

## ORIGINAL ARTICLE

# Uterine-Artery Embolization versus Surgery for Symptomatic Uterine Fibroids

The REST Investigators\*

## ABSTRACT

**BACKGROUND**

The efficacy and safety of uterine-artery embolization, as compared with standard surgical methods, for the treatment of symptomatic uterine fibroids remain uncertain.

**METHODS**

We conducted a randomized trial comparing uterine-artery embolization and surgery in women with symptomatic uterine fibroids. The primary outcome was quality of life at 1 year of follow-up, as measured by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).

**RESULTS**

Patients were randomly assigned in a 2:1 ratio to undergo either uterine-artery embolization or surgery, with 106 patients undergoing embolization and 51 undergoing surgery (43 hysterectomies and 8 myomectomies). There were no significant differences between groups in any of the eight components of the SF-36 scores at 1 year. The embolization group had a shorter median duration of hospitalization than the surgical group (1 day vs. 5 days,  $P<0.001$ ) and a shorter time before returning to work ( $P<0.001$ ). At 1 year, symptom scores were better in the surgical group ( $P=0.03$ ). During the first year of follow-up, there were 13 major adverse events in the embolization group (12%) and 10 in the surgical group (20%) ( $P=0.22$ ), mostly related to the intervention. Ten patients in the embolization group (9%) required repeated embolization or hysterectomy for inadequate symptom control. After the first year of follow-up, 14 women in the embolization group (13%) required hospitalization, 3 of them for major adverse events and 11 for reintervention for treatment failure.

**CONCLUSIONS**

In women with symptomatic fibroids, the faster recovery after embolization must be weighed against the need for further treatment in a minority of patients. (ISRCTN.org number, ISRCTN23023665.)

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**U**TERINE FIBROIDS ARE THE MOST COMMON type of tumor in the female reproductive system. The presence of these tumors may cause menstrual disorder and can be associated with subfertility, miscarriage, and pressure effects.<sup>1</sup> For women who no longer plan to give birth, the established treatment is hysterectomy. In the United Kingdom, approximately 42,500 hysterectomies are performed annually, with approximately 30% indicated for fibroids (the second-most-frequent indication).<sup>2</sup> For women wishing to maintain their fertility, myomectomy is the principal option.

Uterine-artery embolization was introduced in 1995 as an alternative technique for treating fibroids.<sup>3</sup> Since then it has become increasingly accepted as a minimally invasive, uterine-sparing procedure, and more than 100,000 procedures have been performed during the past decade, mainly in the United States and Western Europe.<sup>4</sup> Early analysis of an open, prospective, voluntary U.S. registry including 3160 patients revealed major complications in 5.5% of patients at 30 days, with 0.1% requiring a hysterectomy.<sup>5</sup> In the United Kingdom, the National Institute for Health and Clinical Excellence issued guidelines in October 2004, stating that the procedure appeared to be safe for routine use and that the majority of patients have short-term symptomatic relief.<sup>6</sup> However, there has been a need for a careful assessment of the effects of the procedure on quality of life, particularly in comparison with standard surgical approaches.<sup>7</sup> We designed a randomized trial comparing uterine-artery embolization and surgery to assess quality of life and other outcomes at 1 year of follow-up.

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## METHODS

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We conducted the trial in 27 hospitals in the United Kingdom. Each hospital was associated with one of four regional centers. Patients were randomly assigned to study groups from November 2000 through May 2004. The 12-month follow-up was completed in September 2005.

The study was approved by the Multicenter Research Ethics Committee and local ethics committees at each center. All patients provided written informed consent. Potential patients were provided with written information describing the study and possible risks, including the unknown effect of embolization on subsequent pregnancy.

Experienced interventional radiologists performed the embolizations; patients were referred to specialist centers from district units in which embolization was not available. Hysterectomy and myomectomy were performed at each local center.

