/downloads/Complex%20endometriosis%20surgery-%20coding%20and%20tarriffs%20May13.pdf). These codes are not completely suitable for the economic model, since they don't consider adnexal endometriosis and make the distinction of costing based on site of lesion rather than complexity of operation, which the Committee argued was the more relevant factor. Additionally, the document carries a disclaimer that it should not be used to inform wider coding decisions. Consequently it was thought appropriate to calculate the cost of more complex operations from first principles, using the literature described in Table 29 which reports the expected recovery time in hospital following different complexities of operation. An estimate of the total cost of treatment can be made from this.

The NHS Reference Costs give the cost of an excess inpatient bed day following a 'Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedures' as £387 (the cost code for 'Minor' does not exist and the cost code for 'Intermediate' is higher, with many fewer entries; it is assumed that this is a statistical aberration and the 'Major' value is more stable). If it is assumed this is a reasonable proxy for the cost of a planned bed day and use the figure of 0.5 days in hospital following superficial operation given in Table 29 then we can calculate

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that of the £1494.89 cost of superficial operation, £193.50 (13%) is hospital-based recovery time and the remaining £1301.39 is the cost of the 32.35 minute operation plus theatre prep time. By scaling these values in accordance with Table 29 we produce our estimates for the mean cost of deep and complex deep surgery in Table 30. The maximum cost for complex deep endometriosis is in line with NHS recommendations, which suggests charging for £11974 for the most complex procedure 'Laparoscopic excision which involves dissecting rectum off the vagina and removing the lesion with bilateral ureterolysis and anterior resection of the rectum with creation of an ileostomy'.

Table 30: Estimated cost of surgical procedures for progressive endometriosis (not including complications).

	Operating time (including theatre prep time)	Recovery / bed day time	Total
Superficial Endometriosis	£1,301.39	£193.50	£1,494.89
Adnexal	£3,620.56	£580.50	£4,201.06
Deep	£6,034.27	£580.50	£6,614.77
Complex Deep	£9,654.83	£967.50	£10,622.33

Costs relating to adverse outcomes

Surgery for progressive endometriosis carries a number of risks, especially relating to surgical excision performed near the bowel. These risks are mostly corrected with further surgery. Committee opinion was that sometimes the damage to the bowel caused by endometriosis was so extensive that it was much safer to resect the bowel as a planned part of the operation than risk a major complication occurring during treatment – this leads to distinguishing an unexpected 'complication' and a planned 'complexity' class of bowel resection, which does not exist for other adverse outcomes. Table 31 gives these costs

Table 31: Cost of adverse events related to surgery for progressive endometriosis.

Event	Treatment	Cost	Source
Segmental rectosigmoid resections (as unexpected 'complication' of treatment)	Bowel resection	£15160.99	Pritts (1999) cost of 'nonpathway group'
Segmental rectosigmoid resections (as anticipated 'complexity' of treatment)	Bowel resection	£10563.57	Pritts (1999), cost of 'pathway group'
Rectovaginal fistulae	Temporary ileostomy	£8138	NICE CG131 – price of diverting colostomy, given lack of appropriate sources for cost of temporary colostomy
Ureterovaginal fistula	Ureteric stent	£1669	NHS Reference Costs, Non-Elective Inpatient cost for 'Unilateral, Percutaneous

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Event	Treatment	Cost	Source
			Insertion of, Ureteric Stent or Nephrostomy'
Ureteric damage	Ureteric stent	£1669	NHS Reference Costs, Non-Elective Inpatient cost for 'Unilateral, Percutaneous Insertion of, Ureteric Stent or Nephrostomy'
Death	N/A	£0	Assumption

(a) Note that these costs include postoperative bed days, which are already accounted for in existing postsurgical bed days, with the exception of rectovaginal fistulae, which would add 3 additional bed days as described in Table 29. The model makes necessary adjustments for this effect.

(b) Source for NHS Reference Costs is https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016

Other costs

All other costs information, including generic time-in-state costs, were as per the Diagnosis and Treatment economic model described in Section K.1.

K.2.3.7 Event probabilities

Progressiveness probability

For ethical reasons, there is very little controlled data on the natural history of endometriosis – especially on the natural history of the infiltration of endometriosis to the bowel. Consequently in the main diagnosis and treatment model described in section K.1 it was thought inappropriate to try and describe the observed phenomenon that some women appear to have their endometriosis progress over time, which appears to lead to worse outcomes. However, since this question explicitly deals with the effects of such a delay, it was thought appropriate to make some tentative assumptions about the way in which endometriosis might progress in otherwise healthy women.

Evers (2013) collects data on published studies of the progressiveness of endometriosis and finds that over a short period (usually six months) 29% of disease is progressive, 29% is stable and 42% spontaneously regresses

This presents an interpretation challenge – it is possible that 29% of disease is fundamentally 'progressive' and 71% is 'not progressive', or it is possible that the disease will naturally fluctuate, so that a patient who is 'progressive' at time T might be 'stable' at time T+1 and 'regressive' at time T+2 (which might put them back to where they started). Both interpretations are supported by the evidence. Committee opinion is that both interpretations could be true simultaneously for different patient groups, but they note that a known problem with this kind of study is that the interpretation of whether endometriosis has progressed or not is heavily confounded by the point in the woman's menstrual cycle in which the observation took place. Additionally, 'progression' in the Evers study is not always synonymous with moving from superficial endometriosis to bowel involvement (or from bowel involvement to complex bowel involvement, where applicable).

Consequently, Committee opinion was that a simple model where 29% of patients were progressive, 29% were stable and 42% were regressive would best represent the evidence without making any unwarranted assumptions. Regressive patients were modelled as being patients who had stable superficial endometriosis, since it was assumed that this was the state where they would gravitate.

The model additionally estimates the virulence of genuinely progressive endometriosis. As mentioned above, Evers finds that in six months endometriosis has progressed visibly in

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some patients, but this is not the same as finding that it has infiltrated the bowel in these patients; Committee opinion is that progress might occur in around a year, so a 'virulence' value of 0.13 was chosen in order than exactly 50% of progressive endometriosis cases would have progressed in four time periods (equivalent to a year in the model). This value was chosen using the following formula:

$$0.5 = 1 - (1 - p)^{t+1}$$

Where p is the 'virulence' (chance of transition in a given time period) and t is the relevant number of time periods. This formula ensures that in sensitivity analysis the probability of detecting progression in a set time period can be varied linearly.

Treatment effectiveness

In all cases, the treatment for progressive endometriosis is surgical excision or ablation. Evidence from the literature gives no indication this treatment can 'fail' in the sense of not excising visible endometriosis, and Committee opinion is that 'failure' in this sense occurs in a negligible number of cases. However treatment failure in the sense of not (significantly) improving the quality of life of the woman with endometriosis is somewhat common, and this is modelled in section K.2.3.8, where time-in-state utilities are discussed.

Side effect probabilities

The probability of a particular side effect occurring depends on many factors, including the skill of the surgical team and restrictions on the site or aggressiveness of operation (for example, if the surgical team is trying to preserve fertility). However the most important predictor of complications following surgery for endometriosis is the spread and site of the endometriosis; if the endometriosis is superficial (and has not spread to the bowel) then the surgeon should not need to touch the bowel and hence the rate of resections will be minimal – only occurring after a major surgical error or equipment malfunction. If the infiltration of the bowel is extensive then the risks of surgery increase accordingly. Committee opinion is that the rate of serious complications following surgery is around 2% given bowel involvement and around 10% given complex bowel involvement.

Although the side effects of surgery for endometriosis have been extensively studied, there are fewer papers on the risks of side effects following surgery for deep infiltrating endometriosis. Slack (2007) considers a cohort of 128 UK women who underwent laparoscopic laser surgery over a seven year period. Both Dousset (2010) and Koninckx (1996) describe similar cohorts of women undergoing excision, but both resected every woman in the cohort – this suggests it is possible to argue that resection is not a side-effect in some cases, but a necessary aspect of treatment. This observation is strongly supported by Committee opinion. Consequently Slack (2007) is preferred for our source of transition probabilities, because it reflects a UK cohort and a surgical team attempting to avoid resecting the bowel, but Slack's figures for bowel resections are subdivided into 'planned' and 'unplanned' varieties. These risks are described in Table 32.

Table 32: Risk of side effects as a direct result of bowel surgery.

Complication	Slack (2007) probability[a]	Probability | Serious Complication[c]	Absolute probability | deep endometriosis (0.9% risk of serious complication)	Absolute probability | complex deep endometriosis (7.3% risk of serious complication)
Segmental rectosigmoid resections (as	2.34%	16.7%	0.15%	1.22%

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Complication	Slack (2007) probability[a]	Probability | Serious Complication[c]	Absolute probability | deep endometriosis (0.9% risk of serious complication)	Absolute probability | complex deep endometriosis (7.3% risk of serious complication)
unexpected 'complication' of treatment)				
Segmental rectosigmoid resections (as anticipated 'complexity' of treatment)	N/A[b]	16.7%	0.15%	1.22%
Rectovaginal fistulae	2.34%	33.3%	0.30%	2.43%
Ureterovaginal fistula	0.78%	11.1%	0.10%	0.81%
Ureteric damage	1.56%	22.2%	0.20%	1.68%
Death	0.00%	N/A	N/A	N/A

(a) No deaths were reported as a direct result of endometriosis surgery in any of the studies listed above, but some deaths were recorded as a consequence of (for example) a resection (Nawar, 2011). These are recorded later, in Table 34

(b) Slack (2007) did not distinguish between a planned and unplanned resection, so it was assumed that there was an even ratio between them

(c) Closure of a rectal wall defect and postoperative urinary retention are so common that Committee opinion is that they should not be considered a 'side effect', but rather an anticipated consequence of performing the surgery

*(d) Worked example: 33.3% of all complications recorded by Slack were rectovaginal fistula, and the probability of a serious complication given complex deep endometriosis is 7.3%. Therefore the probability of a rectovaginal fistula given complex deep endometriosis is 33.3% * 7.3% = 2.43%*

It is assumed that the treatment for a segmental rectosigmoid resection (whether anticipated or not) is a bowel resection, the treatment for a rectovaginal fistulae is a temporary ileostomy and the treatment for both a ureterovaginal fistula and ureteric damage is a ureteric stent. There are a variety of treatments for postoperative urinary retention, of which the most common is likely a urinary catheter. Committee opinion was that postoperative urinary retention was such a common side effect of surgery that it would not be accurate to classify it as a specific risk of bowel surgery.

