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Synopsis

# Clinical and cost-effectiveness of medical management versus surgery for deep infiltrating endometriosis: synopsis from the DIAMOND RCT

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## Abstract

**Background:** Deep endometriosis causes significant pain which adversely affects quality of life and utilises healthcare and wider societal resources. Laparoscopic excision of endometriosis has shown to improve pain symptoms in observational series but 1 in 14 patients experience serious surgical complications. Medical management centres around hormonal treatment, which is less risky and has been shown to be efficacious but can cause troublesome side effects and is incompatible with conception. There are no randomised controlled trials providing conclusive comparative evidence on clinical and cost-effectiveness of these treatments.

**Objective(s):** To compare the clinical and cost-effectiveness of laparoscopic surgery versus optimised medical treatment for managing deep endometriosis.

**Design and methods:** A multicentre randomised controlled trial, with an internal pilot phase, and economic evaluation, to compare early planned laparoscopic surgery (first attempt at definitive surgery) with or without adjuvant medical treatment versus optimised medical management alone in women with deep endometriosis.

**Setting and participants:** Women presenting with pelvic pain associated with surgically or radiologically confirmed deep endometriosis, suitable for either surgical or medical management, recruited and managed at accredited British Society for Gynaecological Endoscopy Endometriosis Centres.

**Interventions:** Early planned laparoscopic surgery to excise deep endometriosis (with or without medical treatment) or medical management alone.

**Main outcome measures:** The primary outcome was condition-specific quality of life measured using the pain domain of the Endometriosis Health Profile-30 at 18 months post randomisation. The primary health economic outcome was to be incremental cost per quality-adjusted life-year gained at 18 months. Secondary outcomes included quality of life (Endometriosis Health Profile-30), pain, complications, occupational and reproductive outcomes.

**Results:** Three hundred and seventy-seven patients were screened, 103 were eligible and 18 were randomised. Of the eight patients allocated surgery, only one had had their surgery by the time of trial closure and six participants (2/4, 50% allocated surgery and 4/8, 50% allocated medical treatment) had reached the first trial end point at 3 months. No participant reached the primary outcome at 18 months post randomisation.

**Limitations:** The overriding limitation was failure to recruit participants at a satisfactory rate resulting in a final sample of only 18 patients with a target of 320 (inflated to 400 to account for a projected 20% attrition rate). Given the nature of the intervention, it was not possible to blind either the care providers, investigators or participants to their allocated group.

**Conclusions:** The clinical question regarding the effectiveness of surgical removal or optimised medical treatment for deep endometriosis remains relevant. It remains unanswered because of the early closure of the trial due to

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failure to recruit participants. To deliver important surgical studies in this area will require potentially different study designs with new and innovative strategies to educate, enthuse and incentivise both patients and clinicians. There is a need for simplified processes to expedite study site set up, along with increased accountability and funding to motivate local research and development departments and principal investigators.
**Future work:** The DIAMOND trial has shed light on some of the obstacles preventing the successful delivery of robust trials in deep endometriosis thereby informing future study designs.
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## Introduction

### *Rationale for research and background*

Endometriosis affects up to 10% of women of reproductive age[1,2] and involves the growth of endometrial tissue in sites other than the uterine cavity, causing inflammation and adhesions, leading to pain and infertility. Deep endometriosis (DE), which affects up to 2% of women,[3] is its most severe form. It is characterised by the presence of endometrium-like tissue lesions in the abdomen, extending on or under the peritoneal surface. They are usually nodular, able to invade adjacent structures, and associated with fibrosis and disruption of normal anatomy.[4]

Women with endometriosis have been shown to have significantly impaired quality of life (QoL), affecting work, relationships and education[5] and causing psychological distress.[6,7] Endometriosis is difficult to treat successfully[8] and poses a significant public health burden.[6,7]

The current clinical pathway for management of women with pain due to DE involves initial medical management using a variety of hormonal agents, but ultimately many women go on to have surgery. Laparoscopic excision of endometriosis has been shown to improve pain symptoms in DE[8] but surgery for DE is very invasive and can lead to potentially serious complications in about 1 in 14 patients.[8] Some women undergoing surgery will also request concomitant hysterectomy and or bilateral oophorectomy if they have completed their family and it is felt that this may reduce the need for further treatment.

Hormonal treatment is less invasive, but can cause side effects that may impact on compliance and is not suitable for women trying to conceive. A recent review of observational studies suggests that long-term hormonal treatment could be a viable alternative to surgery for DE,[9] although there are no randomised controlled trials (RCTs) to provide conclusive comparative evidence on clinical and cost-effectiveness.

There is very little evidence in the literature to inform decision-making in DE. An overview of 17 Cochrane reviews assessed the effectiveness of treatments for endometriosis but was unable to comment specifically on women with DE.[10] Ovarian suppression by gonadotrophin-releasing hormone (GnRH) analogues, the levonorgestrel releasing intrauterine system (LNG-IUS) and danazol was found to be effective in terms of alleviating pain but unsuitable for women wishing to conceive. Laparoscopic surgery improved pain symptoms in women with endometriosis, but there were no head-to-head trials of medical versus surgical interventions.

In a small trial of 60 women with DE affecting the rectum,[11] conservative surgery (shaving or disc excision) versus rectal resection offered similar functional outcomes. A search of ClinicalTrials.gov identified a single ongoing trial (MEdical Versus SUrgical Treatments of Rectal Endometriosis), comparing oral cyproterone acetate (unlicensed for endometriosis in the UK) with percutaneous estradiol versus surgery (rectal shaving; rectal disc excision; colorectal resection) in 78 women aged 35–50 years who have DE with bowel symptoms. Our search of the relevant databases has not revealed any other randomised trials (either completed or in progress) comparing medical versus surgical treatment in women with DE.

Observational data from 87 women with colorectal endometriosis show that, at 12 months, 78% of those who chose hormonal medical treatment were satisfied with the level of their symptoms compared with 76% of those who chose surgery.[12] In a UK cohort study of 5162 women with rectovaginal endometriosis, improvement in pain, bowel symptoms and QoL was reported by 4721 women who had had laparoscopic excision.[8] In a review of eight case series ($N$ = 420) of women with colorectal endometriosis, treatment with the combined oral pill, progestogens, GnRH analogues and aromatase inhibitors was able to control most symptoms in the absence of bowel obstruction.[8] Two-thirds of all women were satisfied with the level of their symptoms, regardless of the drug used, suggesting

that long-term hormone use could be an alternative to surgery for DE in women for whom fertility is not a priority.

The National Institute for Health and Care Excellence (NICE) and the European Society for Human Reproduction and Embryology (ESHRE) suggest that both medical and surgical treatments can be used for DE but highlight the lack of evidence to guide practice and highlight the need for a large, multicentre, adequately powered, randomised trial comparing the two strategies.[1,13]

To provide this evidence, the DIAMOND study aimed to compare optimised medical management alone versus early planned laparoscopic surgery (first attempt at definitive surgery) with or without adjuvant medical treatment in women with DE.

## Objectives

The primary aim of DIAMOND was to compare the clinical and cost-effectiveness of optimised medical (hormonal ± neuromodulators ± analgesia) treatment versus laparoscopic surgery (with or without adjuvant medical treatment) for the management of DE.

The research question was:

> What is the clinical and cost-effectiveness of optimised medical management alone versus laparoscopic surgery (with or without adjuvant medical treatment) in women with deep endometriosis?

The primary objectives were:

- To compare medical (hormonal ± neuromodulators ± analgesia) treatment with laparoscopic surgery for DE (with or without adjuvant medical treatment) in terms of condition specific QoL measured using the pain domain of the Endometriosis Health Profile-30 (EHP-30) and health status using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) questionnaire at 18 months after randomisation.
- To assess the cost-effectiveness of optimised medical (hormonal ± neuromodulators ± analgesia) treatment with laparoscopic surgery (with or without adjuvant medical treatment) for DE in terms of the incremental cost to the health service per quality-adjusted life-year (QALY) gained at 18 months post randomisation and modelled up to the time of menopause (QALYs derived from participant responses to the EQ-5D-5L).

Secondary outcomes were satisfaction, pain, condition specific QoL, generic QoL, need for further medical treatment or gynaecological surgery, serious adverse events, discontinuation of randomised allocation, sexual function, occupational outcomes, reproductive outcomes, indirect costs due to loss of productivity and number in medical treatment arm going on to have surgery and vice versa.

## Methods for data collection and analysis

### *Pre-trial survey of trial viability*

Prior to submitting the application for this commissioned call from National Institute for Health and Care Research-Health Technology Assessment (NIHR-HTA), a survey was undertaken of clinicians working in endometriosis centres and also patient representatives. This showed that 75/81 (93%) clinicians and 31/66 (47%) of patient representatives supported a randomised comparison of surgery versus medical treatment for women suffering from DE.

