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PROTOCOL

SOMA-trial: surgery or medication for women with an endometrioma? Study protocol for a randomised controlled trial and cohort study

E. van Barneveld[1,2,†,*], V.B. Veth[1,2,†], J.M. Sampat[1,2], A.M.F. Schreurs[3], M. van Wely[4], J.E. Bosmans[5], B. de Bie[6], F.W. Jansen[7], E.R. Klinkert[8], A.W. Nap[9], B.W.J. Mol[10], M.Y. Bongers[1,2], V. Mijatovic[3], and J.W.M. Maas[1]

[1]Department of Obstetrics and Gynaecology, Máxima Medical Centre, Veldhoven, the Netherlands [2]Research School Grow, Maastricht University, Maastricht, the Netherlands [3]Department of Reproductive Medicine, Endometriosis Center, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands [4]Methodology, Department of Obstetrics and Gynaecology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands [5]Department of Health Sciences, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, The Netherlands. [6]Endometriosis Foundation of the Netherlands (Endometriose Stichting), Sittard, The Netherlands [7]Department of Obstetrics and Gynaecology, Leiden University Medical Centre, University of Leiden, Leiden, the Netherlands [8]Department of Obstetrics and Gynaecology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands [9]Department of Obstetrics and Gynaecology, Rijnstate Hospital Arnhem, Arnhem, the Netherlands [10]Department of Obstetrics and Gynaecology, Monash Medical Centre Melbourne, Melbourne, Australia

*Correspondence address. Department of Obstetrics and Gynaecology, Máxima Medical Centre, Postbox 7777, 5500 MB Veldhoven, The Netherlands. E-mail: esther.van.barneveld@mmc.nl https://orcid.org/0000-0003-2801-8248

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STUDY QUESTIONS: The objective of this study is to evaluate the effectiveness and cost-effectiveness of surgical treatment of women suffering from pain due to an ovarian endometrioma when compared to treatment with medication (analgesia and/or hormones). The primary outcome is defined as successful pain reduction (−30% reduction of pain) measured by the numeric rating scale (NRS) after 6 months. Secondary outcomes include successful pain reduction after 12 and 18 months, quality of life, affective symptoms, cost-effectiveness, recurrence rate, need of adjuvant medication after surgery, ovarian reserve, adjuvant surgery and budget impact.

WHAT IS KNOWN ALREADY: Evidence suggests that both medication and surgical treatment of an ovarian endometrioma are effective in reducing pain and improving quality of life. However, there are no randomised studies that compare surgery to treatment with medication.

STUDY DESIGN, SIZE, DURATION: This study will be performed in a research network of university and teaching hospitals in the Netherlands. A multicentre randomised controlled trial and parallel prospective cohort study in patients with an ovarian endometrioma, with the exclusion of patients with deep endometriosis, will be conducted. After obtaining informed consent, eligible patients will be randomly allocated to either treatment arm (medication or surgery) by using web-based block randomisation stratified per centre. A successful pain reduction is set at a 30% decrease on the NRS at 6 months after randomisation. Based on a power of 80% and an alpha of 5% and using a continuity correction, a sample size of 69 patients in each treatment arm is needed. Accounting for a drop-out rate of 25% (i.e. loss to follow up), we need to include 92 patients in each treatment arm, i.e. 184 in total. Simultaneously, a cohort study will be performed for eligible patients who are not willing to be randomised because of a distinct preference for one of the two treatment arms. We intend to include 100 women in each treatment arm to enable standardization by inverse probability weighting, which means 200 patients in total. The expected inclusion period is 24 months with a follow-up of 18 months.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Premenopausal women (age ≥ 18 years) with pain (dysmenorrhoea, pelvic pain or dyspareunia) and an ovarian endometrioma (cyst diameter ≥ 3 cm) who visit the outpatient clinic will make up the study population. Patients with signs of deep endometriosis will be excluded. The primary outcome is successful pain reduction, which is defined as a 30% decrease of pain on the NRS at 6 months after randomisation. Secondary outcomes include successful pain reduction after 12 and 18 months, quality of life and affective symptoms, cost-effectiveness (from a healthcare and societal perspective), number of participants needing additional surgery, need

[†]The authors consider that the first two authors should be regarded as joint First Authors.

of adjuvant medication after surgery, ovarian reserve and recurrence rate of endometriomas. Measurements will be performed at baseline, 6 weeks and 6, 12 and 18 months after randomisation.