In the model, each time a patient enters the 'treatment' state, an additional check is run to see if that patient has any operative complications. If the patient does have a complication, the relevant costs and QALYs are added to that patient's lifetime totals. The patient then re-enters the main schema of the model and is assumed to be no different from the general population after the side-effects have been treated.

It is assumed that in the absence of surgery the base rate of adverse events other than death is zero. The rate of all-cause mortality in the absence of surgery is given by ONS life tables as described in Section K.1.3.7.

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K.2.3.8 Health state utilities

Time-in-state utilities

There is no comparative data on how the quality of a woman's life varies by the progressiveness of her endometriosis (although there is excellent data on how having endometriosis represents a quality of life decrement). Consequently in the base case all women with untreated endometriosis are considered to have the same average quality of life (although the quality of life for each individual woman will vary depending on how they are randomised at the beginning of the model run). In the base case, this quality of life is 0.68.

There is some evidence from the literature that those with deep endometriosis have a lower health-related quality of life than those without (Kent, 2015), and some evidence from the same sources that their postoperative quality of life is lower than the postoperative quality of life of the cohort forming the base case of the model (taken from Abbott, 2004). The differing values are contrasted in Table 33. This issue will be considered in sensitivity analysis, but Committee opinion was that too little was known about the natural history of the disease to justify switching away from the base case, since the women seen in the Kent et al study (and the cohort of women forming the data for British Society of Gynaecological Surgeons' grey literature) are potentially not representative of the cohort of all progressive women – the two study centres tend to treat only the most severe cases.

Table 33: Possible values for pre- and post-operative time-in-state utilities for progressive endometriosis.

Data source	QoL preoperatively	QoL 12 months postoperative	Average improvement at 12 months
Abbott et al (2004)[a]	0.68	0.85	0.17
Kent et al (2015)	0.60	0.80	0.20
BSGE database cohort[b]	0.53	0.77	0.24

(a) Base case for model
(b) Unpublished grey literature

Side-effect health state utilities

Table 34 shows the estimated QoL burden of side effects of treatment

Table 34: Estimated QoL burden of potential adverse effects of treatment.

Event	QoL burden	Temporary or permanent?	Source
Segmental rectosigmoid resections (as unexpected 'complication' of treatment)	0.09	Permanent – QALY loss occurs once per year	Committee opinion, based on experience of BSGE-certified specialist centres,
Segmental rectosigmoid resections (as anticipated 'complexity' of treatment)	0.00	Permanent – QALY loss occurs once per year	Committee opinion, based on experience of BSGE-certified specialist centres

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Event	QoL burden	Temporary or permanent?	Source
Rectovaginal fistulae[a]	0.07	Temporary	van der Valk et al (2015)
Ureterovaginal fistula	0.15	Temporary	Arguedas et al (2002)
Ureteric damage	0.15	Temporary	Arguedas et al (2002)
Death	0	N/A	Definition

(a) The treatment for rectovaginal fistulae – an ileostomy – is the subject of considerable debate in the health economics literature (for example Drossman, 1989), relating to patient 'adaption' (patients with an ileostomy have a higher quality of life with the bag than after its removal). This effect is not considered in the model as it would only affect a fraction of the women operated on.

Other QALYs

All other quality of life information, including generic time-in-state QALYs, were as per the Diagnosis and Treatment economic model described in Section K.1

K.2.3.9 Sensitivity Analysis

Probabilistic Sensitivity Analysis

In reporting clinical effectiveness it is usual and good practice to take into account the uncertainty of a relative treatment effect by reporting confidence intervals around the point estimate. Similarly, in health economic analysis it is important to take into account the uncertainty around model inputs. This can sometimes be achieved through one way sensitivity analysis, where one input value is altered at a time in order to assess what change that input has on the model's results. However, whilst that can often provide useful insights into what inputs are driving the models results it is inadequate to address the uncertainty which exists simultaneously across all model inputs.

Probabilistic sensitivity analysis, using Monte Carlo simulation techniques, allows for uncertainty across all model inputs to be addressed. Simulation involves running the model many times. In each simulation, rather than using the point estimate of the input, the value is sampled from its probability distribution. For inputs that are based on a large sample the probability distribution will be relatively narrow and the sampled inputs will reflect that. This model assessed the cost-effectiveness of the various treatment alternatives using probabilistic sensitivity analysis.

Deterministic Sensitivity Analysis

The model included some deterministic inputs, such as costs based on published prices for example. Health state utilities were also deterministic inputs in the model as, given the way they were estimated, it was difficult to define a meaningful distribution from which to sample. However, to address this limitation in the model, extensive one way sensitivity analysis was undertaken on those variables influencing QALY gain to assess the extent to which cost-effectiveness was influenced by changes to these inputs.

All model analyses presented in Section K.2.4 are based on probabilistic sensitivity analysis to reflect uncertainty in parameter estimates. However, for some variables there is parameter uncertainty other than that accounted for by sampling variability. Therefore, a number of sensitivity analyses were undertaken whereby a deterministic input is changed before running the probabilistic sensitivity analysis. These can help assess how sensitive the model is to changes in particular parameters especially where simplifying assumptions were used. Furthermore, these sensitivity analyses can also be used to validate the model by checking that the model changes in a predictable way in response to its inputs.

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K.2.4 Results

Each run of the model, one hundred possible probabilities for suspecting endometriosis were selected, corresponding to integer percentage probabilities. At each probability, one thousand women were simulated. The model was run ten times per figure, giving a total of one million patient simulations per graph. Each datapoint in the graphical displays below represents the average of the 10,000 patients simulated at that probability. Other values were varied as described in the relevant section.

Table 35 in Section K.2.4.1 below summarises these results

K.2.4.1 Summary table of results

Table 35 summarises the results of Figure 18 - Figure 36. Detail of how the table is populated can be found in the relevant subsections below.

Table 35: Summary table of health economic results by subgroup.

Subgroup	Cost 1 yr faster diagnosis	QALY gain 1 yr faster diagnosis	ICER of 1 year faster diagnosis	Probability 1 year faster diagnosis cost-effective at £20,000 / QALY
Pain only	£806	0.20	£4075	93.7%
Infertility only	£1907	0.19	£10,000	82.9%
Both	£1068	0.21	£5093	84.6%
Asymptomatic[a]	£1584	0.01	£179,943	N/A[b]

(a) See section K.2.4.5 – the most intuitive definition of 'asymptomatic progression' is covered in other subgroups Because so much of the cost-effectiveness of treating asymptomatic endometriosis is to do with random variation in the patient population, this value is not stable across runs of the model – it is approximately 40%-60%, and should have a mean value of slightly above 50% indicating that early treatment is cost-effective half the time (i.e. no better than random) except where the patient goes through menopause in the intervening year

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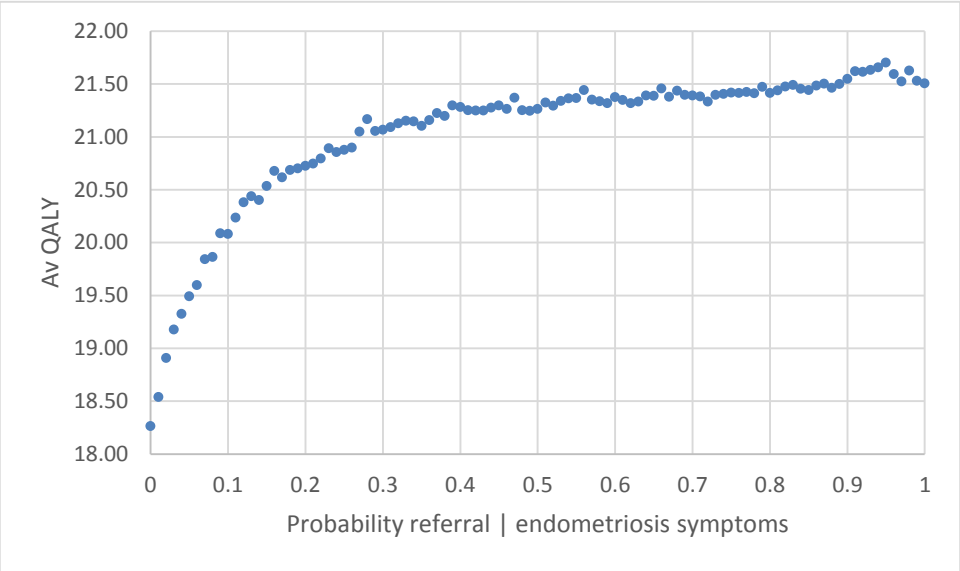
K.2.4.2 Women with pain as the primary symptom