### *Early closure*

Recruitment for the DIAMOND trial opened in July 2022. Due to difficulties with recruitment, the funder made the decision to stop the trial early (October 2023). Recruiting sites and participants were notified, and no further follow-up occurred.

As a result, the methods of what was achieved during DIAMOND have been summarised below in accordance with Consolidated Standards of Reporting Trials reporting guidelines (Schulz *et al.*),[14] where possible. For detailed information on the methods originally planned that were not implemented due to the early closure, refer to the full trial protocol (DIAMOND protocol – NIHR). The original research pathway flow diagram is included (*Figure 1*).

Due to the early study closure, few 12-week participant follow-up questionnaires were issued, and no 12- or 18-month follow-up of participants occurred.

### *Trial design*

DIAMOND was intended to be a multicentre RCT, with a planned internal pilot phase and an embedded qualitative substudy. The qualitative substudy aimed to evaluate patients' attitudes towards being approached for the trial and what influenced their decision-making in taking part or not, as well as recruiters' experience of discussing the trial with potential participants.

### *Important changes to methods after trial commencement*

The trial inclusion criteria was updated to allow the use of magnetic resonance imaging (MRI) and again to allow the use of other routinely used investigative radiology

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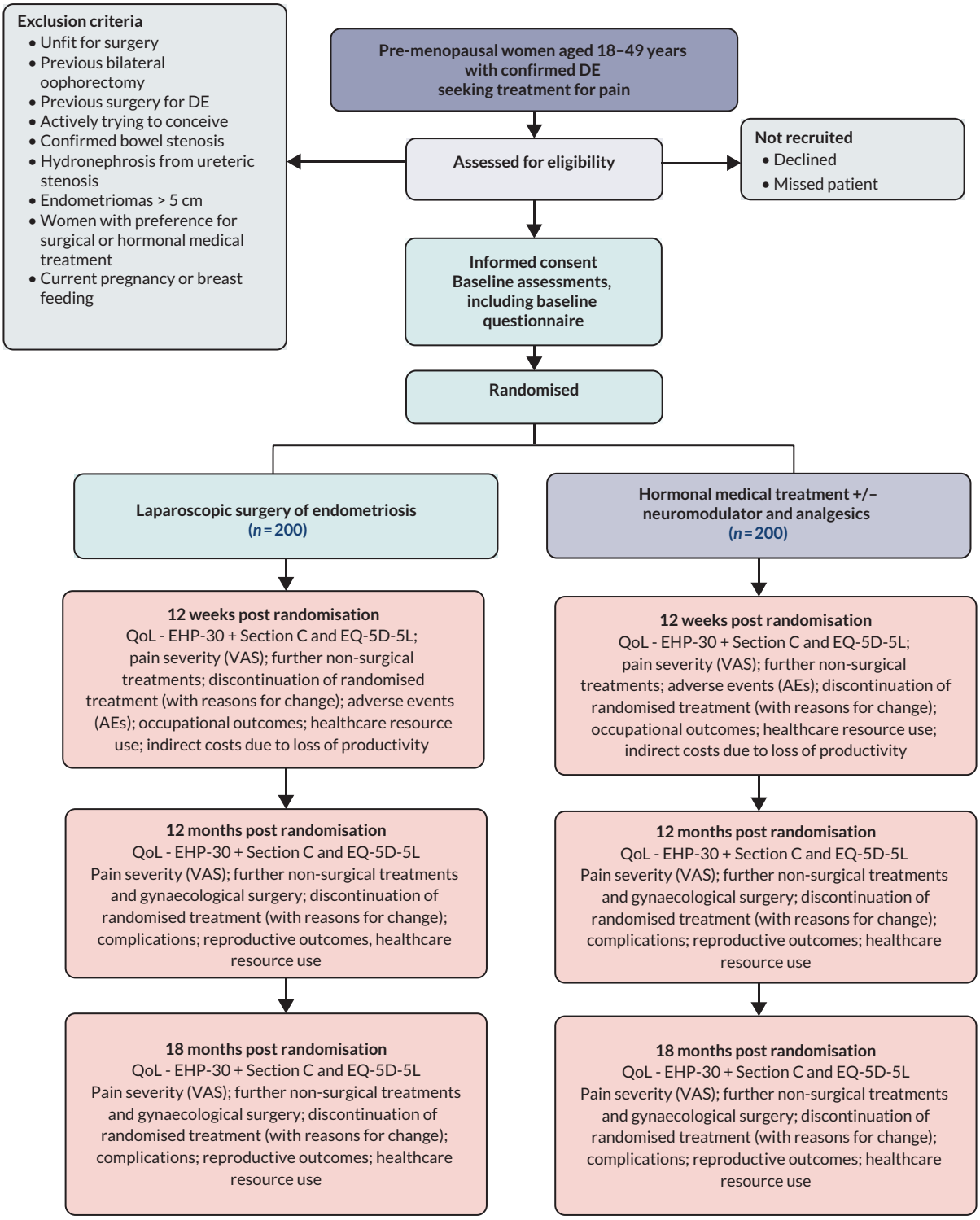


**FIGURE 1** Planned research pathway. Note: due to early trial closure, few 12-week follow-up questionnaires were issued, and no 12- or 18-month follow-up questionnaires were issued. VAS, visual analogue scale.

technique (as well as laparoscopy) for confirmation of DE. This was updated in line with updated guidelines and to reflect current routine practice.

### *Participants (eligibility)*

Participants were women aged between 18 and 49 years presenting to accredited or provisional British Society for Gynaecology Endoscopy (BSGE) UK Endometriosis centres with pelvic pain associated with DE (diagnosed by laparoscopic surgery or other routinely used investigative radiology techniques), who were suitable for either medical or surgical management. Women were excluded from trial entry if any of the following criteria were met: unfit for laparoscopic surgery, had used or currently

using GnRH analogues without satisfactory relief of pain symptoms, previous bilateral oophorectomy, previous surgery for DE, actively trying to conceive, confirmed bowel stenosis, hydronephrosis or hydroureter caused by ureteric stenosis, endometrioma > 5 cm in diameter, a preference for hormonal medical or surgical treatment or were currently pregnant or breastfeeding.

All participants were provided with information about the study and provided fully informed written consent.

### *Treatment allocation*

Eligible and consenting patients were randomised to one of the two treatment arms using the web-based randomisation application at the trial office at the Centre for Healthcare Randomised Trials (CHaRT). The randomisation algorithm used recruitment site, and age (18–30; 31–40; 41–49 years) as minimisation covariates to allocate to treatment intervention and control groups in a ratio of 1 : 1. A random element was incorporated into the randomisation algorithm.

### *Interventions*

The interventions to be compared were:

- Medical management: hormonal treatment for 18 months. The choice of hormonal medication was at the discretion of the treating clinician in discussion with the participating woman, avoiding any treatment which had either failed or caused unacceptable side effects in the past. Any of the following preparations could be used: the combined contraceptive pill/patch, progestogen-only preparations (oral tablets), depot injections (depot medroxyprogesterone acetate), subcutaneous implants (e.g. Nexplanon) or intrauterine systems LNG-IUS, danazol and GnRH analogues with add back hormone replacement therapy. Women on hormonal treatment could also receive additional neuromodulator drugs, analgesics and other interventions for pain relief, under direction from pain specialists, therefore optimising medical care. Medical treatment was prescribed in line with normal and accepted clinical practice, as recommended by NICE guidelines on management of endometriosis in the UK.[13]
- Laparoscopic surgery (with or without adjuvant medical treatment): a laparoscopic approach to treat DE but the choice of energy modalities and the need for concomitant hysterectomy and/or oophorectomy were at the discretion of the surgeon in consultation with their patient. Surgery was planned to involved division of dense adhesions to separate affected pelvic structures, restore normal anatomy and removal of all endometriotic deposits, including deep nodules. Excision of DE using laparoscopic instruments such as scissors, hooks and ultrasonic scalpels along with a variety of energy modalities including electricity and ultrasound scan (USS) were acceptable. If adjuvant medical management was needed, the same medical options used in the medical treatment arm could be utilised including hormones, neuromodulators and pain relief medication. For pragmatic reasons, changes to medical treatment used prior to surgery would have been accepted, in line with NICE guidelines.[13]

### *Sample size*

We estimated that with a sample size of 320 participants randomised 1 : 1 to laparoscopic surgery or optimised medical treatment, the study would have 90% power at a 2-sided 5% level of significance assuming a standard deviation of 22 points to detect an 8-point difference for the EHP-30 pain domain at 18 months. The 8-point improvement was based on clinically important difference used in Pre-Empt trial.[15] An attrition rate of 20% for the primary outcome was assumed, requiring 400 women to be randomised.