## PATIENTS

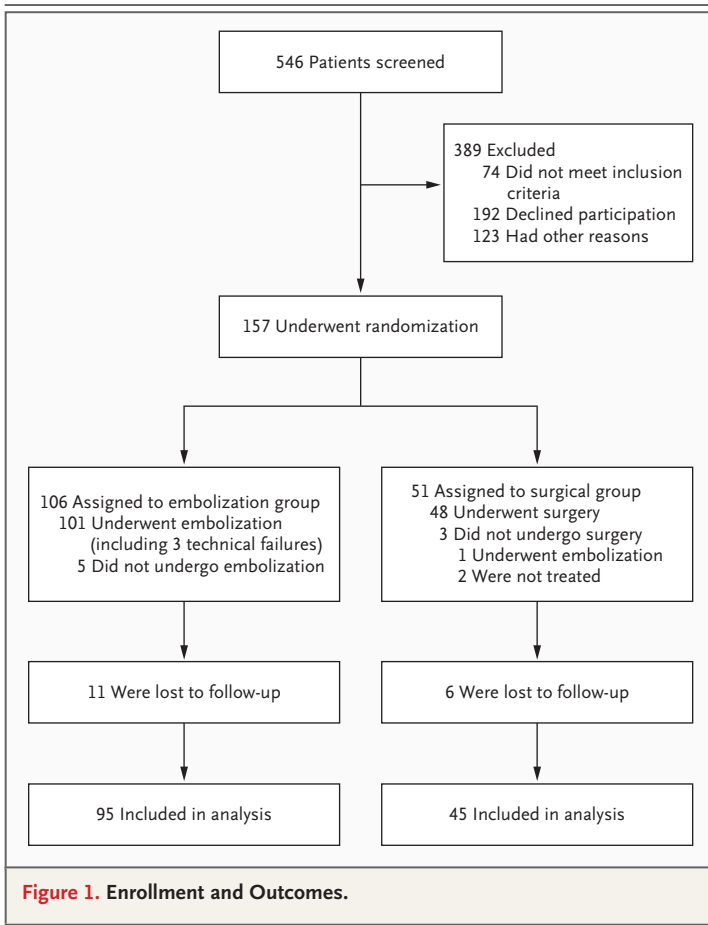
Women at least 18 years old were eligible if they had one or more fibroids of more than 2 cm in diameter that could be adequately visualized with the use of magnetic resonance imaging (MRI), caused symptoms (such as menorrhagia or pelvic pain and pressure), and were considered by the patient's physician to justify surgical treatment. Exclusion criteria included a contraindication to MRI, severe allergy to iodinated contrast media, subserosal pedunculated fibroids, recent or ongoing pelvic inflammatory disease, pregnancy, and any contraindication to surgery. There was no upper limit on the size or number of fibroids.

## PROCEDURES

Patients were randomly assigned to study groups according to a computer-generated schedule (permuted blocks) held by the trial coordinator. Randomization was stratified by center and was performed in a 2:1 ratio, with twice as many patients allocated to the embolization group as to the surgical group. This design allowed better characterization of the outcomes of the embolization procedure with minimal reduction in statistical power. The method of hysterectomy or myomectomy was not specified; the choice between these options depended on whether the patient wished to retain her uterus for fertility or other reasons. Both operations were included, since virtually all operations for fibroids are performed by the open route, allowing appropriate comparison of outcomes. The technique for embolization was also not specified, but both uterine arteries had to be embolized and the particle size of the embolic agent was standardized (500 to 710  $\mu\text{m}$ ).

## OUTCOME MEASURES

The primary outcome measure was quality of life, as assessed at 12 months on the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36), with scores ranging from 0 to 100, with higher scores indicating better function. This assessment has been validated in women with menorrhagia.<sup>8</sup> Secondary outcomes included an assessment of findings on the EuroQol-5D ques-



tionnaire, an instrument used to measure preferences for certain health outcomes, including hysterectomy,<sup>9,10</sup> with a range of scores paralleling that of the SF-36; an 11-point symptom score, ranging from -5 (markedly worse) to +5 (markedly better); the time until the resumption of usual activities; a satisfaction score measuring whether patients would recommend the procedure to a friend; a linear-analogue pain score at 24 hours; the presence or absence of complications; and treatment failure, defined as the need for subsequent intervention for symptom control, including hysterectomy or repeated embolization.

Complications were graded with the use of the classification system of the Society of Interventional Radiology, as recommended in the Standards of Practice<sup>11</sup> as follows: no therapy required or no consequence (grade 1); nominal therapy required or no consequence, including overnight admission for observation only (grade 2); therapy required, including minor hospitalization of less than 48 hours (grade 3); major therapy required, including an unplanned increase in the level of

care or hospitalization for at least 48 hours (grade 4); and permanent adverse sequelae (grade 5). Grades 1 and 2 were considered to be minor; grades 3 through 5 were considered to be major. Two of the investigators (a gynecologist and a radiologist) independently categorized the grades of complications. In 56% of cases, the investigators were in complete agreement; in 91% of cases, they were in agreement to within one grade of complication. In discordant cases, the worse grade was used. Major adverse events included any major complication, a life-threatening event, initial or prolonged hospitalization, an intervention required to prevent permanent impairment or damage, and death. Treatment failures requiring subsequent intervention were considered separately.