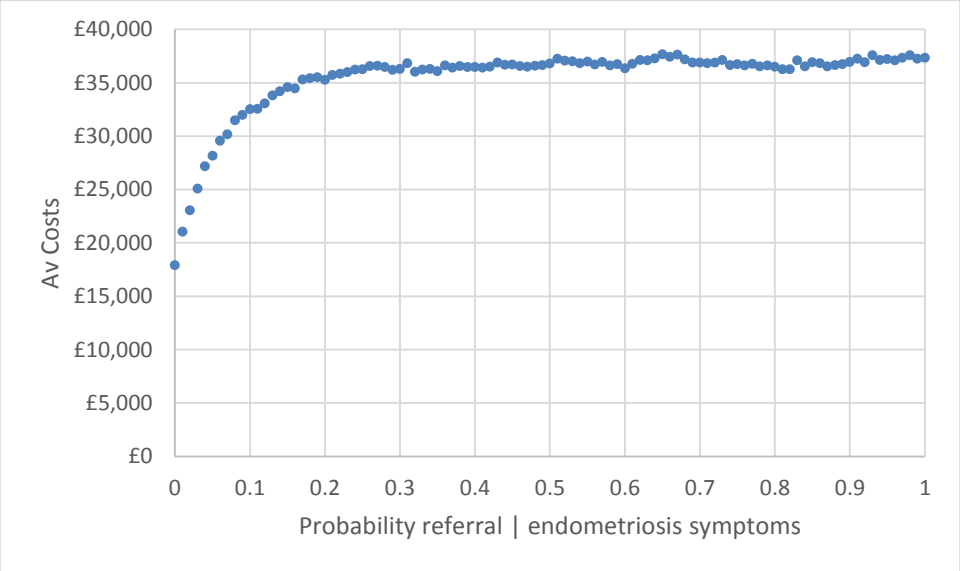
Base Case - Pain

Figure 18: Base Case (Pain) – Probability of suspecting endometriosis vs average lifetime QALYs.



Source: Economic model

Figure 19: Base Case (Pain) – Probability of suspecting endometriosis vs average lifetime cost.



Source: Economic model

We see from the main schedule of results in Figure 18 and Figure 19 that varying the probability of referring for concerns over endometriosis leads to a change in both costs and QALYs. Specifically, increasing the chance of referral increases both the average cost and average QALYs a woman can expect to accrue. This is unsurprising, as treating the condition more aggressively results in more operations (which are expensive) but is likely to prevent progression to more harmful types of endometriosis.

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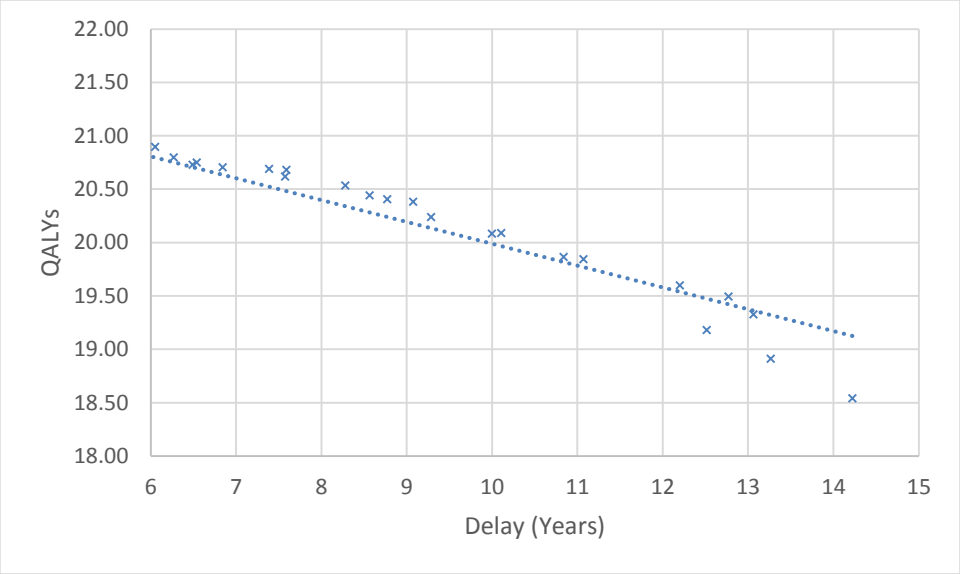
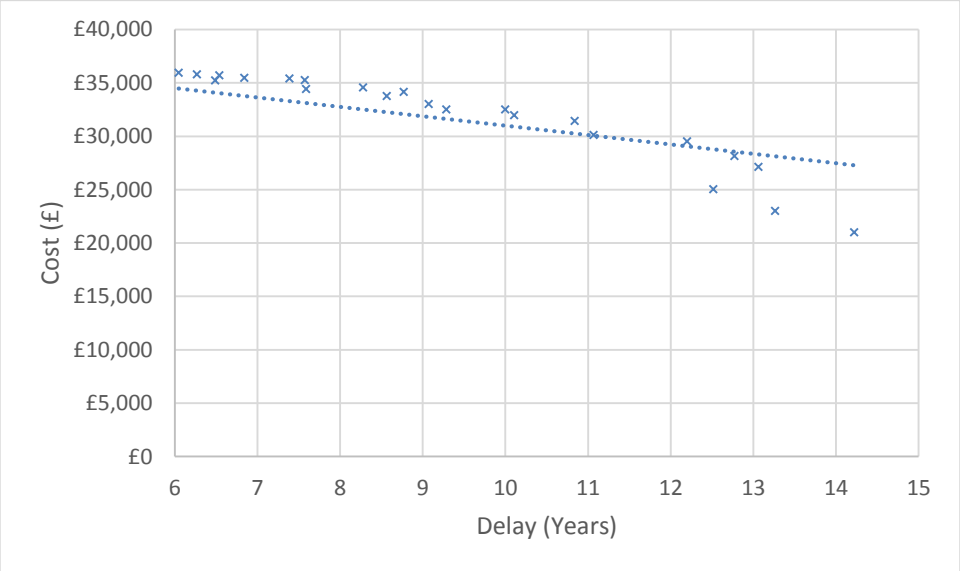
The results are easier to understand when probability of referring is converted into an 'average delay' in years, which is what is demonstrated in Figure 20 and Figure 21. Here we see that the relationship between cost, QALY and years of delay is approximately linear for realistic values of the delay time.

Figure 20: Base case (Pain) – Average delay vs average lifetime QALYs.



Source: Economic model

Figure 21: Base Case (Pain) – Average delay vs average lifetime cost.



Source: Economic model

This represents a straightforward health economic tradeoff; we can spend (expected) resources by reducing the delay in diagnosis by one year, and for that resource spend we gain QALYs. The cost of such a decision would be £806 per woman, and the QALY gain 0.20. Since this represents 'purchasing' QALYs at a rate of £4075 per QALY, it is highly likely that this intervention would be considered cost-effective at a threshold of £20,000 / QALY. Figure 22 demonstrates that at £20,000 / QALY speeding diagnosis by a year is 93.7% likely

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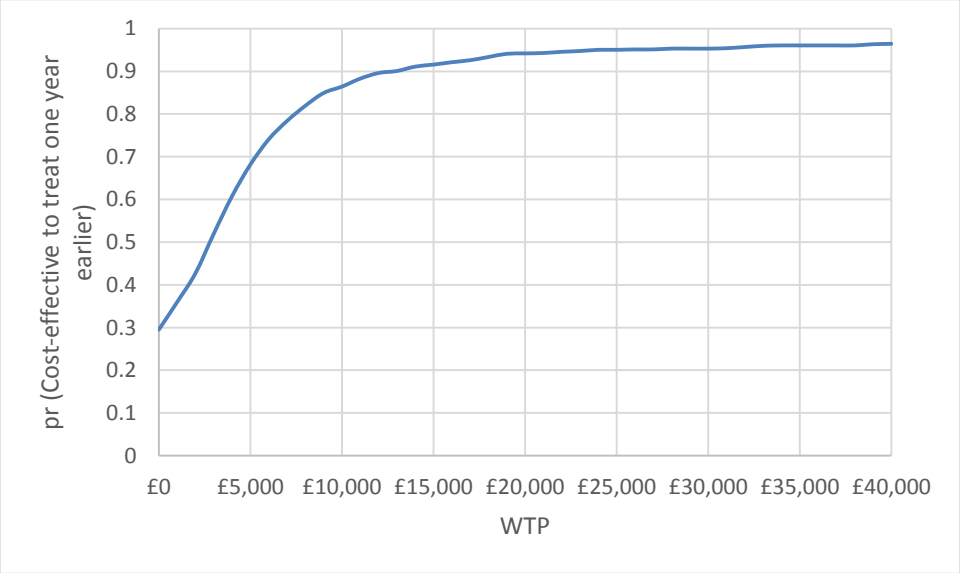
to be cost-effective, and that the intervention is likely to be cost-effective with 90% probability at a willingness-to-pay of £13,000 / QALY.

Figure 22: Base case (Pain) - Cost-effectiveness acceptability curve.