### *Post-closure survey of sites*

Following the early closure of the DIAMOND trial due to poor recruitment, we aimed to gather as much information from all BSGE endometriosis centres to determine local and wider issues with recruitment to the study and to establish any lessons to be learnt for future research. An e-mail link to an online survey was sent to all BSGE centres involved in DIAMOND. Three versions of the survey were utilised based on whether the BSGE centre had opened to recruitment, were in set up but not opened before recruitment closed, and those who had indicated they would not participate in DIAMOND (not in set up and not opened to recruitment). To boost response rates, reminder e-mails with the link to the surveys as well as reminders by the Chief Investigators (CIs; in person, by phone, text etc.).

### *Analysis*

Baseline and follow-up data were summarised using appropriate descriptive statistics. No formal statistical analysis was performed.

### *Embedded process evaluation*

It is well documented that surgical trials face numerous challenges, particularly around informed consent and recruitment, from both the patient and surgeon perspective.[16–18] To support trial delivery, an embedded process evaluation, as part of the DIAMOND internal pilot phase, was conducted and modelled on the Quintet Recruitment Intervention.[17]

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### *Aim and objectives*

The aim of the process evaluation was to support trial delivery and facilitate recruitment during the internal pilot as well as the main phase of the trial.

Using in-depth, semistructured interviews, the original objectives were to:

1. understand how surgery and/or hormone treatments are experienced by women with DE, investigating trade-offs between fertility and pain with respect to treatment choices
2. explore aspects of decision-making regarding trial involvement by both clinical teams and patients.

### SEAR participant flow data

An important addition within the process evaluation component (non-contracted), was the inclusion of collecting participant flow data using the SEAR framework.[18] Data on the number of participants screened, eligible, approached and randomised were extracted from screening logs and the trial database for all recruiting centres.

The decision to pivot and include these data was designed to be responsive to the 'needs' of the trial, to better identify the complexity of recruitment processes within and between centres, illustrate variation between centres and identify any areas of good practice that could be shared. These data were shared on a rolling basis at trial team meetings, to help inform critical aspects for enquiry in the interviews and guide decisions and prioritisation for site feedback.

### Interviews with potential DIAMOND participants

Interviews were conducted between July 2023 and October 2023. The interview findings address objective two of the process evaluation, focusing on the experiences of women invited to take part in DIAMOND.

A full description of the methods used for sampling, recruitment, data collection and analysis (including ethics) are reported (see *Report Supplementary Material 2*).

Due to early closure of the trial, we were unable to collect data for planned objective one. For objective 2, only interviews with patients were conducted. It was not possible to interview clinical trial staff before trial closure, as sites were required to reach an initial threshold of three recruited trial participants per site, before any staff interviews would be initiated (there was no perceived value in interviewing site staff with no or limited experience of patient recruitment).

## *Results*

### Centres

All 63 UK NHS BSGE accredited endometriosis centres and their research and development (R&D) departments were contacted about participation in DIAMOND; 30 centres were in active set up and 22 centres were opened between July 2022 and October 2023 (*Figure 2*).

### Participants

In total, 377 patients were identified/screened, 359 were excluded because they were ineligible, or declined/

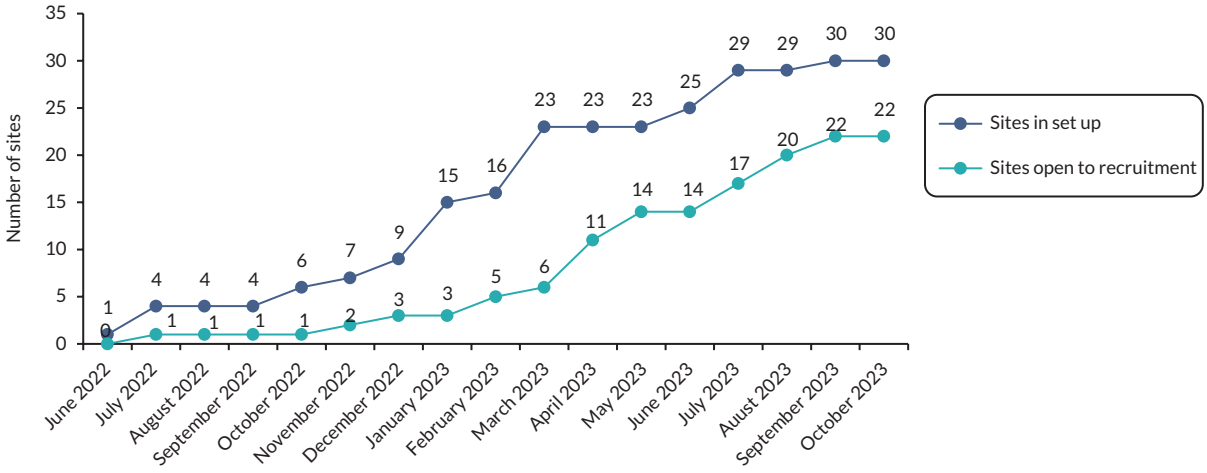


**FIGURE 2** Centre progress.

were missed and 18 participants consented and were randomised to the DIAMOND study between 13 July 2022 and 19 October 2023 (*Figure 3*), from 11 of the 22 opened sites.

Baseline characteristics were generally well balanced between the groups (*Table 1*). The mean age was 31 years and < 11% were current smokers. Baseline EHP-30 and EuroQol-5 Dimensions (EQ-5D) scores are shown in *Table 1*. The baseline endometriosis status was also well balanced (*Table 2*). Additional baseline data are presented in *Report Supplementary Material 1* (tables a and b).

Of the eight participants randomised to the surgical arm, one received surgery, but DE was not identified. As of 18 October 2023, when HTA notified the study team of the decision to terminate funding early, 12 participants (4 in the surgical arm and 8 in the medical management arm) had reached the 3-month follow-up time point. Of these, the 3-month participant reported questionnaire was completed for six: four in the medical management arm and two in the surgical arm (both of which had not received surgery at the time of completing the questionnaire). The summary of follow-up data is presented in *Report Supplementary Material 1* (tables c, d and e).

## Clinician surveys

Of the 22 sites opened to recruitment, responses from 13 sites to the clinician survey were received. In total, 3 of the 13 responding sites indicated they had protected research time for the DIAMOND trial. Twelve of 13 sites said they received adequate support from their R&D departments and all 13 had a dedicated research nurse (*Table 3*). Ten of the responding sites indicated they had support from their gynaecological colleagues to recruit to DIAMOND. In terms of difficulties with recruitment, 11 of the 13 responding sites recorded a strong patient preference for surgery, with two of these sites also noting a strong patient preference for medical treatment. A strong clinical preference for surgery was noted in 2 of the 13 sites. There were no reported difficulties of a strong clinical preference for medical treatment. Nine of the 13 sites indicated recruitment issues were influenced by surgical waiting list pressures.

Of the eight sites in set up but not opened prior to the decision to close early, seven sites completed the clinician survey. Of these seven, two had protected time for research, four had support from their R&D department and five sites had a dedicated research nurse. Other reasons indicated for lack of progress to open for recruitment (other than early close-down) were staffing issues/shortages in R&D and patient preference (*Table 4*).

During site set-up, we approached all 63 NHS BSGE centres about participation in the DIAMOND trial. Those who did not respond about participation in DIAMOND or who indicated they would not participate (22) were also asked to complete a clinician survey. Responses were received by 18 sites (*Table 5*). The reasons for not participating in DIAMOND included no protected time for research ($n$ = 8), conflict with other research projects targeting the same population ($n$ = 6), expectation for surgery from patient or referring clinician ($n$ = 6), lack of support from R&D ($n$ = 4), and clinician preference for surgery ($n$ = 3).

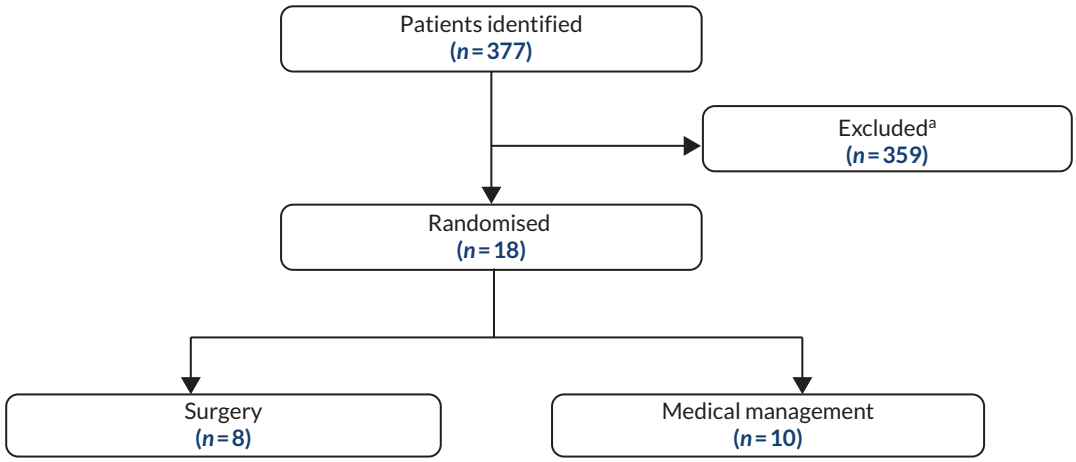


**FIGURE 3** Participant flow. a, Reasons included ineligible ($n$ = 274), declined/missed/not randomised ($n$ = 104). Participants might have more than one reason to be excluded.