We assessed outcome measures (with the exception of the 24-hour pain score) at 1, 6, 12, and 21 months and annually thereafter. In this study, we present the 12-month results, with two exceptions: major adverse events requiring hospitalization and subsequent intervention for treatment failure, which are reported through September 2005 (maximum follow-up, 58 months).

#### ECONOMIC ANALYSIS

We prospectively collected data on the total use of financial resources up to 12 months after treatment. These data included the time in the operating room and recovery room, the total length of stay in the hospital, outpatient visits associated with the procedure, treatment failure, and any associated complications. We obtained unit costs for all resources used from routinely collected data and published literature; we used such data to determine the direct health care costs associated with each patient from the perspective of the National Health Service. Since the trial showed no significant differences between groups in the primary outcome, we considered the appropriate form of economic evaluation to be a cost-minimization analysis.<sup>12</sup> We calculated the 95% confidence intervals (CIs) for the differences in costs between groups with the use of the bias-corrected and accelerated bootstrap method.<sup>13</sup> We performed one-way sensitivity analysis on key unit cost components by varying one measure at a time.

#### STATISTICAL ANALYSIS

We analyzed all patients in the group to which they were randomly assigned, regardless of the treatment actually received. Analysis of covariance was used to compare quality-of-life scores (on the

basis of results on the SF-36 and EuroQol questionnaires) between groups, adjusting for baseline values. Other comparisons between groups were made with the use of a two-sided Student's t-test and the Mann-Whitney test for continuous data and the chi-square test for categorical data. The original power calculation required the enrollment of 200 patients to give a power of 90% to detect a difference of 10 points in the SF-36 score at 12 months (the primary end point) at the 0.05 significance level. Because of slower-than-expected recruitment, the decision was subsequently made to reduce the power to 80%, which required the enrollment of 150 patients.

An independent data and safety monitoring committee reviewed the results and serious adverse events every 12 months. The panel followed the highly conservative Haybittle-Peto approach of requiring a significance level of less than 0.001 in the comparison between groups before making any recommendation to terminate the trial prematurely.<sup>14</sup>

The manufacturers of the embolic agents used in the study (William Cook Europe, Cordis, and Biocompatibles) had no role in the design of the

study; data collection, analysis, and interpretation; or the writing of the final report. The Writing Committee members assume responsibility for the accuracy and completeness of the data and for the overall content and integrity of the article.

## RESULTS

A total of 157 women were randomly assigned to study groups: 106 to undergo uterine-artery embolization and 51 to undergo surgery, including 43 hysterectomies and 8 myomectomies (Fig. 1). Eight patients (5%) did not receive their allocated treatments (five in the embolization group and three in the surgery group). In addition, there was one technical failure in the surgical group (a myomectomy converted to hysterectomy owing to technical difficulties) and there were three technical failures in the embolization group (owing to difficulty in the identification or catheterization of one or both uterine arteries). All the hysterectomies and myomectomies were performed through an abdominal incision. The groups were well matched at baseline (Table 1).

**Table 1. Baseline Characteristics of the Patients.\***

| Characteristic                    | Embolization Group<br>(N=106) | Surgical Group<br>(N=51) | P Value |
|-----------------------------------|-------------------------------|--------------------------|---------|
| Age — yr                          | 43.6±5.5                      | 43.3±7.1                 | 0.77    |
| Largest fibroid diameter — cm     | 7.5±3.0                       | 8.5±3.9                  | 0.12    |
| Uterine volume — ml               | 579±447                       | 701±627                  | 0.23    |
| SF-36 score†                      |                               |                          |         |
| Physical function                 | 82±19                         | 77±20                    | 0.16    |
| Physical role                     | 51±41                         | 45±42                    | 0.35    |
| Bodily pain                       | 52±22                         | 50±22                    | 0.60    |
| General health                    | 61±19                         | 60±23                    | 0.92    |
| Vitality                          | 41±22                         | 42±23                    | 0.93    |
| Social function                   | 63±27                         | 58±30                    | 0.34    |
| Emotional role                    | 60±43                         | 57±43                    | 0.76    |
| Mental health                     | 63±18                         | 63±22                    | 0.91    |
| EuroQol score†                    | 70±16                         | 63±20                    | 0.04    |
| Main presenting symptom — no. (%) |                               |                          | 0.92    |
| No. of patients                   | 102                           | 50                       |         |
| Bleeding                          | 56 (55)                       | 29 (58)                  |         |
| Pain                              | 19 (19)                       | 7 (14)                   |         |
| Pressure                          | 23 (23)                       | 12 (24)                  |         |
| Other                             | 4 (4)                         | 2 (4)                    |         |

\* All study participants were premenopausal. Plus-minus values are means ±SD. SF-36 denotes Medical Outcomes Study 36-Item Short-Form General Health Survey.