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DATE OF FIRST PATIENT'S ENROLMENT: First inclusion in randomised controlled trial October 4, 2019. First inclusion in cohort May 22, 2019.

Key words: endometrioma / pain / quality of life / cost-effectiveness / affective symptoms / recurrence / ovarian reserve / surgery / medication / randomised controlled trial

WHAT DOES THIS MEAN FOR PATIENTS?

Endometriosis is a painful condition in which tissue similar to the lining inside the womb (uterus) is found outside the uterus. This is described as an endometrioma when this tissue has caused an ovarian cyst. When these ovarian cysts cause pain, two therapeutic strategies are currently available. They include treatment with medication (pain relief and/or hormones) and surgery. Evidence suggests that both treatments are effective in reducing pain symptoms and increasing quality of life. However, it is not clear which treatment is the most effective. In this study, women with an endometrioma receiving medication will be compared to women treated by surgery. We will investigate the effect on pain and quality of life. We also want to investigate whether surgery could save costs both for the healthcare system and society in general (e.g. if women cannot work because of illness).

Introduction

Endometriosis is defined as the presence of endometrium-like tissue outside the uterine cavity causing a chronic inflammatory reaction. The prevalence varies between 2 and 10% among the general female population of reproductive age (Eskenazi and Warner, 1997), but rises up to 30–40% in women suffering from cyclical pain and/or infertility (Meuleman *et al*., 2009). Endometriosis is associated with symptoms of pelvic pain, dysmenorrhea, dyspareunia and infertility, causing a significant reduction in quality of life (QoL), which is largely mediated by psychological distress (De Graaff *et al.,* 2013). The population of women suffering from endometriosis shows 0.81 quality-adjusted life years (QALY) (Simoens *et al.,* 2012), resulting in a high socio-economic burden. The EndoCost study calculated these annual costs at €2.6 billion in the Netherlands (Simoens *et al.,* 2012). This burden is largely caused by the indirect costs of productivity loss (loss of 10.8 working hours per week, €6298 per woman per year) (Nnoaham *et al*., 2011; Simoens *et al*., 2012). One of the most common manifestations of endometriosis is the formation of an ovarian endometrioma, affecting 17–44% of women with endometriosis (Eskenazi *et al*., 1997). Endometriomas are ovarian inclusion cysts lined with endometrial tissue in which the internal fluid is thought to result from the accumulation of menstrual blood deriving from the shedding of endometrial lining inside the cyst. Optimal, evidence-based and cost-effective treatment of an endometrioma is necessary in order to decrease pain, improve QoL and affective symptoms, and lower the socio-economic burden.

Two therapeutic strategies, including treatment with medication (analgesia and/or hormones) and surgery, are available for the treatment of ovarian endometriomas. None of these treatment options offer a cure, but aim to reduce pain and increase QoL. Evidence from observational studies suggests that both therapeutic strategies are effective in reducing pain symptoms.

When performing surgery, cystectomy is superior to drainage and coagulation in women with an ovarian endometrioma (≥3 cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of endometriomas. Two randomised controlled trials (RCTs) comparing cystectomy to drainage and coagulation by bipolar diathermy demonstrated 24-month cumulative recurrence rates of dysmenorrhea, deep dyspareunia and non-menstrual pelvic pain of 10–20%. These studies indicated that laparoscopic cystectomy achieved relief of pain symptoms (visual analogue scale (VAS) score ≤ 5) in 80–94.7% in the first year after treatment (Beretta *et al*., 1998; Alborzi *et al*., 2004).

The use of low-dose cyclic oral contraceptives is effective in reducing pain symptoms in patients with endometriosis. At the end of a 6-month treatment period with low-dose combined oral contraceptives, non-menstrual pain (40%), dyspareunia (75%) and dysmenorrhoea (82.6%) were reduced to mild or zero in comparison with baseline. These results were compared to the GnRH agonist goserelin. For dyspareunia, goserelin was superior to oral contraceptives, while for non-menstrual pain there was no difference (Vercellini *et al*., 1993; Brown *et al.,* 2010). Anti-progestogens are efficient in reducing dysmenorrhoea (resulting in none or mild painful dysmenorrhoea after 6 months of follow-up) in 67.3% of cases and depot progestin in 89.5% (Brown *et al*., 2012).

Table I Secondary outcomes in a comparison of surgery or medication for women with an endometrioma.