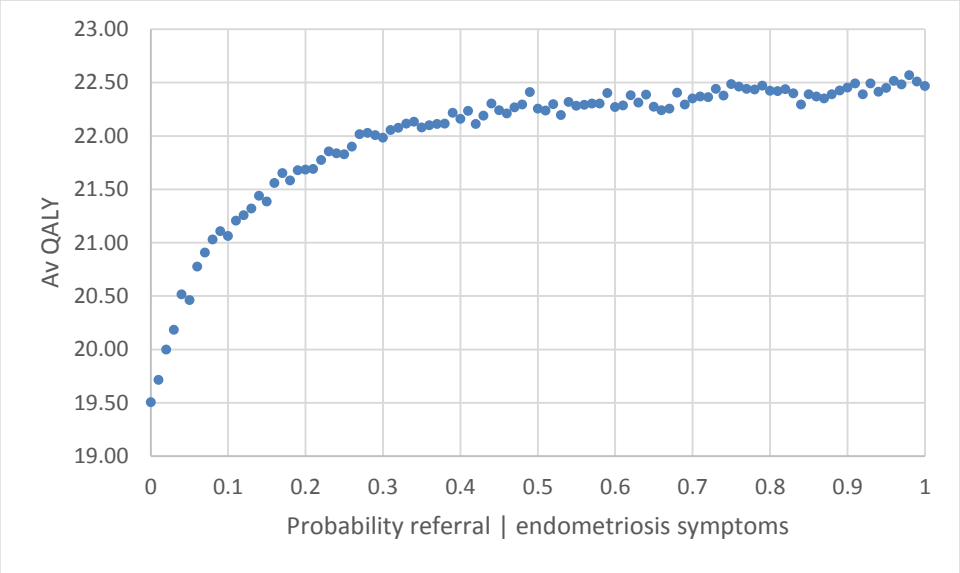


Source: Economic model

K.2.4.3 Women with infertility as the primary symptom

Base case – Infertility

Figure 23: Base Case (Infertility) – Probability of suspecting endometriosis vs average lifetime QALY.



Source: Economic model

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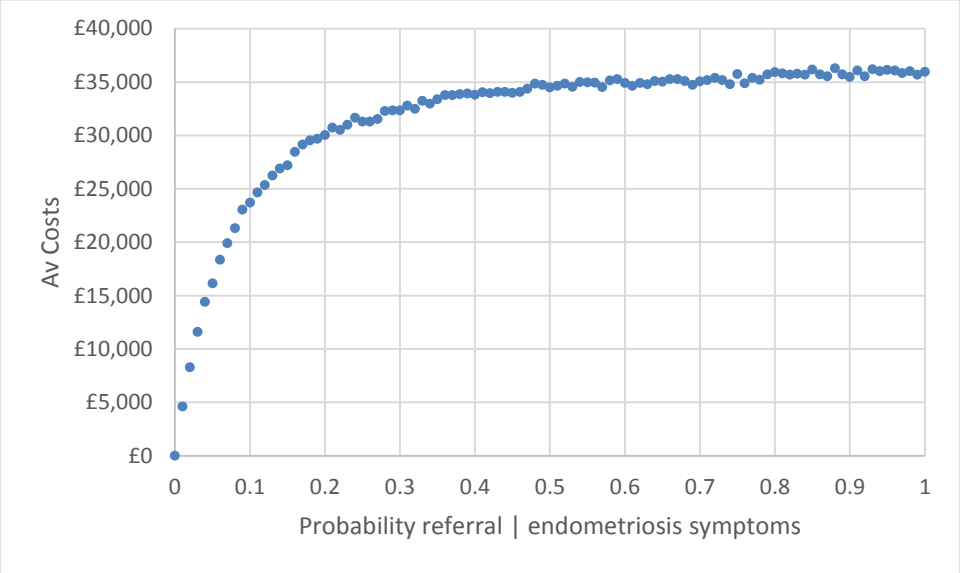
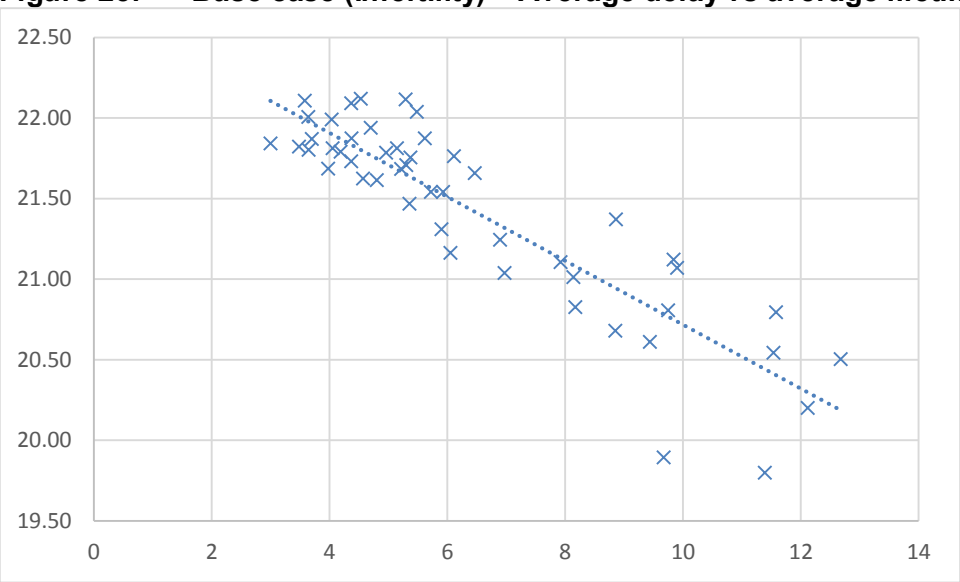
Figure 24: Base Case (Infertility) – Probability of suspecting endometriosis vs average lifetime cost.



Source: Economic model

As with the pain subgroup, increasing the probability of referral increases both costs and QALYs as demonstrated in Figure 23 and Figure 24. Converting the probability of referral into an average years of delay metric gives Figure 25 and Figure 26. These averages are produced by taking the mean of all treatment outcomes subsequent to the test.

Figure 25: Base case (Infertility) – Average delay vs average lifetime QALY.



Source: Economic model

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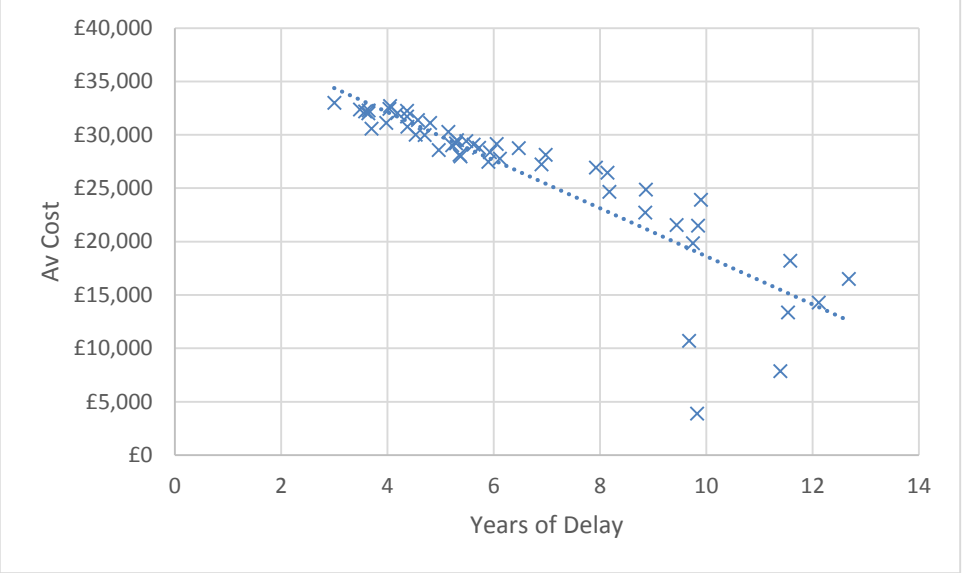
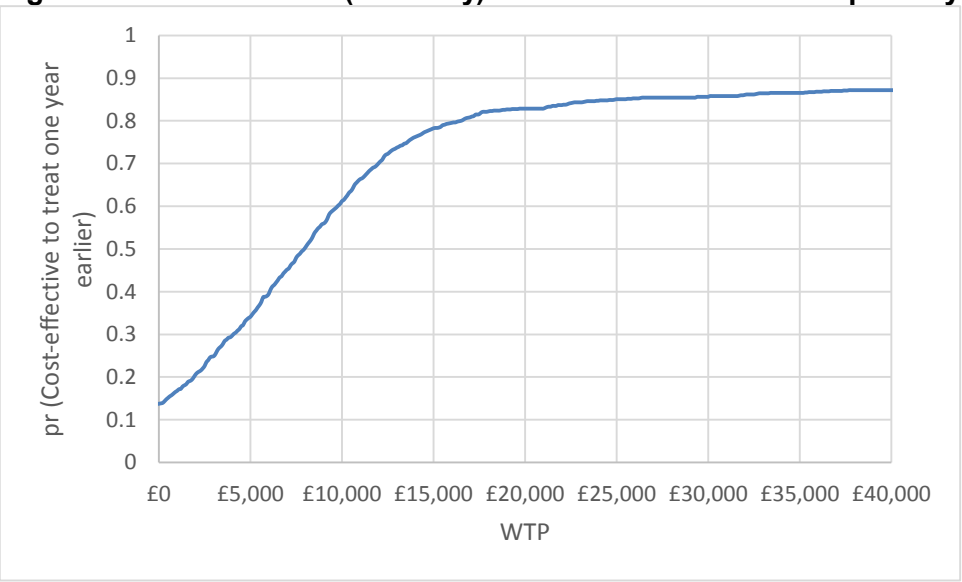
Figure 26: Base case (Infertility) – Average delay vs average lifetime costs.