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**TABLE 1** Key baseline characteristics

| | Surgery | Medical management |
|---|---|---|
| | *N* = 8 | *N* = 10 |
| ***Age group, n (%)*** | | |
| 18–30 | 2 (25.0) | 6 (60.0) |
| 31–40 | 5 (62.5) | 3 (30.0) |
| 41–49 | 1 (12.5) | 1 (10.0) |
| ***No. of pregnancies (including miscarriage, ectopic pregnancies and terminations), n (%)*** | | |
| 0 | 6 (75.0) | 7 (70.0) |
| 1 | 1 (12.5) | 1 (10.0) |
| 2 | 1 (12.5) | 0 |
| 4 | 0 | 1 (10.0) |
| 5 | 0 | 1 (10.0) |
| ***No. of deliveries (parity), n (%)*** | | |
| 0 | 6 (75.0) | 8 (80.0) |
| 1 | 1 (12.5) | 1 (10.0) |
| 2 | 1 (12.5) | 0 |
| 3 | 0 | 1 (10.0) |
| ***Ethnicity, n (%)*** | | |
| English/Welsh/Scottish/Northern Irish/ British | 7 (87.5) | 9 (90.0) |
| African | 1 (12.5) | 0 |
| Caribbean | 0 | 1 (10.0) |
| ***Smoking status, n (%)*** | | |
| Current | 1 (12.5) | 1 (10.0) |
| Former smoker | 2 (25.0) | 5 (50.0) |
| Never | 5 (62.5) | 4 (40.0) |
| *BMI, mean (SD); (N)* | 29.02 (6.49); (*N* = 8) | 24.83 (4.61); (*N* = 10) |
| ***EHP-30[a] (range 0–100), mean (SD); (N)*** | | |
| Pain | 46.02 (23.55); (*N* = 8) | 56.36 (25.05); (*N* = 10) |
| Control and Powerlessness | 71.35 (17.60); (*N* = 8) | 62.50 (27.07); (*N* = 10) |
| Emotional well-being | 47.40 (11.34); (*N* = 8) | 51.25 (18.95); (*N* = 10) |
| Social support | 65.63 (17.36); (*N* = 8) | 60.63 (17.44); (*N* = 10) |
| Self-image | 58.33 (27.82); (*N* = 8) | 72.50 (26.66); (*N* = 10) |
| Total score | 57.75 (12.48); (*N* = 8) | 60.65 (13.74); (*N* = 10) |
| *EHP sexual score,[a] mean (SD); (N)* | 72.00, (21.68); (*N* = 5) | 58.75, (29.87); (*N* = 9) |
| ***EQ-5D,[b] mean (SD); (N)*** | | |
| Total score | 0.571 (0.223); (*N* = 8) | 0.701 (0.122); (*N* = 10) |
| Visual analogue score (VAS) | 64.8 (18.8); (*N* = 8) | 58.5 (18.1); (*N* = 10) |

a 0 indicates the best possible health status whereas 100 indicates the worst possible health status.
b High values represent better state of health.

**TABLE 2** Baseline endometriosis status and symptoms

| | Surgery | Medical management |
|---|---|---|
| | *N* = 8 | *N* = 10 |
| ***Methods used to diagnose DE***[a] | | |
| Laparoscopy | 4 (50.0) | 5 (50.0) |
| MRI | 4 (50.0) | 6 (60.0) |
| USS | 2 (25.0) | 2 (20.0) |
| ***Site of DE***[b] | | |
| Rectovaginal septum | 2 (25.0) | 4 (40.0) |
| Uterosacral ligament/pelvic side wall | 6 (75.0) | 5 (50.0) |
| Bowel (excluding rectovaginal septum) | 1 (12.5) | 4 (40.0) |
| Other | 4 (50.0) | 4 (40.0) |
| ***When was DE diagnosed, n (%)*** | | |
| ≤ 3 months | 0 | 3 (30.0) |
| 4–6 months | 2 (25.0) | 1 (10.0) |
| 7–11 months | 2 (25.0) | 1 (10.0) |
| ≥ 12 months | 4 (50.0) | 5 (50.0) |
| ***Referred to chronic pain service*** | | |
| Yes | 0 | 3 (30.0) |
| No | 8 (100.0) | 7 (70.0) |
| *Dysmenorrhoea (pain during period), mean (SD); (N)* | 8.00 (1.58); (*N* = 5) | 7.89 (1.27); (*N* = 9) |
| Not applicable (no periods/bleeding), *n* (%) | 3 (37.5) | 1 (10.0) |
| *Dyspareunia (pain during intercourse), mean(SD); (N)* | 5.40 (2.61); (*N* = 5) | 5.00 (2.74); (*N* = 9) |
| Not applicable (no sexually active), *n* (%) | 3 (37.5) | 1(10.0) |
| *Non-cyclical pelvic pain (not during period or intercourse), mean (SD); (N)* | 5.75 (2.60); (*N* = 8) | 5.80 (2.35); (*N* = 10) |
| ***Dyschezia (pain during bowel movements)*** | | |
| At time of period, mean (SD); (*N*) | 5.80 (1.79); (*N* = 5) | 6.22 (2.77); (*N* = 9) |
| Not applicable (no periods/bleeding), *n* (%) | 3 (37.5) | 1 (10.0) |
| At other times, mean (SD); (*N*) | 4.75 (1.75); (*N* = 8) | 4.10 (2.69); (*N* = 10) |
| *Fatigue, mean (SD); (N)* | 6.50 (2.51); (*N* = 8) | 7.50 (1.51); (*N* = 10) |

a Participants can have more than one method used to diagnose DE.
b Participants can have more than one site of DE.

## Embedded process evaluation

### *SEAR participant flow data*

At the point of the funder decision to close the trial, SEAR data (presented as SEAR for DIAMOND – see details in *Figure 1*) were logged by 19 of 22 DIAMOND trial sites (86%). The table presented in *Figure 1* shows SEAR data at sites from July 2023 until trial closure in October 2023.

In October 2023, SEAR data showed:

- *n* = 355 potential participants Screened (i.e. assessed for potential trial eligibility trial)
- *n* = 86 women Eligible for the trial
- *n* = 116 potential participants Approached (i.e. provided with participant information sheets for the trial)

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**TABLE 3** Clinician survey response – 22 opened sites (13 site responses received)

| Survey questions opened sites | | |
|---|---|---|
| Are you the endometriosis lead for your centre? | Yes | 9 |
| | No | 2 |
| Did you have protected time to for your work as principal investigator for DIAMOND? | Yes | 3 |
| | No | 10 |
| Did you have adequate support from your R&D department? | Yes | 12 |
| | No | 1 |
| Did you have dedicated research nurses for the DIAMOND trial? | Yes | 13 |
| | No | 0 |
| Did you have the support of your gynaecology colleagues to recruit to DIAMOND | Yes | 10 |
| | No | 1 |
| Did you have difficulty randomising patients due to strong patient preference for surgery? | Yes | 11 |
| | No | 2 |
| Did you have difficulty randomising patients due to strong patient preference for medical treatment? | Yes | 2 |
| | No | 11 |
| Did you have difficulty randomising patients due to strong clinician preference for surgery? | Yes | 2 |
| | No | 11 |
| Did you have difficulty randomising patients due to strong clinician preference for medical treatment? | Yes | 0 |
| | No | 13 |
| Were recruitment issues influenced by surgical waiting list pressures? | Yes | 9 |
| | No | 4 |
| Were potentially eligible patients referred with DE given the DIAMOND trial information leaflet? | Yes | 11 |
| | No | 0 |
| Reasons for any delay in set up the Diamond trial at your site[a] | Not applicable | 5 |
| | Surgical waiting list pressures | 3 |
| | Lack of clinician equipoise | 1 |
| | No protected time | 1 |
| | Patient preference | 3 |
| Please provide any other reasons affecting recruitment and ANY other comments about why you think the trial could not recruit. | Patient preference | 7 |
| | Organisational pressures | 1 |
| | Research question not clinically relevant | 1 |
| | Eligibility criteria[b] | 1 |

a Respondents were asked to tick any of the following reasons: not applicable, surgical waiting list pressures, lack of clinician equipoise, lack of support from R&D, no protected time, or other. More than one response from respondents were possible.
b Initial protocol mandated eligibility based upon surgical diagnosis of DE. Protocol amendments allowed for radiological diagnosis using MRI or USS.