Successful pain reduction after 12 and 18 months	NRS at 12 and 18 months.
Quality of life	EuroQoL-5D-5L and EHP30 questionnaires.
Affective symptoms	GAD-7 and PHQ-9 questionnaires.
Costs effectiveness	iMCQ and iPCQ.
Recurrence rate	Recurrence of either pain symptoms (measured on the NRS as described above) and the endometrioma itself (measured with ultrasound).
Need of adjuvant medication after surgery	Patients' medical file.
Ovarian reserve	Measured by blood test (serum AMH levels*) and ultrasound (AFC).
Adjuvant surgery	Rate of adjuvant surgery after treatment with medication for endometrioma.
Budget impact	Total costs from the group treated with medication and the group treated by surgery.

EuroQol-5D-5 L = European quality of life – 5 Dimensions – 5 Levels; EHP-30 = Endometriosis Health Profile-30; QALY = quality-adjusted life year; GAD-7 = Generalized Anxiety Disorder-7; PHQ-9 = Patient Health Questionnaire-9; iMCQ = Medical Consumption Questionnaire; iPCQ = Productivity Cost Questionnaire; NRS = numeric rating scale; AMH = anti-Müllerian hormone; AFC = antral follicle count.
*AMH will not be measured in the prospective cohort study. See Fig. 1 (flowchart with study procedures) for details about the timing of measuring the parameters.

However, there are no randomised studies that compare surgery to medication in the treatment of an ovarian endometrioma. This forces women with endometriosis and their physicians to take decisions in uncertainty about the benefits, risks and cost-effectiveness of surgery in direct comparison to treatment with medication.

As a result of this uncertainty about the relative effectiveness and cost-effectiveness of the two treatments, usual care is characterised by the co-existence of two therapeutic strategies. Treatment with medication (analgesics and/or hormones) may alleviate symptoms, but the effect is temporary and considered less effective since the endometriosis cyst is not removed. This strategy requires chronic use of analgesics and hormones, plus frequent monitoring of the cyst and the associated symptoms. Furthermore, if endometriomas are not removed women may experience insufficient pain relief, exacerbations of pain symptoms requiring hospital visits and admission and/or cyst-related complications such as rupture and torsion (4%) (Bottomley and Bourne 2009). When this strategy is applied, surgery is frequently still necessary as a result of these disadvantages.

As surgical removal of the cyst implies that the source of pain is eliminated, it is considered to be the most effective treatment in reducing pain symptoms. Surgery also appears to be more cost-effective than conservative treatment, as patients who have undergone surgery are less likely to require additional medication for pain relief or to return to the hospital for scheduled or emergency visits related to complications associated with ovarian endometriomas. Traditionally, there was a general experts' consensus that removal of an endometrioma is the treatment of choice in patients with cysts larger than 3 cm, but this consensus has been challenged by evidence questioning the benefit and harm of surgery. One of the risks of surgery is recurrence of the cyst, causing relapse of symptoms, questioning both the benefit and cost-effectiveness of surgery (Alborzi *et al.,* 2004; Dan and Lemin 2013). Furthermore, several studies showed that healthy ovarian tissue is accidentally removed during cystectomy (Dunselman *et al.,* 2014), potentially causing loss of ovarian reserve and lowering the chances for accomplishing a successful pregnancy in the future. Alternative treatments to cystectomy include (partial) ablation of the endometriosis cyst wall using the CO_2 laser (Donnez *et al*., 2010; Carmona *et al*., 2011) and argon plasma energy (Roman *et al*., 2015). The best treatment of endometriomas is unknown, and this topic has been prioritised as a knowledge gap by ESHRE Guideline Development Group (Dunselman *et al.,* 2014) and the Dutch Society of Obstetrics and Gynaecology (NVOG 2016). In this study, we will investigate surgery in comparison to treatment with medication in order to eliminate the less (cost-)efficient strategy.

Outcomes

Primary outcome

The primary outcome is effectiveness of surgical treatment compared to treatment with medication of an ovarian endometrioma, defined as successful pain reduction (−30% reduction of pain) measured by the numeric rating scale (NRS) after 6 months.

Patients may experience pelvic pain, dysmenorrhea and/or deep dyspareunia caused by an ovarian endometrioma. During follow-up, the patient will be asked to score the average pain level for pelvic pain during the last week and, if applicable, the average pain for dysmenorrhea and deep dyspareunia during the last month. Physicians will be instructed to ask for pain scores using an 11-point numerical rating scale (0–10). These scales should be anchored by 0 = 'no pain' and 10 = 'the worst pain you can imagine' (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and American Society for Reproductive Medicine (ASRM) recommendation).