† Scores on the SF-36 and EuroQol range from 0 (worst possible) to 100 (best possible).

**Table 2.** Effects of Uterine-Artery Embolization and Surgery on Measures of Quality of Life, Symptoms, and Resumption of Usual Activities.\*

| Effect                     | Embolization Group<br>(N = 106) | Surgical Group<br>(N = 51) | Absolute Difference<br>(95% CI)† | P Value |
|----------------------------|---------------------------------|----------------------------|----------------------------------|---------|
| <b>SF-36‡</b>              |                                 |                            |                                  |         |
| At 1 mo                    |                                 |                            |                                  |         |
| No. of patients            | 95                              | 47                         |                                  |         |
| Score                      |                                 |                            |                                  |         |
| Physical function          | 85±16                           | 57±25                      | -26 (-32 to -20)                 | <0.001  |
| Physical role              | 37±44                           | 11±24                      | -25 (-38 to -12)                 | <0.001  |
| Bodily pain                | 50±22                           | 44±24                      | -6 (-14 to 2)                    | 0.16    |
| General health             | 70 ±19                          | 74±17                      | 4 (-1 to 10)                     | 0.13    |
| Vitality                   | 47±22                           | 42±24                      | -6 (-13 to 1)                    | 0.11    |
| Social function            | 64±27                           | 44±29                      | -19 (-28 to -9)                  | <0.001  |
| Emotional role             | 72±41                           | 64±44                      | -7 (-22 to 7)                    | 0.32    |
| Mental health              | 72±17                           | 74±18                      | 2 (-3 to 8)                      | 0.39    |
| At 12 mo                   |                                 |                            |                                  |         |
| No. of patients            | 95                              | 47                         |                                  |         |
| Score                      |                                 |                            |                                  |         |
| Physical function          | 92±14                           | 89±20                      | 0 (-6 to 5)                      | 0.85    |
| Physical role              | 76±40                           | 81±34                      | 7 (-7 to 20)                     | 0.33    |
| Bodily pain                | 76±23                           | 80±26                      | 4 (-4 to 13)                     | 0.28    |
| General health             | 74±20                           | 79±17                      | 6 (0 to 12)                      | 0.07    |
| Vitality                   | 62±21                           | 67±22                      | 4 (-3 to 11)                     | 0.26    |
| Social function            | 84±23                           | 87±26                      | 4 (-4 to 12)                     | 0.35    |
| Emotional role             | 81±35                           | 87±30                      | 7 (-4 to 18)                     | 0.22    |
| Mental health              | 76±17                           | 76±21                      | -1 (-7 to 5)                     | 0.80    |
| <b>EuroQol‡</b>            |                                 |                            |                                  |         |
| At 1 mo                    |                                 |                            |                                  |         |
| No. of patients            | 92                              | 47                         |                                  |         |
| Score                      | 74±17                           | 67±19                      | -4 (-9 to 2)                     | 0.24    |
| At 12 mo                   |                                 |                            |                                  |         |
| No. of patients            | 93                              | 45                         |                                  |         |
| Score                      | 82±16                           | 83±14                      | 4 (-2 to 9)                      | 0.18    |
| <b>24-hour pain score§</b> |                                 |                            |                                  |         |
| No. of patients            | 99                              | 49                         |                                  |         |
| Score                      | 3.0±2.1                         | 4.6±2.3                    | 1.6 (0.8 to 2.3)                 | <0.001  |
| <b>Symptom score¶</b>      |                                 |                            |                                  |         |
| At 1 mo                    |                                 |                            |                                  |         |
| No. of patients            | 98                              | 48                         |                                  |         |
| Score                      | 1.5±2.4                         | 2.8±2.6                    | 1.3 (0.4 to 2.2)                 | 0.004   |
| At 12 mo                   |                                 |                            |                                  |         |
| No. of patients            | 95                              | 45                         |                                  |         |
| Score                      | 3.6±2.0                         | 4.3±1.7                    | 0.7 (0.1 to 1.4)                 | 0.03    |