**TABLE 4** Clinician survey response – eight sites in set up but not opened (seven site responses received)

| Survey questions sites in set up, not opened | | |
|---|---|---|
| Are you the endometriosis lead for your centre? | Yes | 4 |
| | No | 1 |
| | Unknown | 2 |
| Were you going to have protected time for your work as principal investigator on the DIAMOND study? | Yes | 2 |
| | No | 5 |
| Did you have adequate support from your R&D department? | Yes | 4 |
| | No | 3 |
| Did you have dedicated research nurses for the DIAMOND trial? | Yes | 5 |
| | No | 2 |
| Please tick any of the following for reasons for the delay/inability to set up the Diamond trial at your site.[a] | Lack of support from R&D | 1 |
| | Other[b] | 3 |
| Please provide any other reasons affecting recruitment and ANY other comments about why you think the trial could not recruit.[c] | Staff shortages in R&D, lack of time in clinic, concerns over inclusion criteria | |

a Respondents were asked to tick any of the following reasons: surgical waiting list pressures, lack of clinician equipoise, lack of support from R&D, no protected time, or other. More than one response from respondents were possible.
b Other reasons included: trial closed out before we could recruit ($n$ = 1), illogical recruitment ($n$ = 1), patient preference ($n$ = 1).
c Inclusion criteria were too broad so that other causes of pelvic pain were not accounted for.

**TABLE 5** Clinician survey response – 22 sites not opened, not in set up (18 site responses received)

| Survey questions | | |
|---|---|---|
| Are you the endometriosis lead for your centre? | Yes | 12 |
| | No | 6 |
| Please tick any of the following for reasons for your centre not wishing to participate in the DIAMOND study[a] | No protected time for research | 8 |
| | Conflict with other research projects targeting the same population | 6 |
| | Expectation for surgery from patient or referring clinician | 6 |
| | Lack of support from R&D department | 4 |
| | Clinician preference for surgery | 3 |
| | Other[b] | 1 |
| If other, please give details | Proposed principal investigator left site<br>Surgical treatment proven to be effective<br>Lack of surgeon equipoise<br>Funding of the medical treatment<br>Lack of R&D support<br>Competing trials<br>Lac of protected time for research | |

continued

**TABLE 5** Clinician survey response – 22 sites not opened, not in set up (18 site responses received) (*continued*)

| Survey questions | |
|---|---|
| Please provide any other suggestions on what would encourage you to participate in future endometriosis trials | Coordinated timing of trials might be helpful<br>Need more support from R&D department/research fellow or nurse<br>Conflicted with another potential study<br>More funding for research fellow/nurse<br>Clear funding for medical therapies if part of one of the treatment arms<br>More time<br>Research training<br>Having more support in getting R&D on board patient preference |

a Respondents were asked to tick any of the following reasons: felt question was not relevant, clinician preference for surgery, clinician preference for medical treatment, expectation for surgery from patient or referring clinician, lack of support from R&D department, no protected time for research provided by your Trust/Department, conflict with other research projects targeting the same population, or other. More than one response from respondents were possible.
b Other reason was restructuring of services.

- *n* = 18 women Randomised to the trial (from 11 sites) – an eligible to randomised rate of 21%.

Reasons for non-participation in the trial:

- Treatment preference for surgery (*n* = 33/65, 51%) was the most frequently logged reason for participants' decisions not to take part in the trial.

Other reasons logged by sites for non-participation in the trial included:

- 'treatment preference for medical management' (*n* = 8/65, 12%)
- 'did not want to be randomised' (*n* = 8/65, 12%)
- 'other reason for declining' (*n* = 13/65, 20%)
- 'no reason' (*n* = 2/65, 3%)
- 'missed' (*n* = 1/65, 2%).

There were missing data (unlogged at sites) for three people who were eligible for the trial but did not consent to take part.

### *Interviews with women invited to take part*

Participant characteristics:

Five women from four sites consented to take part in semistructured telephone interviews, between July and October 2023. One was a trial decliner; three were trial consenters (of which two had been randomised and one was awaiting randomisation); and one interviewee was still to make a decision (*Table 6*).

Summary of findings:

*Report Supplementary Material 2* provides a table detailing findings from the five interviews with illustrative quotes where applicable.

A common thread among the five interview participants (including the decliner) when considering trial participation was a desire to help with research (or help the interview study, in the case of the trial decliner). For the trial decliner, the fear of disruption to their currently well-managed endometriosis pain was the main reason for not agreeing to take part in the trial.

**TABLE 6** Interview participants' characteristics

| Date of interview | Participant ID | Consenter or decliner | Trial intervention randomised to |
|---|---|---|---|
| 12 July 2023 | S13DP01 | Consenter | Surgery |
| 14 August 2023 | S16DP02 | Consenter | Hormonal medical treatment |
| 8 September 2023 | S23DP03 | Decision pending | N/A |
| 29 September 2023 | S13DP04 | Decliner | N/A |
| 4 October 2023 | S24DP05 | Consenter | Not yet randomised |

For the three trial consenters, a key driver in agreeing to take part in the trial was a reported desire to find solutions to their endometriosis. Further, one of the trial consenters reported uncertainty about which treatment would be best for them, thus willing to be randomised.

Understanding of the trial varied; two (one trial decliner and one undecided) were not able to clearly articulate what the trial involved. The other three interview participants were able to describe aspects of the trial more clearly, for example, describing the two trial interventions (surgery vs. hormonal treatment), as well as the rationale behind the trial (i.e. a lack of understanding of which treatment was better than the other).

One of the trial consenters articulated a preference for surgery. This was due to previous failure and side effects with hormonal treatments, and a hope for a potentially longer time without pain (she was subsequently randomised to surgery). The trial decliner highlighted not wanting surgery, perceiving it to be ineffective.

The main findings from the five interviews are summarised below, under the headings 'barriers and facilitators to trial participation'.

Barriers to and facilitators of trial participation:

Interviewees reported *actual* (perspectives base on their experiences) and/or *potential* (perspectives based on what might influence other women's participation) barriers and facilitators to trial participation (see *Report Supplementary Material 2* for full details).

Barriers to trial participation:

Actual trial-related barriers to participation were reported by the trial decliner, who described not wishing to be randomised to surgery as perceived it to be ineffective,

Interview participants highlighted what they perceived as potential barriers for others considering participation in the DIAMOND trial. These are grouped under 'internal trial-related' and 'external life-related' issues.

Potential internal trial-related barriers to participation which were reported included:

- treatment preference
- limited awareness about the trial among women living with DE
- considerations of the aftercare experience following laparoscopy
- concerns about the negative side effects of medicines
- misconceptions about RCTs.

Potential external-life related barriers to participation included:

- schedule conflicts, that is the timeline of the trial does not fit personal schedules
- wanting to get pregnant
- distance to trial site
- childcare considerations (due to time spent on trial intervention)
- time constraints, due to the recovery time spent off work after undergoing surgery.

Facilitators of trial participation

Actual reasons described by interviewees as facilitating trial participation, related to the provision of well-presented oral and written information about the trial, as well as frequent communication with the trial site team. Four of the interviewees described positive experiences with trial site staff, perceiving them to be helpful and supportive. Two women highlighted that they would have preferred face-to-face conversations with trial site staff, instead of phone calls or letters through the post.

It was suggested by one interviewee that providing more information on laparoscopy recovery times, and sharing case studies of successful pain management would be helpful for women considering trial participation in the future.

## *Discussion/interpretation*

### Principal findings and achievements

The early closure of the DIAMOND trial because of poor recruitment prevented any meaningful clinical conclusions being drawn from the 18 women randomised, none reached the 18-month primary outcome time-point. The trial had aimed to assess the relative reduction in pain and impact on QoL between laparoscopic surgery and optimised medical treatment for women with DE. The lack of clinical data also precluded the planned economic analysis.

The clinician survey and combined process evaluation data indicated that treatment preferences for either surgery or medical management were important in decisions not to participate in the trial. This treatment preference was cited as the main reason for poor recruitment. Most patients who expressed a treatment preference wanted surgery, often due to previous medical treatment failure, or an expectation for surgery once they had been

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referred to a specialist endometriosis centre, as reasons. Women that did participate in the trial reported positive interactions with trial staff and satisfaction with the trial information provided.

It is unfortunate that the initial support for the trial, as indicated by a survey of clinicians and patient representatives, did not translate into participation once the trial was funded and rolled out. The reasons for this discrepancy are unclear as most clinicians who undertook the pre-trial survey remained unchanged. It is possible that the onset of COVID-19 which dramatically affected theatre list waiting times could have impacted, although most UK health boards had prioritised DE surgical lists to ensure that centres attained their required operative numbers to maintain endometriosis centre status. There is no doubt however that the true impact of patient treatment preference did not reflect the pre-trial survey results.

The post-trial survey of endometriosis centre clinicians also revealed a change in views from the pre-trial survey, but the response rate was disappointingly low despite many reminders. This low response rate hindered efforts to fully understand the reasons for trial to recruit.