Secondary outcomes

The secondary outcomes are listed in Table I. Measurements will be performed at baseline (t0), 6 weeks (t1), 6 months (t2), 12 months (t3) and 18 months (t4) after randomisation.

Baseline characteristics

The baseline characteristic collected at start of the study will include demographic data and medical history. Pre-treatment characteristics include hormonal treatment and previous surgery, ultrasound data and mean pain scores for dysmenorrhea, dyspareunia and chronic pelvic pain.

Materials and Methods

This protocol describes a multicentre RCT with cost-effectiveness analysis and preference cohort study. The study will be performed in a research network of university and teaching hospitals in the Netherlands.

Study population

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Premenopausal woman aged ≥18 years;
- Patients who report at least one of the endometriosis related pain symptoms: dysmenorrhoea, pelvic pain or dyspareunia;
- Ovarian endometrioma with a cyst diameter ≥ 3 cm (measured by transvaginal ultrasound or MRI).

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Women with signs of deep endometriosis* (by physical examination and transvaginal ultrasound or MRI);
- Not able or willing to provide written informed consent;
- Not able to read, write and understand Dutch or English.

**Deep endometriosis extends beneath the peritoneum and may affect the uterosacral ligaments, pelvic sidewalls, rectovaginal septum, vagina, bowel, bladder or ureter* (Dunselman *et al*., 2014).

The study schedule is presented in the flowchart (Fig. 1). Patients meeting the inclusion and exclusion criteria will be verbally informed about the study by their physician who will provide them with written information. Each subject will be informed that participation in the study is voluntary and that withdrawal of consent will not affect her right to the most appropriate treatment or affect the patient–doctor relationship. If a patient agrees to participate in the study after the consideration time of 1 week, written informed consent will be obtained after which randomisation will be performed. Women will be randomly allocated in a 1:1 ratio to either surgery or treatment with medication, with use of dynamic block designed randomisation with blocks of 2, 4 or 6. Stratification by centre will be performed.

Women who decline randomisation due to a specific treatment preference for one of the treatments will be asked to participate in a prospective cohort according to the study protocol. The primary outcome of the randomised trial (successful pain reduction (−30% reduction of pain) measured by the NRS after 6 months) will be presented as the headline result. Addition of the prospective cohort enables us to:

- Observe the expected outcome outside the context of the trial and to compare this to the outcome of the RCT, which will provide knowledge on the generalizability of the findings;
- Increase the precision of the estimate of the findings from the RCT by making groups comparable (standardization by inverse probability weighting by propensity scores).