Source: Economic model

Unlike the pain subgroup, there is clear heteroscedasticity towards the extreme end of the delays – this is likely due to the fact that births after fourteen years of infertility are extremely unlikely, so small random variation in the natural underlying fertility of this group of women will have a disproportionate impact on the results. Nevertheless, there is a clear linear trend at least up until ten years of delay, indicating that the NHS could purchase 0.19 QALY for £1907, equating to £10,000 / QALY. This would be considered cost-effective at a threshold of £20,000 / QALY, although not quite as cost-effective as treatment for pain. Despite this, Figure 27 indicates that the model has similar confidence in this result as in the pain subgroup – at £20,000 / QALY the intervention is 82.9% likely to be cost-effective.

Figure 27: Base case (Infertility) - Cost-effectiveness acceptability curve.



Source: Economic model

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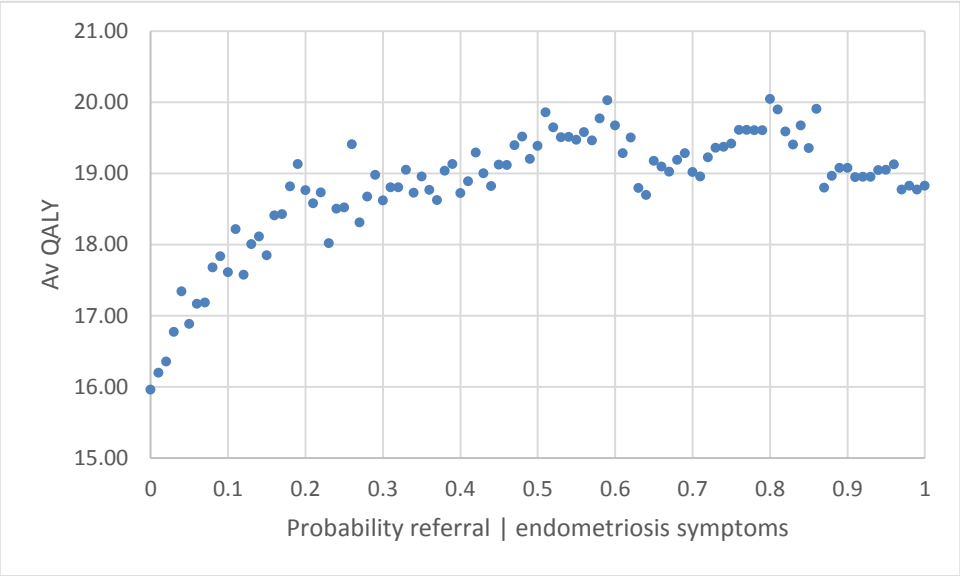
K.2.4.4 Women with both pain and infertility as the primary symptom

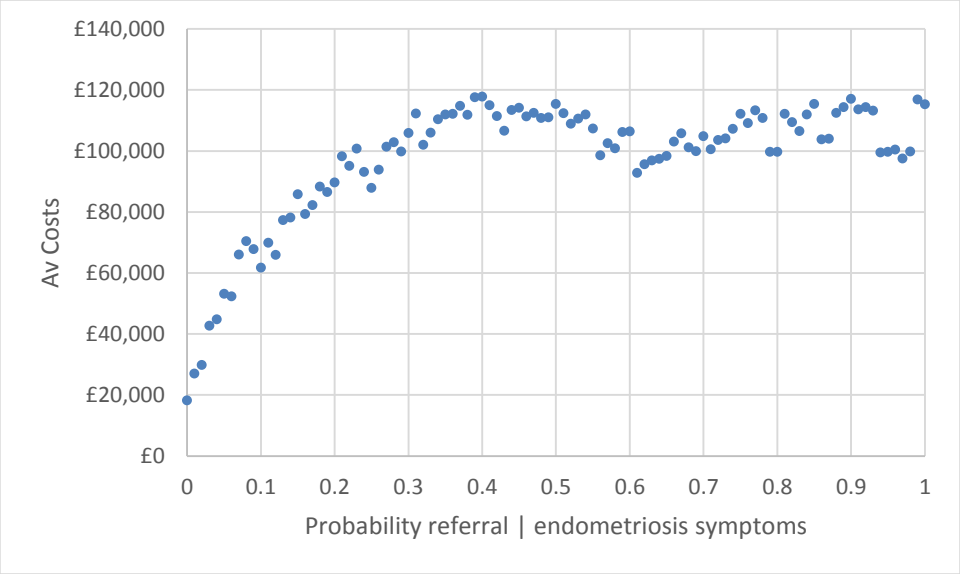
Base case – Both

Figure 28: Base Case (Both) – Probability of suspecting endometriosis vs average lifetime QALY.



Source: Economic model

Figure 29: Base Case (Both) – Probability of suspecting endometriosis vs average lifetime costs.



Source: Economic model

Since both the pain and infertility subgroups demonstrate increasing costs and QALYs with respect to a delay, it is logical that the 'both together' subgroup will demonstrate the same behaviour. Figure 28 and Figure 29 demonstrate that this is the case, and Figure 30 and Figure 31 demonstrate that the direction of effect is consistent throughout.

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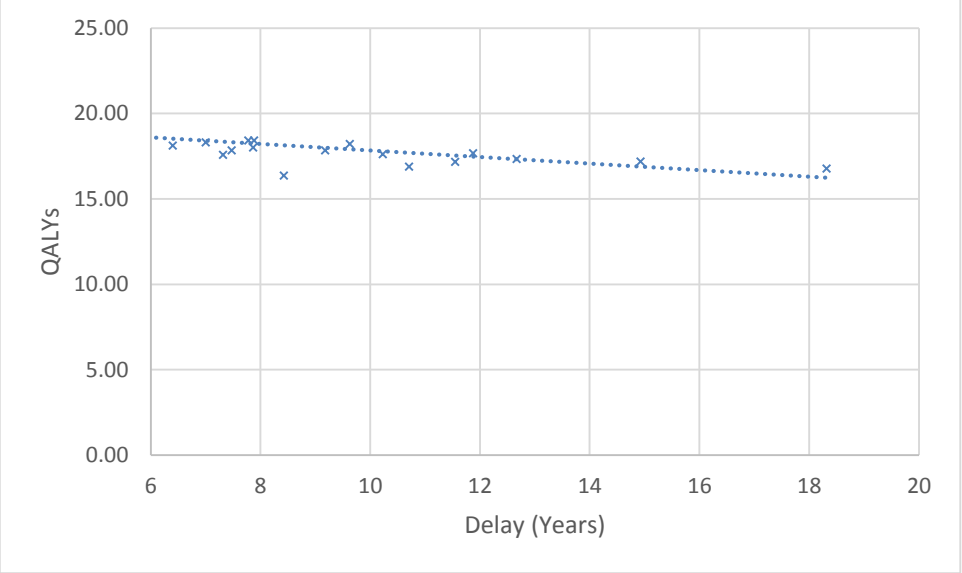
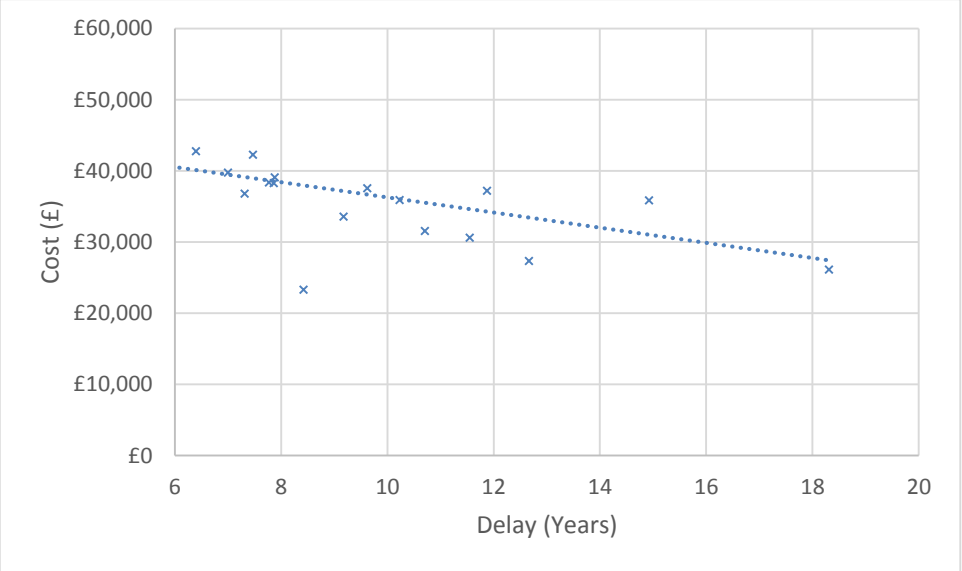
Figure 30: Base case (Both) – Average delay vs average lifetime QALY.



Source: Economic model

Figure 31: Base case (Both) – Average delay vs average lifetime costs.