## Contribution to existing knowledge

The failure of the DIAMOND trial to recruit effectively resulted in no new clinical or economic information pertaining to the relative merits of surgical or optimised medical treatment of DE. This condition affects up to 1 in 50 women and causes significant morbidity and economic consequences, arising from workplace absenteeism and utilisation of scarce healthcare resources.[6,7,19,20] Large-scale, multicentre surgical RCTs that can answer clinically important questions are rare because they are difficult to execute.[21–25] Surgical trials seem to face greater challenges than non-surgical trials because of patient and clinician preferences and lack of equipoise.[26,27] Treatment preference or dislike of randomisation are the most common patient-reported reasons for non-entry into surgical RCTs.[28,29] Where treatments are markedly different, there is an increased likelihood of patients or clinicians declaring a preference.[22,30,31] Prolonged waiting times for surgery can further diminish patients' willingness to participate. More than 20% of such trials are discontinued earlier than anticipated and poor recruitment is the main reason. These factors were pivotal in the failure to recruit to the DIAMOND trial.

## Embedded process evaluation

The embedded process evaluation was limited in terms of the numbers of participants in the interview study. However, although only 5 interviews were conducted, this number from a total of 18 randomised to the DIAMOND trial, combined with the SEAR patient flow data, provided useful insights on the recruitment challenges.

Treatment preferences for surgery or medical management were pivotal in participants' decisions not to participate. Women who consented to participation were motivated by a desire to find a solution to DE, with participants reporting positive interactions with trial staff and satisfaction with trial information.

While it is not possible to suggest specific recommendations for good practice for ongoing and future trials, there were two aspects of trial conduct that the DIAMOND process evaluation usefully contributed towards:

- using the SEAR data on an ongoing basis to help guide decisions and prioritise targeted site feedback, helping inform critical aspects for inquiry in the interviews
- identification of communication lapses between patients and clinical trial staff, especially when patients expected further follow-up from recruiters, but did not receive it requiring site-specific feedback.

## Strengths and weakness

A robust, multicentre RCT was designed using validated outcome measures and incorporating an economic cost-effectiveness analysis and an embedded qualitative process evaluation. The study aimed to address an important and relevant clinical question and was informed by a pre-trial viability survey which included input from endometriosis clinicians and patient representatives. The RCT design represents the gold standard for evaluating effectiveness, minimising the influence of confounding variables and the risk of selection bias. The findings would have been generalisable considering its multicentre nature. Randomisation included allocation concealment and was stratified according to the potential prognostic variables of recruiting site and patient age.

Recruiting sites were restricted to the BSGE accredited specialist endometriosis centres to minimise confounding arising from variation in surgeon proficiency (including the availability of colorectal and urological surgeons)[8] and access to comprehensive and appropriate pain management. This comprehensive approach incorporates medical treatment, dedicated endometriosis nurse specialists, physiotherapy, psychologists and pain management specialists. While recruitment was suboptimal, the women who did participate, and who contributed to the qualitative process

evaluation, reported positive interactions with trial staff and satisfaction with the trial information provided.

The main limitation was the failure to recruit participants at a satisfactory rate resulting in a final sample of only 18 participants out of the target sample size of 400. Moreover, of the eight participants allocated to surgery, only one had actually had their surgery by the time of the trial closure. At the time of trial closure only six participants (two in the surgery arm and four, in the optimised medical treatment arm) had reached the first trial assessment end point at 3 months. No participant reached the primary outcome end point (18 months post randomisation).

## Take home messages

A key take home message is that the trial question posed, 'What is the clinical and cost-effectiveness of medical management alone versus laparoscopic surgery (with or without adjuvant medical treatment) in women with DE?', remains important and relevant in contemporary women's health care and has not yet been answered. The James Lind Alliance (JLA) Priority Setting Partnership, which includes clinicians, patients and carers, has 'outcomes and/or success rates for surgical or medical treatments which aim to cure or treat endometriosis, rather than manage it' as one of its top 10 research priorities.[32] In addition, the Cochrane systematic review of laparoscopic surgery for endometriosis[33] states under 'Implications for research' that

> *Further research is required comparing laparoscopic interventions with holistic and medical interventions. Trials should be of high methodological quality, including the routine collection and reporting of the core outcome set for endometriosis, adequately powered for the primary outcome which should be improvement in quality of life, and with five-year follow-up.*

The DIAMOND trial tried to address an important question about the relative merits of surgical and medical interventions for a complex condition; DE, in keeping with the research call of the JLA and the Cochrane Collaboration and complying with the latter's request for a methodologically robust trial design. We included many of the outcomes defined in the Core Outcome Set (COS) for endometriosis,[34] but we did not use the full COS because it had not been developed and published before the DIAMOND trial was designed and funded.

The failure of the DIAMOND trial to meet its recruitment goals is disappointing because it could have helped guide clinical practice and improve the outcomes for women with symptomatic DE and use health resources most efficiently. The scarcity of clinical trials in this area[33,35] is concerning given the prevalence and difficulty managing DE which causes significant morbidity and associated societal economic consequences.

Despite early termination, the DIAMOND trial can shed some light on the hurdles to successfully conducting robust trials in DE. These insights can inform the design and successful delivery of future research studies in this field, whether RCTs or alternative, more feasible study designs. Our clinician survey supported the need for enhanced research funding to facilitate protected clinician time to more thoroughly counsel patients and explain the rationale for the study and the nature of randomisation. It has been previously observed that recruiting clinicians often struggle to explain concepts such as randomisation and equipoise to patients.[36–38]

Future trials should continue to include embedded process evaluations to identify and address challenges relating to trial design, thereby supporting trial delivery.

## Reflections on the project and what could have been done differently

The original DIAMOND trial protocol underwent several amendments to overcome issues that became apparent during the lifetime of the trial. The two main amendments related to trial eligibility criteria, namely, the desire for pregnancy and diagnosis of DE. As regards fertility plans, the original protocol exclusion criteria stated 'planning to conceive in the next 18 months' but uncertainty around the timescale for considering pregnancy led some women to decline participation. In light of this feedback, the exclusion criteria were relaxed and changed to 'actively trying to conceive'. Regarding confirmation of DE, the original protocol stipulated a laparoscopic (surgical) diagnosis. However, it became apparent from collaborating centre feedback that many such specialist centres used radiological imaging, in the form of MRI or pelvic USS to diagnose, especially in light of the lack of surgical capacity following the COVID-19 pandemic.[2]

The DIAMOND trial was funded and planned prior to the COVID-19 pandemic, which significantly impacted its execution. The 18-month post-randomisation pain and QoL assessment was based on an anticipated 6-month surgical waiting list time, such that the primary outcome assessments would take place at approximately 12 months post surgery. However, the fallout from the pandemic meant that surgical waiting times increased dramatically, especially those in women's health where many operations were designated as 'non-urgent'.[39,40] Thus, surgery was unlikely to be executed within 12–24 months [from a

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review of DIAMOND principal investigator (PI)]. It was hoped that the fact the DIAMOND trial would allocate 50% of eligible patients to medical treatment, and thereby patients not added to the already burgeoning surgical waiting lists, would encourage clinicians to recruit. However, our clinician survey and qualitative study suggested that patients, cognisant of the lengthening surgical waiting lists, were less prepared to be allocated a non-surgical treatment and lose their place in the queue.

There were further consequences of the COVID-19 pandemic. A decision had to be made as to when to open the DIAMOND trial in light of the slow restoration of clinical services after the pandemic. The lack of paid or protected time for clinical PIs made trial engagement difficult while restoration and recovery of clinical services took priority. R&D departments had to reallocate research priorities and deal with staff shortages because of redeployment of staff to clinical areas and long-term sickness. Our post-trial closure clinician survey identified a lack of R&D support and lack of clinician time as factors impairing recruitment. Furthermore, RCTs need to gain a critical mass of collaborating centres actively recruiting. We encountered difficulties gaining momentum due to the slow accrual of centres gaining local approval to open. Thus, with hindsight, we were too optimistic as regards restoration of clinical and research infrastructure within the NHS and should have delayed commencement of trial recruitment for at least 12 months. This is despite a positive response from the pre-trial survey of potential participating endometriosis clinicians and patient representatives.

Incorporating adaptative trial designs that can accommodate changes in clinical practices and unexpected global events (like pandemics) can help mitigate the impact of such disruptions. By learning from the challenges faced by the DIAMOND trial, future research can be better positioned to navigate similar obstacles and achieve successful outcomes.

## Challenges faced and limitations

The trial was funded prior to the COVID-19 pandemic, which had a major impact on global health services. The clinical and research infrastructure was put under great stress with non-essential clinical services being shut down and surgical waiting times rising exponentially, especially those in women's health where many operations were designated as 'non-urgent'.[40] Thus, it was a difficult decision for our trial team to decide when to commence the trial; on the one hand, it is an important clinical question that needs an answer for the many patients affected by symptoms of DE, but on the other hand we did not want to embark on a major, multicentre RCT when the clinical and research environment could not support it. With hindsight we may have opened the trial to recruitment too early as the restoration of clinical and research services was slower than anticipated with clinical and research staff diverted to alternative duties and long-term sickness of staff affecting several R&D departments. We encountered significant delays with local R&D departments due to lack of capacity and accountability. Clinical capacity was also compromised because of the pressures of clinical work (outpatient clinics and operating time) as well as a lack of protected time for PIs according to responses to our post-trial closure survey of clinicians.