**Table 2. (Continued.)**

| Effect   | Embolization Group<br>(N=106) | Surgical Group<br>(N=51) | Percent Difference<br>(95% CI) <sup>†</sup> | P Value |
|--|-------------------------------|--------------------------|---|---------|
| <b>Patients who would recommend treatment to a friend</b>          |                               |                          |   |         |
| At 1 mo — no./total no. (%)  | 74/97 (76)                    | 37/48 (77)               | 1 (–14 to 15)                               | 0.92    |
| At 12 mo — no./total no. (%)                                       | 84/95 (88)                    | 42/45 (93)               | 5 (–5 to 15)                                | 0.32    |
| <b>Hospital stay and time until resumption of usual activities</b> |                               |                          |   |         |
|  |                               |                          | <b>95% CI<sup>  </sup></b>                  |         |
| <b>Hospital stay — day</b>   |                               |                          |   |         |
| Median   | 1                             | 5                        | 3 to 4                                      | <0.001  |
| Interquartile range  | 1–2                           | 3–6                      |   |         |
| <b>Made cup of tea — day</b>                                       |                               |                          |   |         |
| Median   | 2                             | 6                        | 3 to 5                                      | <0.001  |
| Interquartile range  | 1–3                           | 4–11                     |   |         |
| <b>Made meal — day</b>   |                               |                          |   |         |
| Median   | 6                             | 17                       | 6 to 14                                     | <0.001  |
| Interquartile range  | 3–9                           | 10–23                    |   |         |
| <b>Drove car — day</b>   |                               |                          |   |         |
| Median   | 8                             | 34                       | 22 to 30                                    | <0.001  |
| Interquartile range  | 5–10                          | 27–43                    |   |         |
| <b>Returned to work — day</b>                                      |                               |                          |   |         |
| Median   | 20                            | 62                       | 28 to 53                                    | <0.001  |
| Interquartile range  | 14–30                         | 39–90                    |   |         |
| <b>Had sexual intercourse — day</b>                                |                               |                          |   |         |
| Median   | 21                            | 53                       | 18 to 45                                    | <0.001  |
| Interquartile range  | 13–31                         | 29–91                    |   |         |

\* Plus–minus values are means  $\pm$ SD. CI denotes confidence interval, and SF-36 Medical Outcomes Study 36-Item Short-Form General Health Survey.

<sup>†</sup> For the differences in quality-of-life scores (on the SF-36 and EuroQol) between the surgical group and the embolization group, the analysis of covariance adjusted for baseline values, so the differences between the groups are not the simple numerical differences. Negative values indicate higher scores in the embolization group, and positive numbers indicate higher scores in the surgical group.

<sup>‡</sup> Scores on the SF-36 and EuroQol range from 0 (worst possible) to 100 (best possible).

<sup>§</sup> Scores on the 24-hour pain scale range from 0 (no pain) to 10 (continuous, severe pain) on a continuous scale.

<sup>¶</sup> Symptom scores range from –5 (markedly worse) to +5 (markedly better) on an integer scale.

<sup>||</sup> The 95% CIs are for the difference in medians. Data are excluded for patients who did not have a response to a category (e.g., nondrivers).

#### PRIMARY OUTCOME

The primary outcome measure (the SF-36 quality-of-life score at 12 months) was available for 140 of the 157 women (89%). The results on the SF-36 and EuroQol at 1 and 12 months are shown in Table 2. There were no significant differences between groups in any of the eight components of the SF-36 at 12 months, although at 1 month, the embolization group had significantly greater improvement in scores than the surgery group for the physical function, social function, and physical-role components.

#### SECONDARY OUTCOMES

Women in the surgical group had a significantly higher pain score at 24 hours (Table 2). Symptom scores at 1 and 12 months after the procedure were significantly better in the surgical group. At 12 months, the percentage of women who reported that they would recommend their treatment to a friend was high in both treatment groups (93% in the surgical group and 88% in the embolization group) ( $P=0.32$ ).

The median hospital stay after uterine-artery embolization was significantly shorter than that

after surgery (1 day vs. 5 days,  $P < 0.001$ ). The median time until patients could resume all recorded usual activities was significantly lower in the embolization group (Table 2).

#### MINOR COMPLICATIONS

Minor complications were reported by 36 women (34%) in the embolization group and 10 (20%) in the surgical group ( $P = 0.06$ ) (Table 3). Minor complications were usually related to the postembolization syndrome (52%), which includes pyrexia, pain, and elevated inflammatory markers, in the embolization group and to minor infections (25%) in the surgical group.

#### MAJOR ADVERSE EVENTS

There were 16 major adverse events (15%) in the embolization group, as compared with 10 (20%) in the surgical group during a median follow-up of 32 months (interquartile range, 23 to 41) (Table 3). When we categorized these events with respect to the timing of their occurrence (i.e., during the hospital stay, during the first year of follow-up, or after the first year), 8 of the 10 major adverse events in the surgical group occurred during the hospital stay, whereas 15 of the 16 events in the embolization group occurred after discharge from the hospital.