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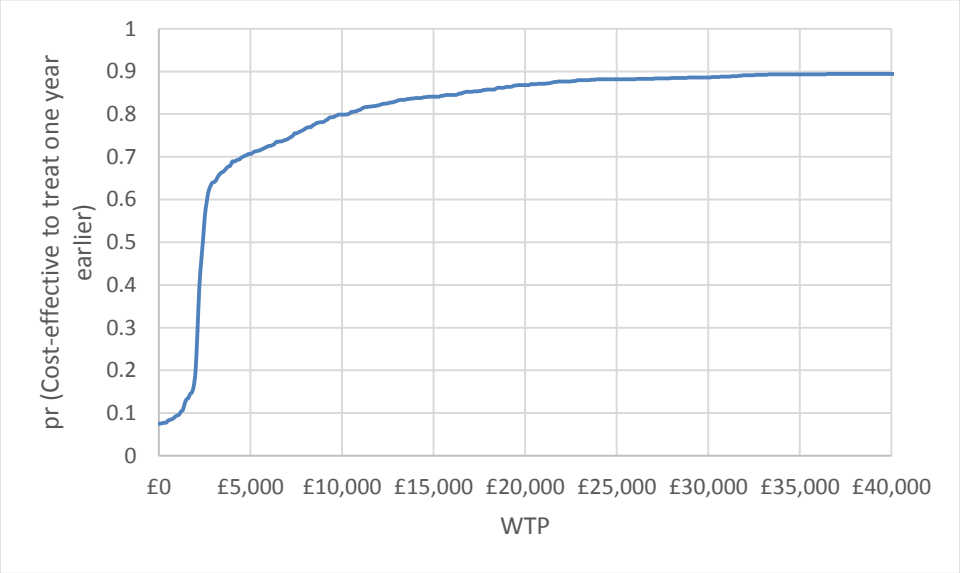
Source: Economic model

Figure 32: Base case (Both) - Cost-effectiveness acceptability curve.



Source: Economic model

As with the pain and infertile subgroups, the health economic tradeoff in the case of the 'both' subgroup is straightforward; it costs more to diagnose early but we gain more QALYs. It is therefore obvious in a group with two sources of disutility (their pain and their infertility) that early intervention is likely to be beneficial.

K.2.4.5 Women with asymptomatic endometriosis

Base case – Asymptomatic

It is conceptually difficult to understand what 'progression' in an asymptomatic woman might mean; on the one hand a woman who has no symptoms when the endometriosis is superficial but has symptoms when the endometriosis progresses to her bowel might be considered 'asymptomatic progression', but these women are already included in the main schedule of the pain, infertility and 'both' subgroups, and is not how the asymptomatic group is defined in the model. On the other hand if the subgroup in this population is the same as defined in section K.1.4.4 then the results of this analysis are functionally known a priori; since treatment is not the correct strategy in the subgroup, the correct timing of treatment will be 'never'.

Figure 33 and Figure 34 show that the results of running the model for the asymptomatic group. Figure 33 appears to be essentially random noise, and statistical analysis suggests virtually no relationship between diagnosis and lifetime QALYs. On the other hand Figure 34 clearly shows increasing cost with probability of suspecting endometriosis. Expressed in terms of cost-effectiveness ratios, each year diagnosis is sped up by costs £1584 and gains 0.0088 QALY, which results in an ICER of £179,943, which is well outside the usual acceptable range for the NICE cost-effectiveness threshold. Note that this is likely an artefact of statistical variation; fundamentally there doesn't seem to be any reason to offer treatment to women who will never suffer sequelae from endometriosis – note that the CEAC is completely consistent with no benefit from treatment.

This strongly confirms that treatment should not be offered to women with progressive endometriosis where the progression is strongly likely to be asymptomatic. In all other cases,

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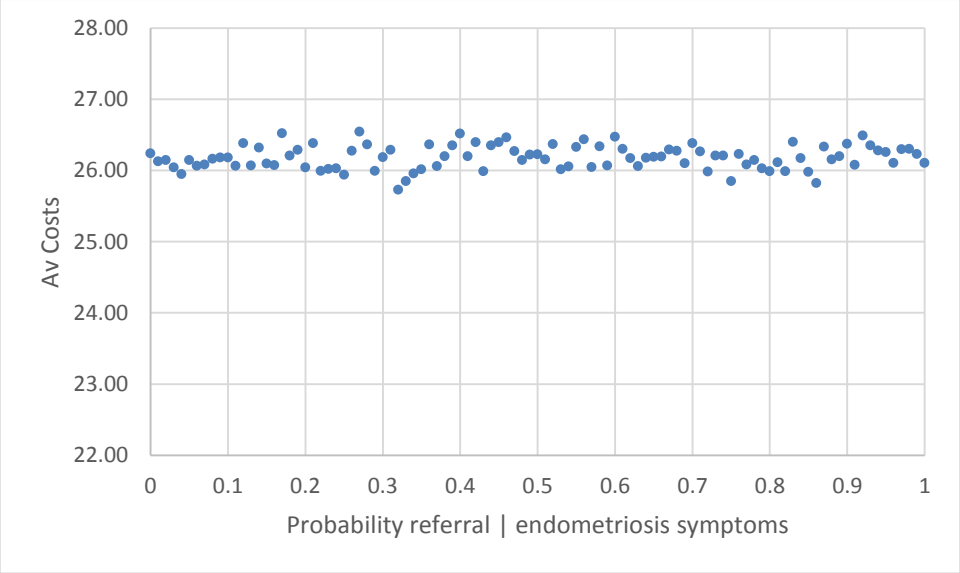
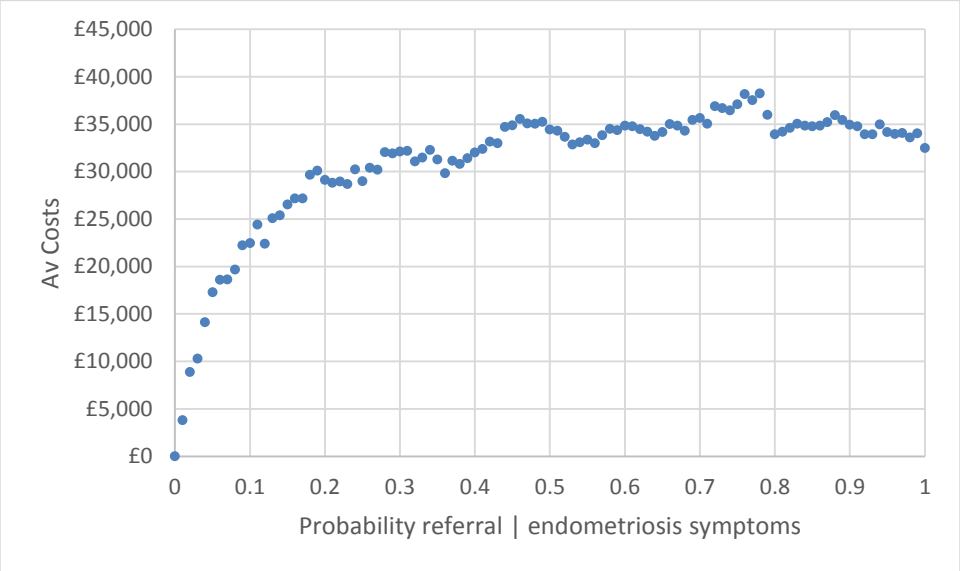
including cases where it is unclear if the progression will be symptomatic or not, the results of sections K.2.4.2, K.2.4.3 and K.2.4.4 are more relevant.

Figure 33: Base Case (Asymptomatic) – Probability of suspecting endometriosis vs average lifetime QALY.



Source: Economic model

Figure 34: Base Case (Asymptomatic) – Probability of suspecting endometriosis vs average lifetime costs.