The clinician survey and combined process evaluation data showed that treatment preferences for either surgery or medical management were important in patients' decisions not to participate in the trial. Where a treatment preference was expressed, the majority of women wanted surgery. Our surveys also showed that participating clinicians also seemed to favour surgical management and this lack of clinical equipoise impacted on trial recruitment and the trial discussion with patients. This preference was contrary to the results of the pre-trial survey.

Our original trial protocol stipulated a surgical, laparoscopic, confirmation of DE. In light of changes to clinical pathways, driven by new guidance[2] and the lack of surgical capacity following the COVID-19 pandemic, we relaxed the confirmation of DE to allow for radiological diagnosis utilising MRI or transvaginal pelvic USS. Furthermore, some centres reported patients were reluctant to participate because of uncertainty regarding future fertility plans. We had originally stipulated no desire for pregnancy within 18 months but in response to feedback we revised this exclusion criteria to 'actively trying to conceive'. While the amendments to the protocol were necessary, they contributed to the delays and complexities that hindered recruitment and overall trial progress.

## Engagement with partners and stakeholders

We involved the research and advocacy charity Endometriosis UK from the outset of this project and their chief executive was a key member of the DIAMOND research team and co-applicant (grant holder). We included patient and public involvement (PPI) in a patient survey to help design and better understand the feasibility of our proposed trial. Our multidisciplinary trial team included all necessary expertise including clinical, research, PPI and trial management capability.

### Individual training and capacity-strengthening activities

We do not identify any clinical or research training issues; site initiation training was conducted at each centre opened to recruitment, and the CIs and DIAMOND Clinical Trial Team based at CHaRT Clinical Trials Unit, University of Aberdeen were accessible and responsive, face to face or remotely, with many queries being addressed promptly by e-mail.

### Institutional capacity strengthening

See sections '*Challenges faced and limitations*' and *Impact and learning*.

## Patient and public involvement

The research team included PPI partners from Endometriosis UK who contributed throughout the study informing trial design and helped the development of patient facing study materials. The project management group and independent Trial Steering Committee (TSC) included PPI members who were actively involved in discussions at meetings, reviewing and commenting on patient facing materials and contributing to the review of the plain language summary as well as the close out letter to consented participants. The study outcomes have been disseminated to PPI partners and participants.

## Equality, diversity and inclusion

Deep endometriosis affects biological women, of all races/ethnicities,[41] sexual orientation and social status. To ensure the DIAMOND trial's findings were relevant and generalisable, we approached all patients with DE who satisfied the eligibility criteria to optimise the relevance and generalisability of our findings. At the time of premature trial closure, 2 of the 18 patients recruited were from an ethnic minority, but the numbers were too small to make any reliable inference regarding the equality, diversity and inclusion (EDI) within the study processes and recruitment.

Of the 20 members of the research team (14 grant holders), 5 (25%) were from an ethnic minority and 8 (40%) were women (1 being a PPI representative). Of the 7 members of the trial oversight committees (TSC and Data Monitoring Committee), 4 (57%) were women (one being a PPI representative) but none were from an ethnic minority. We have no information as regards the PPI demographics for the wider PPI partnership run through the research and advocacy charity Endometriosis UK. Thus, overall, we believe we had good representation from an EDI perspective within our trial management teams apart from a lack ethnic diversity within our trial oversight committees. Future efforts should aim to enhance ethnic diversity across all levels of trial management and oversight to better reflect the population affected by DE and ensure inclusive research practices.

## Impact and learning

The main lessons learnt from the DIAMOND trial relates to the reasons for its failure to complete recruitment.

The initial surveys of clinicians and patient representatives conducted prior to securing trial funding and finalising protocol design supported the feasibility of the DIAMOND trial, with numerous centres willing to participate, recruit and randomise patients. However, this initial enthusiasm did not materialise, such that by the time of trial closure (and trial milestone of 40 centres recruiting within 18 trial months), we had only accrued 22 centres.

All trials need to gain a critical mass of collaborating centres actively recruiting. We encountered difficulties gaining momentum. The slow accrual of sites was caused by research and clinical capacity issues. The COVID-19 pandemic influenced this lack of human and material resource and restoration of these services was slow. With hindsight we opened the trial to recruitment too early as the restoration of clinical and research services was slower than anticipated, with clinical and research staff diverted to alternative duties and long-term sickness of staff affecting several R&D departments. The PI and local R&D departments need to confirm site capacity (clinical and research infrastructure) and importantly that clinical colleagues are prepared to take part. That said, there appeared to be a lack of capacity and urgency within local R&D departments to interact with our trial unit in a timely fashion. R&D departments need to be incentivised and become more accountable as regards meeting time frames and opening trials.

The enormity of the clinical burden post COVID may have also impacted upon the time, resource and enthusiasm of clinicians to commit to the DIAMOND trial. The fact that 50% of participating patients would have been allocated medical treatment, thereby not adding to the surgical waiting lists, did not seem to incentivise trial participation among clinicians. Clinicians reported (within our post-trial closure surveys), a lack of time within busy clinics and most PIs did not have protected paid time for this research. Consequently, trial engagement

was compromised against a background of prioritising restoration and recovery of clinical services.

The CHaRT Clinical Trials Unit maintained regular communication with R&D departments in open sites and those in set up or considering participation. The CIs set up a 'WhatsApp' group among PIs to trouble shoot problems, answer queries and encourage recruitment. While more interaction with trial sites and PIs could have been beneficial, the CIs have successfully delivered other multicentre surgical trials, primarily in a pre-COVID environment.[42–44] Post-trial closure surveys and embedded qualitative process evaluation indicated that there was a lack of patient and surgeon equipoise. Patients often expressed a preference for surgery, driven by their ongoing pain symptoms resistant to many medical treatments and expectation of surgery once referred to a specialist BSGE endometriosis centre. Some clinicians preferred surgery based upon their experiences and the existing evidence base.

As described earlier, the need to proactively analyse and make changes to the existing study trial protocol in a timely fashion in response to the trial progress and feedback from recruiting sites was apparent. Incorporating adaptive trial designs that can give flexibility and prevent delays caused by protocol amendments.

## Implications for decision-makers

The DIAMOND trial closed early due to poor recruitment, limiting the ability to draw conclusions about the relative effectiveness and cost-effectiveness, on alleviating pain and enhancing QoL, of laparoscopic surgery compared to medical management for DE.

However, there are implications for decision-makers arising from the failure of this well-designed, multicentre surgical RCT addressing an important clinical question of relevance to thousands of women across the UK, and far more globally, suffering with refractory pain symptoms because of DE. In addition, the economic consequences of this highly prevalent condition on the NHS and wider society are manifest. The failure to recruit to DIAMOND is concerning as the study was run by an experienced Clinical Trials Unit incorporating a multidisciplinary team of clinicians, patients and researchers. Moreover, during the development of the DIAMOND trial, and before funding was granted (and prior to the COVID-19 pandemic), we surveyed clinicians and patients. The results of these surveys supported the trial and the willingness to participate, among both patients and clinicians. However, despite these assurances, the reality on the ground was that fewer centres than anticipated agreed to participate while patients were reluctant to be randomised, expressing a treatment preference, usually for surgery. Clinicians appeared to lack enthusiasm either through lack of clinical equipoise (generally preferring surgery) or limited time (and generally no protected time) and resources. Patients and clinicians both reported the length of waiting times to be seen in specialist endometriosis clinics and prolonged waiting lists to receive surgery influenced treatment decisions. These waiting time and resource pressures were undoubtedly compounded by the fallout from the COVID-19 pandemic, with 'benign' women's health conditions like endometriosis being disproportionately affected as reported by the Royal College of Obstetricians and Gynaecologists (https://rcog.shorthandstories.com/lefttoolong/index.html, www.rcog.org.uk/news/gynaecology-waiting-lists-leave-thousands-of-women-waiting-too-long-for-care/).[1] Similarly, the research infrastructure took some time to recover following the pandemic, but once restored there were substantial delays in site setup and opening by some R&D departments.

Failure of surgical trials result in considerable research and resource waste and leaves important clinical questions unanswered.[45–47] This has financial and ethical implications[48] and the non-ideal situation where patients are offered treatments based on opinion rather than clear scientific evidence. The lack of clinical and research capacity needs to be addressed if meaningful surgical trials answering clinically important questions for patients, the NHS and wider society are to be successfully completed.