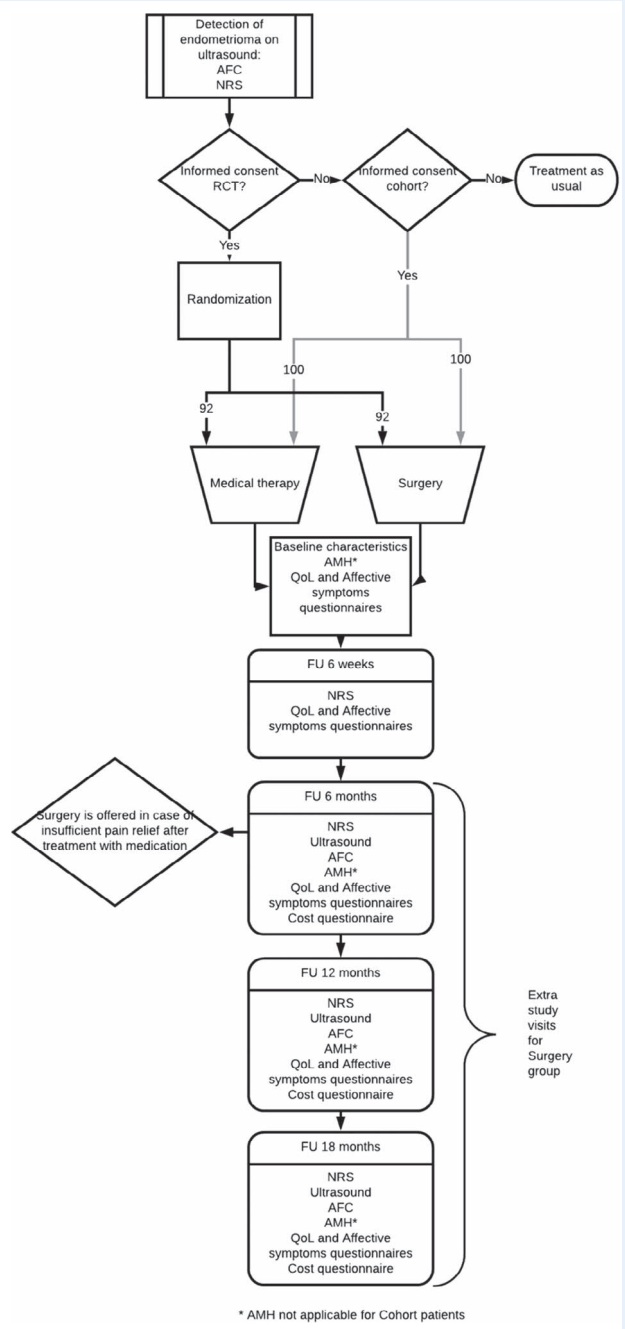

Figure 1 Flowchart of procedures in a study of surgery versus medication for women with an endometrioma. AFC = antral follicle count; NRS = numeric rating scale; RCT = randomised controlled trial; AMH = anti-Müllerian hormone; QoL = quality of life; FU = follow-up.

Surgical treatment of an endometrioma will be compared to treatment with medication. Both treatment strategies are currently used for treatment of women with pain symptoms related to an ovarian endometrioma and are considered as usual care.

Surgical treatment of ovarian endometriomas will be performed by gynaecologists according to the technical description and recommendations by the Working Group of ESHRE, the European Society for Gynaecological Endoscopy and the World Endometriosis Society. The

ESHRE guideline concludes that laparoscopic cystectomy is superior to drainage and coagulation in women with an ovarian endometrioma (≥3 cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of the endometrioma. Cystectomy is probably more effective than CO_2 laser vaporization in women with ovarian endometriomas (≥3 cm) with regard to recurrence of endometriomas Carmona *et al*., 2011). An alternative surgical treatment includes ablation with Argon plasma energy (Roman *et al*., 2015; Lockyer *et al*., 2019). Adherence to the standard operating procedure will be assessed by checking operation reports. Treatment with medication includes analgesics and/or hormonal therapy for 6 months followed by revision of pain relief. Therapy with analgesics is based on the World Health Organisation (WHO) analgesic ladder (WHO, 1986). Options for hormonal therapy are oral contraceptive pills, progestogens, antiprogestogens or GnRH agonists. Women who experience sufficient pain relief will continue treatment with medication. If women experience insufficient pain relief at 6 months of follow-up, surgical treatment will be offered.

During the screening, a transvaginal ultrasound will be performed to determine the diameter of the ovarian endometrioma, the antral follicle count (AFC) and the presence of signs related to deep endometriosis. After randomisation, baseline characteristics and medical history will be listed in the case report file and one blood sample will be obtained in order to measure serum anti-Müllerian hormone (AMH). At baseline, and at 6 weeks, 6 months, 12 months and 18 months of follow-up, participants will be asked to complete validated questionnaires on QoL and affective symptoms. Cost questionnaires will be assigned at 6, 12 and 18 months of follow-up. Transvaginal ultrasounds and blood samples will be repeated in order to determine recurrences of ovarian endometriomas and the ovarian reserve (by AFC and serum AMH) at 6, 12 and 18 months of follow-up.

Missing values are minimised through active trial monitoring within the NVOG Consortium 2.0.

Data are collected prospectively as part of routine care. A secure online tool will be used to collect results from the questionnaires (Castor EDC®).

Most of the study visits will be combined with regular care visits and activities in order to reduce the burden of participation in this study. In regular care, patients treated with medication visit the outpatient clinic four times a year for routine follow-up. Therefore, there are no additional study visits for patients treated with medication. However, patients treated by surgery only visit the outpatient clinic after 6 weeks for post-operative follow-up. Therefore, participating in the surgical arm of the study requires three additional visits (at 6, 12 and 18 months).

Sample size

Olsena *et al*. (2018) included 66 studies to define the minimum clinically important differences (MCID) in chronic pain. Median absolute MCID was estimated between 23 and 34% among studies using the mean change approach (Olsena *et al*. 2018). According to the IMMPACT recommendations, reductions in chronic pain intensity of 30% appear to reflect at least moderate clinically important changes and will therefore be considered as successfully treated and this was used for sample size calculation. We assume that surgery will result in successful pain reduction in 90% of women and treatment with medication will result in successful pain reduction in 70% of women (Vercellini *et al*., 1993; Beretta *et al*., 1998; Alborzi *et al*., 2004; Brown *et al*., 2010; Brown *et al*., 2012). Based on a power of 80% and an alpha of 5% and using a continuity correction, a sample size of 69 patients in each treatment arm is needed. Accounting for a dropout rate of 25% (i.e. loss to follow-up), we need to include 92 patients in each arm, i.e. 184 in total.