Source: Economic model

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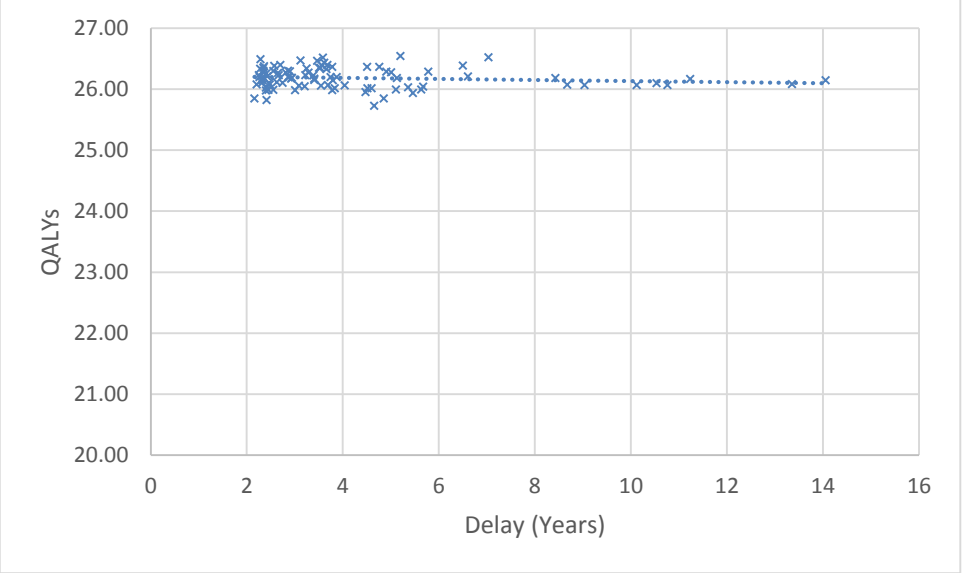
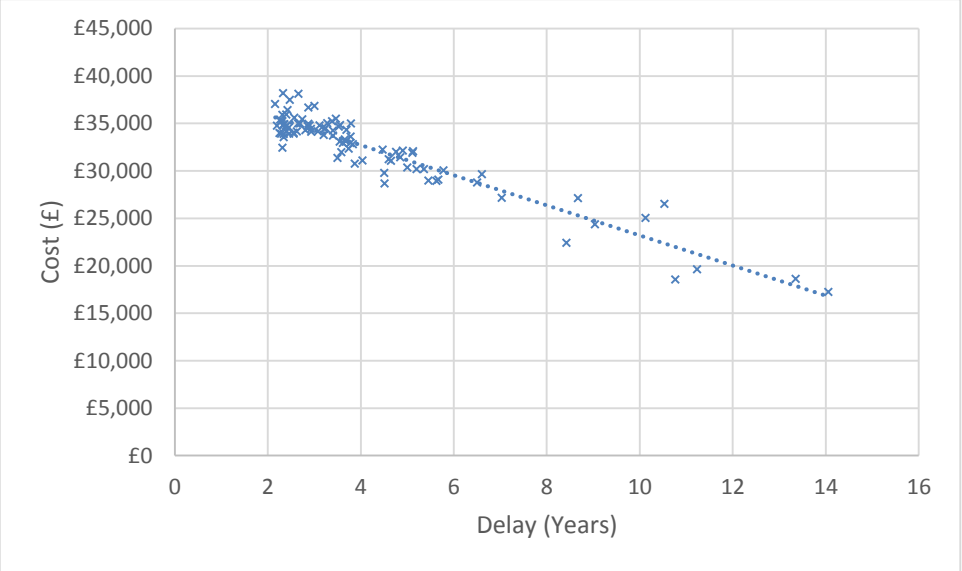
Figure 35: Base case (Asymptomatic) – Average delay vs average lifetime QALY.



Source: Economic model

Figure 36: Base case (Asymptomatic) – Average delay vs average lifetime cost.



Source: Economic model

K.2.5 Discussion

The delay in diagnosis and treatment is cited by patients as a major dissatisfaction with the management of their endometriosis. The health economic analysis confirms that patients are right to raise this point; although speeding up diagnosis is expensive, it is highly cost-effective and the harm to patients of delaying the diagnosis is not compensated by the saving to NHS resources at £20,000 / QALY

The analysis makes no distinction between delay due to NHS factors (such as GPs not recognising the symptoms of endometriosis) and due to patient factors (such as not wanting to 'bother' the GP). It is likely that marginal improvements can be made to the speed of

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diagnosis in both groups, which would increase the cost-effectiveness of these recommendations still further.

K.3 Consideration of economic benefits and harms of diagnostic tests

K.3.1 Introduction

A significant source of dissatisfaction with the current treatment pathway for endometriosis relates to the slow diagnosis and treatment of the condition. Consequently a de novo economic model was constructed to consider the optimal diagnosis and treatment strategies to attempt to increase the speed of accurate diagnosis in a cost-effective way. However, as the choice of diagnostic test depends in part on the choice of treatment (which is itself influenced by the availability of other diagnostic tests) it does not make sense to talk about the 'cost-effectiveness' of one particular diagnostic strategy as though this were independent from the cost-effectiveness of other such strategies.

Therefore all discussion of the economic benefits and harms of diagnostic strategies is located in this section of the Health Economic Appendix, to better allow comparison between competing alternative uses of NHS resources

K.3.2 Economic evidence

One paper was found looking at the costs and benefits of preoperative ultrasound in a population with endometriosis-related Pouch of Douglas obliteration. As this paper (Shakeri et al, 2016) referred to the wrong population and was a conference abstract only it was excluded.

One paper was found looking at the costs only of MRI:

K.3.2.1 Schwartz et al (1994)

This is a US based paper looked at the savings of treatment-switching following an MRI. It was a hypothetical cohort study based on 69 patients who received a pre-MRI treatment decision, followed by an MRI, followed by a change in that treatment decision if necessary. For example, a patient might present with symptoms that would suggest surgical treatment would be optimal but MRI might reveal that medical treatment was better indicated; such a patient would have the saving of this medical treatment vs their hypothetical surgical treatment recorded.

Costs were taken from the US payer database, and no QALYs were recorded. The time horizon was 10.9 months after diagnosis. It is not clear when the MRI took place, or that the cost of the MRI was factored into the putative savings claimed from performing the scan.

The treatment plan changed in 37 of 70 examinations. Of those people who were initially recommended for surgery the saving was $1036 USD (~£1502). Of those people initially recommended for medical treatment the saving was -$2229 USD (~-£3232). This indicates that MRI was cost saving in those who would otherwise receive surgery, but not cost saving in those who would otherwise have received medical treatment only.

K.3.3 Consideration of economic benefits and harms

The cost of diagnostic investigations is difficult to calculate without the aid of an economic model, since – in general – cheaper techniques are more likely to offer a false negative / false positive and so require retesting or overtreatment respectively. One possible strategy

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would be to look for 'dominant' diagnostic techniques (those which are both cheaper and more accurate than another diagnostic technique) but Table 36 demonstrates that only Laparotomy is dominated by another technique (Laparoscopy), and only then because Laparotomy and Laparoscopy are assumed to have identical sensitivity and specificity.

Table 36: Estimated costs for diagnostic tests included in the model.

Diagnostic Test	NHS Reference Cost Description	NHS Reference Cost Area	Cost
Empirical Diagnosis	N/A	N/A	£0
Transabdominal ultrasound[a]	N/A	N/A	£80.00
Pelvic MRI	Magnetic Resonance Imaging Scan of one area, without contrast, 19 years and over	Imaging	£146.00
Peritoneal biopsy[b]	Transvaginal Ultrasound with Biopsy	Outpatient, Gynaecology	£222.37
Nerve fibre biopsy	Transvaginal Ultrasound with Biopsy	Outpatient, Gynaecology	£222.37
CA-125[c]	Haematology	Direct Access Pathology Services	£3.10
Diagnostic laparoscopy	Minor, Laparoscopic or Endoscopic, Upper Genital Tract Procedures	Day Case	£1,404.89
Diagnostic laparotomy	Intermediate Open Upper Genital Tract Procedures	Inpatient	£3,007.96

(a) The cost for a Transvaginal Ultrasound in an Outpatient Gynaecology setting was £149.61. Committee opinion was that this would be a significant overestimate in the case of endometriosis patients, as the currency code is possibly diluted with women receiving an ultrasound for pregnancy-related reasons. Consequently the figure of £80 was picked to better reflect the relative cost of Ultrasound vs MRI, according to the imaging expert on the Committee

(b) Since the cost for Transvaginal Ultrasound was lowered by the Committee, the cost for Ultrasound followed by biopsy has been lowered by the same amount to keep the cost attribution to Ultrasound the same in both

(c) Committee opinion is that this seemed too low, because the cost of explaining the results to the woman with endometriosis were not included. After discussion, the Committee agreed to keep the NHS Reference Costing as the price on the grounds that any reasonable change to the costing didn't change the fact that a CA-125 test was by far the cheapest option

(d) Source for all costs but Transvaginal Ultrasound is NHS Reference Costs (2016-17), https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016

Consequently, the most cost-effective diagnostic choice will depend on factors external to features of that diagnostic test; most pertinently it will depend on the subsequent choice of treatment should the test come back positive and the base rate of endometriosis in the population. This might differ by treatment group (pain vs fertility). Table 37 attempts to estimate the total costs taking this into account for the pain subgroup and Table 38 for the fertility subgroup of the model in section K.1.

Table 37: Estimated costs and QALYs for diagnostic tests included in the model (total costs, pain).

Diagnostic Test	Average cost (pain)	Average QALY (pain)	Cost per QALY
Empirical Diagnosis	£25,519	18.95	£1,346.65
Pelvic MRI	£25,675	18.93	£1,356.31
CA-125	£25,830	18.86	£1,369.57

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Diagnostic Test	Average cost (pain)	Average QALY (pain)	Cost per QALY
Peritoneal biopsy	£26,076	18.93	£1,377.50
Transabdominal ultrasound	£26,069	18.89	£1,380.04
Nerve Fibre	£26,248	18.3	£1,434.32
Diagnostic laparoscopy	£34,608	18.96	£1,825.32
Diagnostic laparotomy	Dominated	Dominated	N/A

Table 38: Estimated costs and QALYs for diagnostic tests included in the model (total costs, fertility).

Diagnostic Test	Average cost (fertility)	Average QALY (fertility)	Cost per QALY
CA-125	£15,150	19.07	£794.44
Transabdominal Ultrasound	£16,642	19.12	£870.40
Pelvic MRI	£18,512	19.16	£966.18
Peritoneal Biopsy	£18,625	19.18	£971.06
Empirical Diagnosis	£18,946	19.16	£988.83
Nerve Fibre	£18,987	19.16	£990.97
Diagnostic Laparoscopy	£27,583	19.17	£1,438.86
Diagnostic laparotomy	Dominated	Dominated	N/A

Given that this is a reasonable test, it would indicate that empirical diagnosis is the preferred diagnostic strategy in the pain group (unless willingness to pay is above £900,000, which is unlikely) and peritoneal biopsy dominates all other diagnostic strategies in the fertility group of the diagnosis and treatment model. However, this is not the most accurate method of identifying the optimal technique to use as the optimal diagnostic test will vary depending on the cost and effectiveness of the planned subsequent treatment. To give an example, a technique which was highly effective at identifying cases of a condition but not very good at ruling out cases of non-condition would become more cost-effective in a scenario where the prevalence of the condition in the population was higher, since the chance of a false positive would decrease. This is possible to see by considering Figure 37 and Figure 38, which are the costs and QALYs for single treatment strategies – the general trend appears to be that there are increasing QALYs through CA-125, Transabdominal Ultrasound, MRI and Laparoscopy, but as the cost of the technique decreases (surgery is much more expensive than hormonal treatment) the difference in QALYs between the least and most accurate technique also decreases.

