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Abstract

EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy

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Objectives: To test the null hypothesis of no significant difference between laparoscopic hysterectomy (LH), abdominal hysterectomy (AH) and vaginal hysterectomy (VH) with regard to each of the outcome measures of the trial, and also to assess the cost-effectiveness of the alternatives.
Design: Patients were allocated to either the vaginal or abdominal trial by the individual surgeon according to their usual clinical practice. After allocation patients were then randomised to receive either LH or the default procedure in an unbalanced 2:1 manner.
Setting: Forty-three surgeons from 28 centres throughout the UK and two centres in South Africa took part in the study.
Participants: Patients with gynaecological symptoms that, in the opinion of the gynaecologist and the patient, justified hysterectomy.
Interventions: Of 1380 patients recruited to the study, 876 were included in the AH trial and 504 in the VH trial. In the AH trial, 584 patients had a laparoscopic type of hysterectomy (designated ALH) and 292 had a standard AH. In the VH trial 336 had a VLH and 168 had a standard VH. A cost–utility analysis was undertaken based on a 1-year time horizon. Quality-adjusted life years (QALYs) were estimated using the EQ-5D.
Results: Compared with AH, LH was associated with a higher rate of major complications, less postoperative pain and shorter hospital stay, but took longer to perform. Securing the ovarian pedicles with laparoscopic sutures was used in only 7% of cases but was associated with 25% of the complications. At the 6 weeks postoperative point, ALH was associated with a significantly better physical component of the SF-12 (QoL questionnaire), better body image scale scores and a significantly increased frequency of sexual intercourse than AH. These differences were not observed at either 4 or 12 months after surgery. There were no significant differences in any measured outcome between LH and VH except that VLH took longer to perform and was associated with a higher rate of detecting unexpected pathology. Compared with VH, VLH had a higher mean cost per patient of £401 and higher mean QALYs of 0.0015, resulting in an incremental cost per QALY gained of £267,333. The probability that VLH is cost-effective was less than 50% for a large range of willingness to pay values for an additional QALY. Compared with AH, ALH had a higher mean cost per patient of £186 and higher mean QALYs of 0.007, resulting in an incremental cost per QALY gained of £26,571.
Conclusions: ALH is associated with a significantly higher risk of major complications and takes longer to perform than AH. ALH is, however, associated with less pain, quicker recovery and better short-term QoL after surgery than AH. The cost-effectiveness of ALH is finely balanced and is also influenced by the choice of

reusable versus disposable equipment. Individual surgeons must decide between patient-orientated benefits and the risk of severe complications. VLH was not cost-effective relative to VH. Recommendations for future research include the application and relevance of QoL measures following hysterectomy, and long-term follow-up; patient preferences; reducing complication rates; improving gynaecological surgical training; surgeon effect in surgery trials; care pathways for hysterectomy; additional pathology identification in LH and meta-analysis/further trial of VH versus LH.

Contents

List of abbreviations

AH	abdominal hysterectomy
ALH	laparoscopic hysterectomy arm of the abdominal hysterectomy trial
BIS	body image scale
BMI	body mass index
CI	confidence interval
DVT	deep vein thrombosis
EQ-5D	EuroQol (EQ) 5D Instrument (a generic preference-based measure of health status)
HDW	high-dependency ward
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IQR	interquartile range
ITT	intention-to-treat
LAVH	laparoscopic-assisted vaginal hysterectomy
LH	laparoscopic hysterectomy
LSH	laparoscopic supracervical hysterectomy
NICE	National Institute for Clinical Excellence
NYCTRU	Northern and Yorkshire Clinical Trials and Research Unit
OR	odds ratio
QALY	quality-adjusted life-year
QoL	quality of life
SAQ	sexual activity questionnaire
SD	standard deviation
SE	standard error
SF-12	Short Form with 12 Items
TLH	total laparoscopic hysterectomy
VAS	visual analogue score
VH	vaginal hysterectomy
VLH	laparoscopic hysterectomy arm of the vaginal hysterectomy trial