As for the cohort study, we expect women to choose both treatment options in a similar ratio (1:1). Simultaneously, a cohort study will be performed for eligible patients who are not willing to be randomised because they have a distinct preference for one of the two treatment arms. We intend to include 100 women in each treatment arm to enable standardization by inverse probability weighting, which means 200 patients in total. The expected inclusion period is 24 months while the follow-up period is 18 months.

Statistical Analysis

Primary and secondary study parameter(s)

Data analysis will be by both intention to treat and per protocol analysis. The primary outcome (successful pain relief) as well as the secondary outcome (recurrence rate) will be expressed as relative risks with 95% CI and as odds ratio (OR) with 95% CI, controlled for centre by using a logistic regression analysis. Differences between groups for change over time will be analysed with Kaplan–Meier analysis and a log rank test, and we will control for centre in a Cox regression analysis. To assess differences in secondary continuous outcomes, such as pain on a continuous scale and QoL and affective symptom measures, we will use linear mixed models. The per protocol analysis will be performed for participants that did not cross over to the other treatment arm and had a follow-up time of at least 12 months. In case of missing outcome data at 12 and 18 months, a sensitivity analysis will be performed using a last case carried forward. With regard to the remaining secondary outcomes, between-group difference of the proportions and means will be expressed as two-sided 95% CI at 6, 12 and 18 months. Multiple imputation will be used in case of missing co-variables.

Cost-effectiveness

The aim of the economic evaluation is to relate the incremental costs of laparoscopic surgical treatment (intervention) in comparison to treatment with medication (analgesics and/or hormones, control) to the incremental health effects. Both a cost-effectiveness analysis and a cost-utility analysis will be performed from a societal and healthcare perspective according to Dutch guidelines with a time horizon of 18 months (Zorginstituut Nederland, 2016).

Measurement and valuation of costs

Costs will be measured from a societal perspective using web-based questionnaires based on the Medical Consumption Questionnaire (iMCQ) and Productivity Cost Questionnaire (iPCQ) after 6, 12 and 18 months of follow-up. Cost categories included are as follows:

- Healthcare costs (primary and secondary care, complementary care and home care);
- Lost productivity costs (absenteeism from paid and unpaid work, and presenteeism);

- Patient costs (informal care and other care services paid for by patients themselves).

Valuation will be carried out according to Dutch costing guidelines (Hakkaart-Van Roijen *et al.*, 2016). For the valuation of healthcare utilization, lost productivity and informal care, the Dutch standard costs will be used. Medication use will be valued using prices of the Royal Dutch Society for Pharmacy. Patient and family costs other than informal care will be valued using self-reported prices. For the valuation of absenteeism from paid work, the friction cost approach will be used.

Patient outcome analysis in the economic evaluation

The following effect measures will be included in the economic evaluation:

- Successful pain reduction (defined as 30% reduction in pain);
- Recurrence rate defined as either recurrence of pain or the recurrence of ovarian endometriomas (ultrasound);
- QALY (EuroQoL-5 Dimensions—5 Levels (EQ-5D-5L) with Dutch reference values) (Versteegh *et al.*, 2016).

Missing cost and effect data will be imputed using multiple imputation according to the MICE algorithm developed by van Buuren (van Buuren *et al.*, 1999). Rubin's rules will be used to pool the results from the different multiple imputed datasets. Bivariate regression analyses will be used to estimate cost and effect differences between intervention and control while adjusting for confounders if necessary. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in the mean total costs between the treatment groups by the difference in mean effect between the treatment groups. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% CI around the cost differences and statistical uncertainty surrounding the ICERs. Uncertainty surrounding ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves will also be estimated showing the probability that the intervention is cost-effective in comparison with control for a range of different ceiling ratios, thereby showing decision uncertainty (Fenwick *et al.*, 2004).

Budget impact analysis

A budget impact analysis (BIA) will be conducted from the perspective of healthcare decision makers according to the Dutch guidelines (Hakkaart *et al.*, 2016) and the recommendations from Sullivan *et al.* (2014). In the BIA, data from the effectiveness and cost-effectiveness analyses regarding the differences in costs and health outcomes will be combined with national prevalence and incidence data to extrapolate the findings to a time horizon of 5 years. The BIA will be conducted from the government perspective (Budget Kader Zorg). Actual Dutch Healthcare Authority (NZA) tariffs will be used to calculate costs.