The addition of nerve fibre biopsy is of potential interest to researchers in the field of endometriosis. Although the sensitivity of the test is quite high based on results of the evidence review, the specificity is not sufficiently high to compensate compared to – for example – a Pelvic MRI. This suggests that if a woman is being considered for a low-cost treatment like an oral contraceptive the novel technique of nerve fibre biopsy might be preferable to the more established MRI. However, as the cost of the technique goes down so too does the penalty for simply prescribing the treatment to all women who are potential candidates for endometriosis, so in practice it would be a very narrow window where nerve fibre biopsy was cost-effective relative to empirical diagnosis, but MRI or surgical diagnosis was not.

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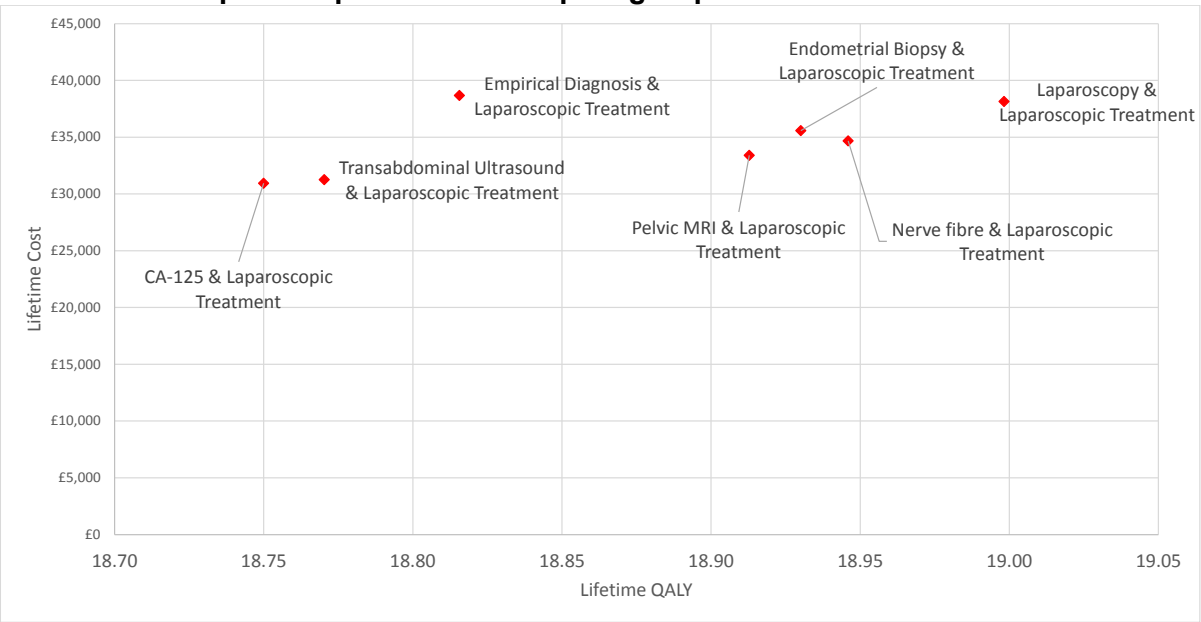
Figure 37: Graphical representation of all possible diagnostic strategies leading into laparoscopic treatment in pain group.



Source: Economic model

Table 39: Tabulation of all possible diagnostic strategies leading into Laparoscopic Treatment

Treatment	Cost	QALY	ICER
CA-125 & Laparoscopic Treatment	£30,933.59	18.750	Dominated
Transabdominal Ultrasound & Laparoscopic Treatment	£31,257.10	18.770	Dominated
Empirical Diagnosis & Laparoscopic Treatment	£38,675.53	18.816	Dominated
Pelvic MRI & Laparoscopic Treatment	£33,404.96	18.913	-£54,218.38
Peritoneal Biopsy & Laparoscopic Treatment	£35,571.56	18.930	Dominated
Nerve fibre & Laparoscopic Treatment	£34,679.99	18.946	£38,475.11
Laparoscopy & Laparoscopic Treatment	£38,142.40	18.998	£66,227.02

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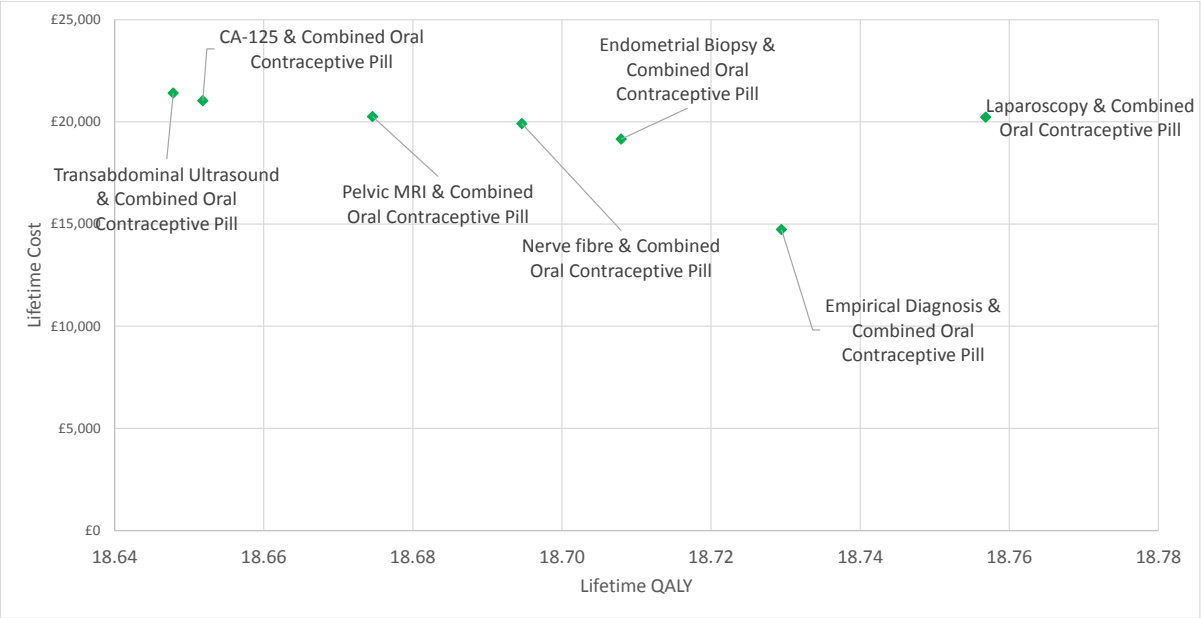
Figure 38: Graphical representation of all possible diagnostic strategies leading into Oral Contraceptive Pill



Source: Economic model

Table 40: Tabulation of all possible diagnostic strategies leading into Oral Contraceptive Pill

Treatment	Cost	QALY	ICER
Transabdominal Ultrasound & Combined Oral Contraceptive Pill	£21,406.63	18.648	Dominated
CA-125 & Combined Oral Contraceptive Pill	£21,031.91	18.652	Dominated
Pelvic MRI & Combined Oral Contraceptive Pill	£20,261.32	18.675	Dominated
Nerve fibre & Combined Oral Contraceptive Pill	£19,910.55	18.695	Dominated
Peritoneal Biopsy & Combined Oral Contraceptive Pill	£19,157.52	18.708	Dominated
Empirical Diagnosis & Combined Oral Contraceptive Pill	£14,735.67	18.729	-£205,619.30
Laparoscopy & Combined Oral Contraceptive Pill	£20,223.79	18.757	£200,330.27

The Committee discussed how multiple rounds of differing diagnostic strategies might be more cost-effective in the long run. For example the NHS could offer a cheap test to rule some women out of having endometriosis before offering an MRI or surgical confirmation. The model was capable of considering these options, but in the final analysis the two most

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plausible treatment strategies involved specific combinations of diagnosis / treatment to be most cost-effective (empirical diagnosis was always preferred when combined with combined oral contraceptives and MRI or laparoscopy was always preferred when combined with surgery, although combinations of this strategy were not more cost-effective)

The Committee also discussed how surgical confirmation could be done at the same time as superficial surgical treatment. This would mean that the cost of surgical diagnosis was offset in the case of true positives by a small QALY gain from surgical treatment. This was considered in sensitivity analysis but did not much change the main conclusions.

There was a concern that some diagnostic techniques might differentiate between multiple competing causes of pelvic discomfort. If this was the case then the 'true' cost of the technique might be lower; either because women are referred into the endometriosis pathway after a diagnosis for some other condition or because the cost of the technique should be shared out between the women who were referred out of the endometriosis pathway into another. The Committee concluded that while this was a theoretical possibility in some instances, in general the structure of endometriosis was subtle enough that even an MRI or surgical procedure not conducted by an expert had a high chance of missing it (this ignores the possibility of an entirely unconnected comorbidity such as a tumour being detected).

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