To enhance recruitment and trial completion, targeted investment in innovative solutions and streamlining of bureaucratic processes is needed. R&D departments need investment but also need to be made more accountable for their performance, especially when trials fail. Overcoming surgeon prejudices and preferences may require a greater emphasis on research contributions during undergraduate and postgraduate training. Formal evaluation of new surgical procedures or those of uncertain benefit (taking into account safety and effectiveness), preferably using adequately powered independently funded trials, should be required before they are introduced into routine practice.

It is incumbent on medical schools, the Royal Colleges and specialist bodies to include research training as part of their curricula if we want successful future engagement in clinical research. We need this if we want to continue the quest to practice evidence-based medicine.

In the UK, the BSGE accredits specialist endometriosis centres. NHS England (NHSE) has disseminated a draft service specification for 'Complex gynaecology: Severe endometriosis' as part of the Women and Children's Programme of Care (www.england.nhs.uk/commissioning/spec-services/npc-crg/group-e/e09/).

This includes various 'service defined' metrics, mainly based upon the pre-existing data collected by the BSGE Endometriosis Centre project, centred around the number and type of surgical cases undertaken in each accredited (and provisional) centre, complications and follow-up of patient-reported outcome measures (PROMs). Rates of follow-up for PROMs have been low, typically < 50% overall, with variation across centres.[8] The new specialist commissioning requirements of NHSE provides an opportunity to mandate more complete patient outcome follow-up to maintain specialist funded status within the NHS. Moreover, the current BSGE database is restricted to surgical intervention for DE and not non-surgical intervention. Considering the failure of the DIAMOND trial, the next best research approach is to collect prospective, non-randomised data on medical and surgical treatment of DE; an adapted BSGE database endorsed by NHSE Specialist Commissioning may allow such a meaningful comparative observational study to be conducted. Moreover, metrics to maintain specialist commissioned status could include participation in relevant endometriosis 'portfolio' studies (i.e. high-quality clinical research studies that are eligible for consideration for research support from the Clinical Research Network in England) such as the now closed DIAMOND trial. This lever may help prioritise the research agenda, especially as regards the conduct and participation in surgical RCTs so that they can be successfully completed and inform future clinical practice in DE and complex gynaecology.

## Research recommendations

The DIAMOND trial was conducted in the UK within accredited BSGE Specialist Endometriosis Centres. This network has successfully published the largest global observational series in the surgical treatment of DE.[8,49,50] Despite this established, national specialist network, the DIAMOND trial was closed due to failure to recruit participants. It is thus unlikely that such a multicentre trial will be feasible elsewhere in the world. Thus, there is a need for alternative, non-randomised study designs, incorporating innovative approaches to attract participants and engage clinicians and other healthcare professionals.

One solution may be the use of comprehensive cohort designs among others. However, such study designs are much more expensive and statistical interpretation of non-randomised cohorts is challenging.

When it became apparent that DIAMOND was struggling to recruit patients due to a preference for surgery as they had waited so long to be seen, we proposed an alternative trial design that was rejected by the funder. This design involved capitalising upon the prolonged surgical waiting lists. Patients on the waiting list with an anticipated surgery date in excess of 1 year could be approached to participate, being randomised to alternative or new hormonal treatment (optimisation of medical care – essentially the medical arm of the original DIAMOND trial) or not (standard medical care). We hoped to then evaluate the primary outcome (improvement in the pain domain of the EHP-30) comparing optimisation of medical care with standard medical care and compare the proportions of women deciding against surgery. The primary outcome could also have been assessed in the group receiving optimisation of medical care at 12 months after surgery. Any significant differences compared with the pre-surgery optimisation of medical care EHP-30 pain score could have been evaluated. Such a trial design, while not as simple or rigorous as the original DIAMOND trial protocol, could have then provided much-needed data on the relative effectiveness of medical and surgical treatment of DE.

The JLA Priority Setting Partnership,[32] the NICE (www.nice.org.uk/guidance/ng73/chapter/Recommendations-for-research) and the ESHRE[2] have all published research recommendations in endometriosis. Most of these recommendations do not relate specifically to DE and the role of surgery. The following recommendations for research are thus aimed at understanding better the role or surgery and patient selection in DE.

### *Pain, quality of life and bowel symptoms*

The long-term alleviation of pain and effect on QoL of laparoscopic excision compared to non-surgical management of DE is needed as well as identifying pre-operative clinical variables that may predict sustained improvement in symptoms. Studies could be less ambitious than DIAMOND and restrict evaluations to more specific non-medical options or medical treatment pathways. Designs to consider would include RCTs and prospective longitudinal cohort controlled studies.

This synopsis should be referenced as follows:
Cooper K, Constable L, Vadiveloo T, Matuluko A, Kennedy C, McCann S, *et al*. Clinical and cost-effectiveness of medical management versus surgery for deep infiltrating endometriosis: synopsis from the DIAMOND RCT [published online ahead of print January 28 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJKC5715

### *Reproduction*

The importance of treating DE to enhance natural and assisted conception as well as optimising pregnancy outcomes remains unknown. Designs to consider would include RCTs and prospective observational cohort controlled studies.

### *Diagnosis*

The accurate diagnosis of the presence and extent of deep rectovaginal endometriosis is of key importance to plan surgery. High-resolution transvaginal imaging is being increasingly adopted and we witnessed this change during the lifetime of the DIAMOND trial. The accuracy of transvaginal USS compared to MRI for the diagnosis of deep rectovaginal/uterosacral endometriosis needs to be assessed as a diagnostic accuracy study and its impact on clinical outcomes in diagnostic effectiveness studies, preferably RCTs.

## Conclusions

Deep endometriosis causes significant morbidity primarily because of chronic pain but also because of bowel, urinary and fertility problems that may coexist.[5,51] Symptoms associated with DE are often resistant to standard medical treatment and other non-surgical treatments and so many women require surgery. However, surgical removal of this type of endometriosis is complex, often requiring multidisciplinary surgical teams and posing risks of serious complications.[8,19,52] To justify the resources and risks of surgery, it is important for patients, doctors and healthcare managers to understand its effectiveness.

To date, only non-comparative observational data are available. While these studies show efficacy, the lack of randomisation or complete patient follow-up introduces significant bias and the lack of comparison with new or multimodal non-surgical management strategies limits clinical inferences. The DIAMOND trial aimed to fill this gap by evaluating the effectiveness of laparoscopic surgery for DE compared to optimised medical management.

The lack of clinical trials evaluating the treatment of DE is concerning, given the condition's prevalence, management challenges, morbidity, and societal economic impact.[33,35] The clinical question remains both relevant but unanswered because of the early closure of the trial. Despite the largest observational data set published by the BSGE specialist endometriosis centre network[8] and initial enthusiasm from pre-trial surveys, recruitment failed due to a lack of equipoise among patients and clinicians and slow processes in local R&D departments.

Delivering important surgical studies in this area will require different study designs, the implementation of novel innovations to educate, enthuse and incentivise both patients and clinicians and simplification of study processes to expedite study site set up, along with increased accountability and funding to motivate local R&D departments and PIs. Hopefully, the DIAMOND trial has shed light on some of the obstacles to successfully conducting robust trials in DE to allow the design and successful delivery of future research studies in this field, whether RCTs or alternative, more feasible study designs.

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## DIAMOND recruiting centres

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### *Patient data statement*

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

### *Data-sharing statement*

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

### *Ethics statement*

DIAMOND was reviewed by the West of Scotland Research Ethics Committee 2 and received ethical approval on 6 January 2022 (Ref 21-WS-0136).

### *Information governance statement*

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## List of supplementary material

**Report Supplementary Material 1**
Additional data tables

**Report Supplementary Material 2**
Embedded process evaluation

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/GJKC5715).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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## List of abbreviations

| | |
|---|---|
| BSGE | British Society of Gynaecology Endoscopy |
| CHaRT | Centre for Healthcare Randomised Trials |
| CI | Chief Investigator |
| COS | core outcome set |
| COVID | coronavirus disease |
| COVID-19 | coronavirus disease 2019 |
| DE | deep endometriosis |
| EDI | equality, diversity and inclusion |
| EHP-30 | Endometriosis Health Profile-30 |
| EQ-5D | EuroQol-5 Dimensions |
| EQ-5D-5L | EuroQol-5 Dimensions, five-level version questionnaire |
| ESHRE | European Society for Human Reproduction and Embryology |
| GnRH | gonadotrophin-releasing hormone |
| HTA | Health Technology Assessment |
| JLA | James Lind Alliance |
| LNG-IUS | levonorgesterol-releasing intrauterine system |
| MRI | magnetic resonance imaging |
| NHSE | National Health Service England |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| PI | principal investigator |
| PPI | patient and public involvement |
| PROM | patient-reported outcome measure |
| QALY | quality-adjusted life-year |
| QoL | quality of life |
| RCT | randomised controlled trial |
| R&D | research and development |
| TSC | Trial Steering Committee |
| USS | ultrasound scan |

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