#### TREATMENT FAILURES

Twenty-one patients (20%) in the embolization group required an additional invasive procedure (hysterectomy or repeated uterine-artery embolization) for continued or recurrent symptoms, 10 during the first 12 months of follow-up (2 of which were due to technical failures) and 11 subsequently. In the surgical group, there was one conversion of myomectomy to hysterectomy at the time of the primary procedure.

#### ECONOMIC ANALYSIS

Uterine-artery embolization was associated with a lower use of resources than was surgery at the initial hospitalization. However, during the 1-year follow-up period, when compared with surgery, embolization was associated with more imaging studies and a longer mean hospital stay.

Table 4 shows the results of the cost-minimization analysis and one-way sensitivity analysis.<sup>15-18</sup> Uterine-artery embolization was associated with total costs significantly lower than those for surgery (mean difference, £951 [\$1,712 at an exchange

rate of £1=\$1.80]; 95% CI, £329 to £1480 [\$592 to \$2,664], suggesting that at 1 year, embolization was more cost-effective than surgery for patients with symptomatic uterine fibroids, from the perspective of the National Health Service. Sensitivity analyses showed the result was robust when assumptions were varied around the cost of MRI and the embolization agent. The results were sensitive to the cost per inpatient-day, with no significant difference in costs between the two procedures when the cost per inpatient-day was halved. Threshold analysis indicated that uterine-artery embolization was more cost-effective over a 12-month period only if the cost per inpatient-day exceeded £291 (\$524).

#### OTHER OUTCOMES

Through September 2005, eight pregnancies had occurred in five women (seven in the embolization group and one in the myomectomy group). Four of the pregnancies resulted in miscarriage, three in successful live births (two by cesarean section, including one patient from each group, and one spontaneous vertex delivery), and one intrauterine death of the fetus at 33 weeks (with no abnormalities found on postmortem examination).

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## DISCUSSION

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In this randomized trial comparing uterine-artery embolization with standard surgical treatment for women with symptomatic fibroids, we found no significant differences between the groups in measures of quality of life at 12 months, although women in both groups had substantial improvements in each component of the SF-36 score relative to baseline. In contrast, the adverse-event profiles were very different. Surgery was associated with the expected acute morbidity, but only one major adverse event was recorded after the initial hospital stay. Uterine-artery embolization was associated with a significantly faster recovery, including the resumption of usual activities.

Rates of minor complications or major adverse events did not differ significantly between the study groups, although the nature and timing of these events varied between groups; major adverse events in the surgical group typically occurred during the hospital stay, whereas in the embolization group, such events more commonly occurred after hospital discharge. Of note, three of the major adverse events in the embolization group

**Table 3. Minor Complications within First Year and Major Adverse Events and Interventions for Treatment Failure Occurring during Median Follow-up of 32 Months.\***

| Variable  | Embolization Group (N = 106)   | Surgical Group (N = 51)  |
|---|--|--|
| <b>Minor complications at 1 yr</b>                  |  |  |
| Patients reporting any minor complication — no. (%) | 36 (34)  | 10 (20)  |
| Complications reported                              |  |  |
| Total number  | 50   | 16   |
| Type of complication                                | Postembolization syndrome (26 patients), vaginal discharge (9), sepsis (6), other (9)  | Infection (4 patients), hemorrhage (3), other (9)  |
| <b>Major adverse events</b>                         |  |  |
| Patients reporting any adverse event — no. (%)      | 16 (15)  | 10 (20)  |
| During hospital stay                                |  |  |
| Total number  | 1  | 8  |
| Type of event                                       | Severe vasovagal event requiring atropine (1 patient)  | Operative hemorrhage, with 1 requiring left oophorectomy (2 patients); anesthetic complication (2); wound infection (2); wound hematoma (1); urinary retention (1) |
| During first year of follow-up                      |  |  |
| Total number  | 12   | 2  |
| Type of event                                       | Breast cancer — both cases diagnosed 2 mo after treatment (2 patients); pain and pelvic infection requiring readmission at 1 and 4 wk (2); severe pain and fibroid expulsion at 3, 4, and 6 wk (3); hematometria at 6 mo — not treated (1); persistent severe pain requiring hysterectomy at 8 mo — necrotic fibroid tissue seen on pathological analysis (1); pelvic abscess requiring hysterectomy at 10 mo (1); temporary amenorrhea for 5 and 9 mo (2) | Wound exploration under general anesthetic (1 patient), wound infection at 3 wk (1)  |
| After first year of follow-up                       |  |  |
| Total number  | 3  | 0  |
| Type of event                                       | Death from adrenal cancer — diagnosis at 12 mo and death at 13 mo (1 patient); severe pain and fibroid expulsion at 13 mo (1); severe, persistent pain requiring hysterectomy at 15 mo — necrotic fibroid tissue seen on pathological analysis (1)   |  |
| <b>Interventions for treatment failure</b>          |  |  |
| Patients reporting any intervention — no. (%)       | 21 (20)  | 1 (2)  |
| During hospital stay                                |  |  |
| Total number  | 2  | 1  |
| Type of event                                       | Technical failure of procedure requiring hysterectomy (2 patients)   | Operative complication requiring conversion of myomectomy to hysterectomy (1 patient)  |
| During first year of follow-up                      |  |  |
| Total number  | 8  | 0  |
| Type of event                                       | Hysterectomy (4 patients), repeated embolization (4)   |  |
| After first year of follow-up                       |  |  |
| Total number  | 11   | 0  |
| Type of event                                       | Hysterectomy (8 patients), repeated embolization (3)   |  |