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Introduction

The introduction of a third method of hysterectomy [laparoscopic hysterectomy (LH)] resulted in the urgent need to determine the appropriate role for the new laparoscopic approach before it became established into routine clinical practice. In 1992–3, before the introduction of LH, abdominal hysterectomy (AH) was used in 81% of the 72,269 hysterectomies performed in England and Wales. Direct comparison between the established techniques was difficult because most gynaecologists regarded the clinical indications for each procedure to be different. A study was therefore set up to compare both standard abdominal and vaginal (VH) methods of hysterectomy with LH, to give indications about the relative roles of all three procedures in this most commonly performed and important surgical operation.

Design

The study was of two parallel, unblinded, multi-centre randomised trials that compared LH with AH and VH. Patients were allocated to either the vaginal or abdominal trial by the individual surgeon according to their usual clinical practice. After allocation to a particular trial, the patient was then randomised to receive either LH or the default procedure in an unbalanced 2:1 manner; 63.5% of patients were allocated to the AH trial and 36.5% to the VH trial.

Setting

A total of 43 surgeons from 28 centres throughout the UK and two centres in South Africa took part in the study.

Subjects

A total of 1380 patients were recruited to the study, of whom 876 were included in the AH trial and 504 in the VH trial. In the AH trial, 584 patients had a laparoscopic type of hysterectomy (designated ALH) and 292 had a standard AH. In the VH trial 336 had a VLH and 168 had a standard VH.

Objectives

The objective of the study was to test the null hypothesis of no significant difference between LH and AH and VH with regard to each of the outcome measures of the trial, and also to assess the cost-effectiveness of the alternative procedures.

Outcome measures

The primary end-point of the trial was the occurrence of death or major complications (haemorrhage requiring blood transfusion, haematoma requiring transfusion/surgical drainage, bowel, bladder or urinary tract trauma, unintended laparotomy, wound dehiscence, pulmonary embolus and major anaesthetic problems). The secondary end-points were minor complication rates, blood loss (intraoperatively), pain assessment, sexual activity, body image, health status, quality of life (QoL) and resource use.

Sample size

The sample size for the AH trial was calculated from a previous study which indicated a 9% major complication rate in AH cases. From previous work we expected a 50% reduction in major complications with LH, which would require 487 patients in each arm to detect. In the same study, the rate of complications noted for VH was only 4%. To detect a similar rate of reduction would require 1141 patients per treatment arm. As VH was relatively infrequently performed, we did not expect to recruit this number but rather to collect as much data as possible as it would represent the largest such trial of VH ever performed and potentially be of value in a meta-analysis.

Economic evaluation methods

A cost–utility analysis was undertaken based on a 1-year time horizon. Costs were estimated from the perspective of the UK NHS. Resource use data included theatre resources, hospital stay and costs incurred during the postoperative period. Quality-

adjusted life years (QALYs) were estimated using the EQ-5D, which was administered at baseline and at 6 weeks, 4 months and 1 year after hospital discharge. Two comparisons were undertaken: VLH (n = 324) versus VH (n = 163) and ALH (n = 573) versus AH (n = 286). To account for the skewed nature of the data, 95% confidence intervals for the differential costs and QALYs were calculated using bias-corrected non-parametric bootstrapping. Missing resource use and EQ-5D data were imputed using a multivariate multiple imputation procedure. To account for uncertainty due to sampling variation, cost-effectiveness acceptability curves were plotted. Given the data collected within the trial, this curve shows the probability of laparoscopic-assisted hysterectomy being more cost-effective than conventional hysterectomy for different maximum levels that the decision-maker may be willing to pay for an additional QALY.