The budget analyses will differentiate between incidental and structural cost (savings) and take into account budgetary consequences of changes within these cost components. Sensitivity analyses will be performed for subgroups of patients, providing budget information for relevant subgroups to decision makers. In addition, sensitivity analyses will address the impact of variations of the main assumptions and input parameters for the BIA. The potential recurrence of symptoms and decreased ovarian reserve is one of the aspects that will be investigated, as this may reduce (but not nullify) cost savings.

Data management

The processing of personal data complies with the EU General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG, UAVG). Data will be collected in a web-based registry (Castor EDC®). The computer will randomly assign a unique numeric code for every subject that bears no relation to initials or date of birth. Data processing will be done with coded data, with the key (code to personal information linkage) only available to the local investigator and the research nurse working in the local centre. Persons who have access to the data include investigators, research staff, monitoring and quality assurance personnel. The personal data will be stored for a maximum of 15 years.

Monitoring

Monitoring will be performed in compliance with Good Clinical Practice and Dutch rules and regulations in order to achieve high quality research and secure patient safety. Qualified and independent monitors from the NVOG Consortium 2.0 will have access to the data and source documents of the trial. Based on the site-specific monitoring plan of the NVOG Consortium 2.0, monitoring visits in each participating Dutch site will be performed every year. The independent monitor will have access to the data and source documents of the trial to review the quality of the participating sites.

Ethical approval

This study is approved by the National Central Committee on Research involving Human Subjects (CCMO—NL67922.015.18) and by the institutional review board ethics committee of the Máxima Medical Centre (Ref. No. W18.149), covering all participating centres under Dutch law and by the boards of all participating hospitals. The trial is registered in the Dutch Trial Register (NTR No. 7689).

Discussion

The best treatment for ovarian endometrioma-related pain symptoms is unknown and this has been prioritised as a knowledge gap by NVOG and the ESHRE Guideline Development Group (NVOG 2016; Dunselman *et al.*, 2014). A review from Johnstone and Link *et al.* (2015) included articles describing the effectiveness of hormonal therapy and surgery in patients with an ovarian endometrioma. The reviewed RCTs did not support a single treatment modality in all cases. The literature reveals many unanswered questions and concludes that RCTs comparing primary treatment with medication to surgery for endometrioma-associated pain are needed. The current lack of evidence obstructs shared decision-making, since women cannot be informed in a balanced way about the risks and benefits of their therapeutic choices. The SOMA-trial is the first well-designed large RCT that will compare surgery to medication in women with an ovarian endometrioma in the absence of deep endometriosis. To our knowledge, there are currently no other trials that evaluate both treatment regimens in this patient population.

The SOMA-trial is a care evaluation. Both treatment with medication and surgery are part of the standard care offered to patients with ovarian endometriomas. Therefore, no additional risks are expected

for SOMA trial participants. Every medical treatment option will be considered as 'control' and will be compared to surgery as one group. Owing to the different application forms of medication and the physical component of surgical treatment, blinding is not feasible in this trial, which could result in detection and performance bias. The risk of bias is reduced by random allocation of patients to the medication or surgery group, respectively. Block randomisation, stratified for each participating centre, will be web-based which will reduce the chance of allocation bias. The sample size calculation was performed by a methodologist from the Consortium 2.0 (MvW). The same methodologist will also perform the data analysis by intention-to-treat principle, which will provide unbiased comparisons among the treatment groups. Because the SOMA-trial is a care evaluation, the intention-to-treat analysis will provide information on the outcomes of treatment strategy (medication versus surgery) rather than on a specific treatment with medication or surgical treatment option.

In order to answer the research questions regarding pain reduction, QoL, affective symptoms and cost-effectiveness, validated questionnaires will be used. These questionnaires have been validated for the English and Dutch language. The Endometriosis Health Profile-30 is a reliable and valid instrument that is particularly appropriate for use in clinical trials in order to assess the effectiveness of medical or surgical therapies for endometriosis on the health-related QoL (Jones *et al.*, 2004; van de Burgt *et al.*, 2011). The Generalized Anxiety Disorder-7 is a valid and efficient tool for screening for general anxiety disorder and assessing its severity in clinical practice and research (Spitzer *et al.*, 2006; Donker *et al.*, 2011). In addition to making criteria-based diagnoses of depressive disorders, the Patient Health Questionnaire-9 (PHQ-9) is also a reliable and valid measure of depression severity. These characteristics and its brevity make the PHQ-9 a useful clinical and research tool (Kroenke *et al.*, 2001; Zuithoff *et al.*, 2010). Costs will be measured from a societal perspective using internet questionnaires based on the iMCQ (Bouwmans, 2013a) and iPCQ (Bouwmans, 2013b). The EuroQol-5D will be used to determine the QALYs, as QALYs are widely used as an outcome for the economic evaluation of health interventions (Versteegh *et al.*, 2016).