\* For major adverse events after 1 year, only those requiring hospitalization are reported. P = 0.047 for the comparison between the embolization group and the surgical group for minor complications. P = 0.22 for the comparison between the two study groups for major adverse events during the first year. The interquartile range for major adverse events and reinterventions for treatment failure was 23 to 41 months.

**Table 4. Results of Cost-Minimization Analysis and Sensitivity Analysis.\***

| Variable   | Embolization Group<br>(N=106) | Surgical Group<br>(N=51)<br><i>mean (95% CI)</i> | Difference†‡      |
|--|-------------------------------|--|-------------------|
| <b>Cost-minimization analysis</b>  |                               |  |                   |
| Mean cost per patient per year — £   | 1727 (1511 to 1943)           | 2673 (2402 to 2944)                              | 951 (329 to 1480) |
| Mean cost excluding patients with missing data                                     |                               |  |                   |
| Number of patients   | 93                            | 44   |                   |
| Cost per patient — £   | 1751 (1522 to 1980)           | 2702 (2414 to 2989)                              | 948 (398 to 1432) |
| <b>Sensitivity analysis‡</b>   |                               |  |                   |
| Cost of MRI and ultrasonography doubled — £  | 2027 (1811 to 2242)           | 2683 (2414 to 2952)                              | 658 (131 to 1137) |
| Cost of MRI and ultrasonography doubled, plus cost of embolization agent (£95) — £ | 2098 (1880 to 2316)           | 2684 (2415 to 2952)                              | 599 (41 to 1186)  |
| Cost of hospital stay reduced to 65% (£316) — £                                    | 1379 (1233 to 1525)           | 1844 (1700 to 2018)                              | 468 (113 to 828)  |
| Cost per inpatient day reduced to 50% (£243) — £                                   | 1229 (1110 to 1348)           | 1489 (1349 to 1628)                              | 257 (–89 to 571)  |

\* £1.00 equals \$1.80. Calculations were based on the following unit-cost estimates updated to 2004 prices: uterine-artery embolization, £1.53 per minute; surgery, £3.08 per minute; embolic agent, £75 per bottle (times four bottles); hospital stay, £485.55 per day; magnetic resonance imaging (MRI), £152.53 per scan; ultrasonography, £17.50 per scan; and outpatient consultation, £77 per visit.

† The differences in costs between the surgical group and the embolization group were calculated with the use of a bootstrap method, so the differences between the groups are not simple numerical ones.

‡ One-way sensitivity analyses were performed on key unit-cost components by varying one measure at a time.

were cancers (two breast cancers, both detected within 2 months after the intervention, and one adrenal cancer), which were highly unlikely to be related to treatment.

At 1 year, however, 10 of the 106 women in the embolization group had required a secondary intervention to treat persistent or recurrent symptoms. After the first year of follow-up, 11 additional women were readmitted for the same indication. These findings are consistent with data from uncontrolled case series indicating complications and treatment failures up to 48 months after embolization.<sup>19,20</sup>

The cost-minimization analysis showed that at 1 year, embolization was more cost-effective than surgery. This finding supports that of one other study addressing the cost-effectiveness of uterine-artery embolization versus surgery.<sup>21</sup> Ongoing follow-up will further assess the efficacy and cost-effectiveness of embolization.

We used a “pragmatic trial” design, in that the particular surgical interventions and technical aspects of the procedures were not dictated by protocol. We included women undergoing either hysterectomy or myomectomy in the surgical group, although in fact only eight women underwent myomectomy. Our primary outcome mea-

sure, the SF-36 score, did not take specific fibroid-related symptoms into account, although it was sensitive to changes in quality of life that resulted from successful treatment of menstrual symptoms.<sup>8</sup> This fact is important, given the cyclical nature of the patients’ menstrual problems. We did not collect data on loss of menstrual blood; comparisons of this measure between groups would not be meaningful, given that only eight women in the surgical group underwent myomectomy.