Results

Clinical

Compared with AH, LH was associated with a higher rate of major complications (11.1 versus 6.2%, p = 0.02), less postoperative pain (visual analogue scale score of 3.51 versus 3.88, p = 0.01) and shorter hospital stay (3 versus 4 days), but took longer to perform (84 versus 50 minutes). Securing the ovarian pedicles with laparoscopic sutures was used in only 7% of cases but was associated with 25% of the complications. At the 6 weeks postoperative point, ALH was associated with a significantly better physical component of the health survey questionnaire (SF-12), better body image scale (BIS) scores and a significantly increased frequency of sexual intercourse than AH. These differences were not observed at either 4 months or 12 months after surgery. There were no significant differences in any measured outcome between LH and VH except that VLH took longer to perform (72 versus 39 minutes) and was associated with a higher rate of detecting unexpected pathology (16.4 versus 4.8%, $p < 0.001$).

Economic

Compared with VH, VLH had a higher mean cost per patient of £401 [95% confidence interval (CI) £271 to £542] and higher mean QALYs of 0.0015 (95% CI –0.015 to 0.018), resulting in an incremental cost per QALY gained of £267,333. The probability that VLH is cost-effective was < 50% for a large range of willingness to pay values for an additional QALY. Compared with AH, ALH had a higher mean cost per patient of £186 (95% CI –£26 to £375) and higher mean QALYs of 0.007 (95% CI –0.008 to 0.023), resulting in an incremental cost per QALY gained of £26,571. If the NHS is willing to pay £30,000 for additional QALYs, the probability that ALH is cost-effective is 56%. The cost-effectiveness of laparoscopic procedures was sensitive to assumptions about the balance of reusable and disposable theatre equipment.

Conclusions

ALH is associated with a significantly higher risk of major complications and takes longer to perform than AH. ALH is, however, associated with less pain, quicker recovery and better short-term QoL after surgery than AH. The cost-effectiveness of ALH is finely balanced and depends on the threshold value the NHS attaches to an additional QALY and the error probability that the system is willing to accept in making its decision. Cost-effectiveness is also influenced by the balance of reusable equipment versus disposable consumables used during ALH. Individual surgeons must determine the optimum balance between patient-orientated benefits and the risk of severe complications. The clinical results from the vaginal trial were inconclusive as the study was under-powered. VLH was not cost-effective relative to VH.

Recommendations for future research

1. Application and relevance of QoL measures following hysterectomy, and long-term follow-up.
2. Patient preferences – balance between risks and benefits of the various forms of hysterectomy.
3. Reducing complication rates.
4. Improving gynaecological surgical training.
5. Surgeon effect in surgery trials.
6. Care pathways for hysterectomy.
7. Additional pathology identification in LH.
8. Meta-analysis/further trial of VH versus LH.

Chapter 1
Introduction

In 1996, Stovall and Summitt[1] asked the question, "Laparoscopic hysterectomy – is there a benefit?" They concluded that "to determine the appropriate role for this new procedure, gynaecologic surgeons must begin to conduct well-designed clinical trials that examine not only the short-term surgical outcomes, but also the overall economics of the procedure and the quality of life that results." Using this as a brief, the E**VAL**UATE trial aimed to assess the relative roles of **V**aginal, **A**bdominal and **L**aparoscopic hysterectomy in routine gynaecological practice.

In particular, there was an urgent need to define the role of the laparoscopic approach to hysterectomy before this procedure was introduced extensively into clinical practice. The possible benefits of this new method for the patient and the NHS were potentially considerable. There were also risks and potential problems.

Clinical indications for hysterectomy

Hysterectomy is indicated for women with dysfunctional uterine bleeding, uterine fibroids, prolapse, endometriosis, adenomyosis, pelvic pain, premalignant changes in cervix and endometrium and cancer. The procedure is a major surgical operation that is indicated only when appropriate drugs or simpler procedures are ineffective or inappropriate.

Conservative surgical procedures such as endometrial resection or ablation and myomectomy are often used as less invasive alternatives to hysterectomy.