The current care for women with endometriosis is described in the ESHRE guideline (Dunselman *et al.*, 2014) and is fully adopted by the NVOG. This guideline recommends clinicians to thoroughly counsel women with symptoms presumed to be due to endometriosis and to empirically treat them with adequate analgesia combined with hormonal treatment or surgery, taking into account the patient's preferences and the side effects, efficacy, costs and availability.

In this guideline, clinicians are recommended to prescribe hormonal treatment (hormonal contraceptives, progestagens, anti-progestogens or GnRH agonists as one of the options), as it reduces endometriosis-associated pain (Vercellini *et al.*, 1993; Brown *et al.*, 2010; Brown *et al.*, 2012). The effectiveness of analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) in treating endometriosis-associated dysmenorrhea is not well established owing to a lack of studies. However, there is good evidence that NSAIDs have a favourable effect on primary dysmenorrhea (Marjoribanks *et al.*, 2010). Surgery is also effective with regard to pain relief (Beretta *et al.*, 1998; Alborzi *et al.*, 2004). In addition, several arguments may be presented in favour of surgical removal of endometriomas. Firstly, if endometriomas are not removed, there is a small risk of rupture and torsion, causing potential loss of the ovary. Secondly, endometriomas are associated with a slightly increased risk of malignancy (OR = 1.34; 95% CI 1.03–1.75 (Borgfeldt and Andolf, 2004)), which may favour removal and histological examination even though prophylactic removal is not recommended (Dunselman *et al.*, 2014). Finally, removal of endometriomas may increase spontaneous pregnancy rates (Nezhat *et al.*, 1989; Vercellini *et al.*, 2006). However, we have to keep in mind that these studies were performed in an observational setting lacking a control group. Therefore, this favourable outcome could be overestimating the benefit of surgery. Furthermore, superficial peritoneal endometriosis may be more easily diagnosed in the surgical arm and we expect surgeons, given their surgical instinct and current best practice, to treat these lesions as well (e.g. excision or ablation). Although this fulfils the intention-to-treat basis, this might influence pain reduction in this group when compared to the control group. Therefore, the presence and (if applicable) subsequent treatment of superficial peritoneal endometriosis will be registered in the SOMA-trial. A disadvantage of surgical treatment could be a decrease in ovarian reserve following surgical excision through removal of cyst lining as well as parts of the underlying ovarian cortex. This is substantiated by the following observations: the rate of spontaneous ovulation is lower in operated ovaries, and serum levels of AMH decrease after surgical excision of an endometrioma (Kovačević *et al.*, 2018). In women selected for IVF, responsiveness to ovarian hyperstimulation, the number of developing follicles and the number of oocytes retrieved are reduced in the ovary where an endometrioma has been surgically treated (Somigliana *et al.*, 2003; Ragni *et al.*, 2005; Gupta *et al.*, 2006; Duru *et al.*, 2007). Last, but not least, after removal of bilateral endometriomas, clinical pregnancy and delivery rates after IVF are significantly impaired (Somigliana *et al.*, 2008).

For the management of pain symptoms, the ESHRE guideline did focus on improving pain prior to using ART, but had no recommendation for treatment of pain symptoms alone.

The SOMA-trial is the first RCT that will compare surgery to medication in women with an endometrioma. This study will add evidence-based information and will improve the quality of future guideline recommendations. Furthermore, it provides the establishment of a unique cohort for long-term follow-up in order to gain prospective knowledge about pregnancy and recurrence rates and malignant potential of endometriomas.

Authors' roles

All authors were involved in the design of this study and made substantial contributions to this manuscript. All authors critically revised and approved the final version of the manuscript.

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Conflict of interest

B.W.J. Mol reports consultancy for ObsEva, Merck KGaA and Guerbet. V. Mijatovic reports grants from Guerbet, grants from Merck and grants from Ferring outside the submitted work. All authors declare that they have no competing interests concerning this publication.

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