Two other randomized, controlled trials compared uterine-artery embolization with hysterectomy.<sup>22,23</sup> The first study used a controversial randomized-consent methodology,<sup>24</sup> in which women who were randomly assigned to the hysterectomy group were not informed about the study or about the possibility of an alternative treatment (i.e., uterine-artery embolization). In addition, this study was small (enrolling only 57 women) and used the length of hospital stay as the primary outcome measure; hospital stays were significantly shorter after uterine-artery embolization, with similar complication rates in both groups.<sup>22</sup> The second trial comparing embolization and hysterectomy enrolled 177 patients; at 6 weeks after treatment, the embolization group

had a significantly shorter mean hospital stay but a higher rate of minor complications and re-admission.<sup>23</sup>

Limitations of our trial must be acknowledged. The original target number of 200 patients was reduced to 150 because of difficulties in recruitment. Thus, the 95% CIs for the differences between groups indicate that plausible results include as much as a 10-point difference between groups in some components of the SF-36. However, there is no suggestion of clinically important differences. The inclusion of only a small number of patients who underwent myomectomy in the surgical group made it difficult to compare such therapy with uterine-artery embolization. It also suggests that a direct comparison of these two treatments would be difficult to perform unless recruitment involved a very large population base. The use of the time until resumption of usual activities as a secondary outcome must be viewed cautiously, since such an interval could be biased by the patient's expectation (or caregivers' guidance) regarding the time to recovery.

The results of our study make clear that the choice between surgery and uterine-artery embolization for symptomatic uterine fibroids involves tradeoffs. The advantages of embolization — including a significant reduction in the length of the hospital stay and 24-hour pain level and a more rapid return to usual activities — need to be weighed against the risk of treatment failure requiring a second intervention and the possibility, although infrequent, of major late adverse events. Longer-term follow-up is necessary, with attention to the need for repeated intervention, to inform future decision making.

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#### APPENDIX

In addition to the Writing Committee, the following investigators participated in the REST trial: **Data and Trial Management:** L.S. Murray (trial coordinator), H. Dewart, B. Ferrie, M. Khaund, L. Lawrie, D. Lyons, F. McLean. **Data Monitoring Committee:** I.T. Cameron (chair), H. Critchley, J. Reidy, P. Warner. **Trial Management Committee:** J.G. Moss (chair), R.D. Edwards, M.A. Lumsden, L.S. Murray (trial coordinator), G.D. Murray, S. Twaddle. **Trial Steering Committee:** J.G. Moss (chair), R.D. Edwards, M.A. Lumsden, L.S. Murray, G.D. Murray, S. Twaddle, C. West, I. Gillespie, M. Thomson, G. Houston, K. Cooper, P. Thorpe. The following centers and investigators (all in the United Kingdom) participated in the trial: *Aberdeen Royal Infirmary, Aberdeen* — K. Cooper, P. Thorpe; *Bolton Royal Infirmary, Lancashire* — J. Tuck; *Murrayfield Hospital, Edinburgh* — I. Gillespie; *Crosshouse Hospital, Kilmarnock* — G. Irvine; *Eastern General Hospital, Edinburgh* — C. Tay; *Edinburgh Royal Infirmary* — C. West, I. Gillespie; *Falkirk Royal Infirmary, Falkirk* — O. Prabu; *Forth Park, Kirkcaldy* — S. Pinion; *Glasgow Royal Infirmary, Glasgow* — M. Rodger, A. Reid; *Hairmyres Hospital, Lanarkshire* — K. Spowart; *Hull Royal Infirmary, Hull* — J. Killick, A. Nicholson; *Inverclyde Hospital, Greenock* — L. Cassidy; *Monklands Hospital, Lanarkshire* — V. Harper; *Ninewells Hospital, Dundee* — M. Thomson, G. Houston; *Perth Royal Infirmary, Perth* — D. Phillips; *Queen Margaret's Hospital, Dunfermline* — S. Pinion; *Raigmore Hospital, Inverness* — L. Caird, D. Nicholls; *Ross Hall BMI Hospital, Glasgow* — J. Moss; *St. John's Hospital, Livingstone* — P. Dewart; *Southern General Hospital, Glasgow* — M. Carty, G. Urquhart; *Stirling Royal Infirmary, Stirling* — F. Morrison; *Stobhill Hospital, Glasgow* — M. Deeney; *Vale of Leven Hospital, Alexandria* — M. Haxton; and *Western Infirmary, Glasgow* — M.A. Lumsden, N. McMillan.

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