Abdominal hysterectomy (AH)

Throughout the world, the abdominal approach is most commonly used. In England in 1992–93, 81% of 72,269 hysterectomies were performed by the abdominal method.[2] The VALUE national hysterectomy study[3] reported that the proportions of women having abdominal, vaginal or laparoscopically assisted hysterectomy were 67, 30 and 3%, respectively. Although frequently performed, abdominal hysterectomy (AH) was associated with a greater morbidity (e.g. haemorrhage, infection and wound dehiscence) than vaginal hysterectomy (VH). Dicker and colleagues[4] reported an overall complication rate of 43% with AH compared with 25% with VH. The main disadvantage of the abdominal approach is the need for a long transabdominal wall incision. This incision produces significant scarring which contributes to postoperative pain and morbidity, thus influencing the length of hospital stay.

Vaginal hysterectomy (VH)

The vaginal approach to hysterectomy enables the uterus to be removed without the need for an abdominal incision. VH was associated with a lower morbidity and shortened hospital stay (mean length of stay 3.8 days versus 4.5 days) in a previous report.[5] The national proportion of hysterectomies performed by the vaginal route has remained around 20–30% for many years. There is, however, a considerable variation in VH rates between individual consultants. Some gynaecologists only rarely perform a VH whereas others[6] perform more than 75% of all their hysterectomies by the vaginal method. Much of the variation may be accounted for by preference, training and skills of the individual surgeon. It may also be influenced by referral patterns. Most gynaecologists believe that the vaginal approach is more technically demanding, particularly when there is restricted vaginal access and/or minimal uterine descent. The presence of uterine or extrauterine pathology (e.g. leiomyomata or endometriosis, respectively) further increases the technical difficulties of the vaginal approach.

Laparoscopic hysterectomy (LH)

The laparoscopic approach to hysterectomy was first described by Reich and colleagues in 1989.[7] Their original description involved performing every step of the procedure with laparoscopic techniques. This is an elegant approach but is technically very demanding and often takes an unacceptably long time to complete.[8] The laparoscope can also be used to facilitate the

performance of a VH. Garry and colleagues[9] described a classification system of the types of LH based on the route by which the uterine artery is secured. If all the procedure is performed with laparoscopic techniques and no vaginal surgery is employed, the technique is called a total laparoscopic hysterectomy (TLH). If the upper uterine pedicles and the uterine artery are secured laparoscopically but the remainder of the uterus is freed and secured by vaginal techniques, the procedure is termed a laparoscopic hysterectomy (LH). If the laparoscopic portion of the operation is discontinued above the level of the uterine vessels, which are subsequently secured from below with vaginal techniques, the procedure can properly be called a laparoscopic-assisted vaginal hysterectomy (LAVH). Other variations in technique such as laparoscopic-assisted subtotal hysterectomy[10,11] and laparoscopic-assisted Doderlein hysterectomy[12] have also been described. LAVH may allow gynaecologists with ordinary rather than exceptional skills and interests to complete a larger proportion of their hysterectomy work without the need for large laparotomy scars.[13] It is possible that both operative benefits and complications may be related to the amount of the procedure completed laparoscopically. The main advantage of all these laparoscopic procedures is to permit both the removal of the uterus and a view of pelvic organs without the need for a large abdominal incision and its associated morbidity (see Appendix 1).

Background literature

There have been 12 previous studies, of which five were performed before the design of this trial (bolded names in *Table 1*), comparing outcomes for AH with those for LH.[14–25]

Of the studies published before this trial was undertaken, those by Nezhat and colleagues[20] in the USA, and Phipps and Nayak[21] and Raju and Auld[22] in the UK represented small studies with a combined total of 112 patients that concluded that the laparoscopic procedures took longer to perform and yet were associated with significantly less postoperative pain, shorter hospital stays and a faster return to work and normal activities. The study by Raju and Auld also reported a significant reduction in postoperative fever in the LAVH group. Later, Olsson's group[19] in Scandinavia reported a larger series of 143 patients in greater detail and Langenbrekke and colleagues[23] in Scandinavia reported a series of 100 cases. The latter study suggested that there was less blood loss with the laparoscopic approach. A study in Italy by Marana and colleagues[18] concentrated on a comparison of techniques in women exclusively with large uteri and reported similar outcomes. Each study suggested that the approaches seemed to be equally safe, with no observed difference in complication rate. Importantly, however, none of these studies was powered to detect clinically important differences in such complication rates (*Table 1*).

At the time of designing the trial, there were two small studies comparing VH with LH (bolded names in *Table 2*). The first, by Summitt and colleagues,[27] reported the use of these techniques for 'day case' hysterectomy and again found longer operating times with LH and no difference in other outcome measures. The other trial, by Richardson and colleagues,[28] was of 45 patients, again demonstrating longer operating times associated with the LH approach and with similar other measures of recovery and morbidity being the same.

Two studies compared LH versus VH versus AH (bolded names in *Table 3*), but neither of these had a randomised design.

No previous trials were powered to investigate the safety of the various procedures.

All of the previous studies were small, single-centre studies with the theoretical risks of selection and reporting bias. For many of these studies the method of selecting the treatment group was insecure or there was no randomisation. None of the above studies provided evidence upon which to base confident recommendations.

Designing the EVALUATE trial to investigate the role of a new approach to hysterectomy raised additional specific difficulties. In current practice there was no general agreement about when to perform a VH and when to perform an AH, and there are very wide variations between surgeons as to the proportion of each which were undertaken. A surgeon who performed a high proportion of hysterectomies by the vaginal route would be unimpressed by a trial of LH against AH because s/he might argue that most of the hysterectomies would have been better performed by the vaginal route and that the trial is merely comparing two bad techniques. Conversely, a trial of LH against VH would not provide a guide for action by clinicians who did most of their work by the abdominal route. The proponents of AH would argue that patients with pathology (endometriosis,

TABLE 1 *Summary of studies of LH versus AH*

Author[a]	Number of cases		Operating time (minutes)		Length of stay (days)		Recovery time (weeks)		Complications[b] (%)	
	LH	AH	LH	AH	LH	AH	LH	AH	LH	AH
Summitt *et al*., 1998[14]	34	31	179.8	146	2.1	4.1	4	38 days	6	10
Lumsden *et al*., 2000[15]	95	95	81 ± 30	47 ± 16	4	6	No difference	–	8	14
Perino *et al*., 1999[16]	51	51	104.1 ± 27.0[c]	87.8 ± 20.4	2.38	6.23	–	–	3.9	11.8
Falcone *et al*., 1999[17]	24	24	180	130	1.5	2.5	14	19	–	–
Marana *et al*., 1999[18]	58	58	91.1	91.8	4	5.9	–	–	1/58 major (1.7%), 2/58 minor	2/58 major (3.4%), 5/58 minor
Olsson *et al*., 1996[19]	71	72	148	85	2	4	16 days	35 days	27	33
Nezhat *et al*., 1992[20]	10	10	160	102	2.4	4.4	3	5	10	50
Phipps and Nayak, 1993[21]	24	29	65	30	2	6	2	6	–	–
Raju and Auld, 1994[22]	40	40	100	57	3.5	6	3	6	–	–
Langebrekke *et al*., 1996[23]	46	54	100 (50–153)	60.5 (22–105)	2 (0–5)	5 (3–12)	19.5 days (0–140)	36.5 days (23–259)	10/46	14/54
Arbogast *et al*., 1994[24 d]	61	65	137	66	1	4.1	–	–	38	68
Howard and Sanchez, 1993[25 e]		15	15	169	119	3.7	5.2	–	–	13 40

[a] Bolded name indicates the study was available when the EVALUATE trial was being designed.
[b] Summitt *et al*.: with regard to complications they only recorded the percentage of patients suffering from major complications intraoperatively. Lumsden *et al*.: this study was not powered to detect a difference in complications; the complication rate shown includes both major and minor complications. Olsson *et al*.: all complications have been recorded. Nezhat *et al*.: all complications were minor, no major complications.
[c] Perino *et al*.: with regard to the length of the operating time for LH, they stated that after the learning curve the plateau time was 93.6 ± 21.4 minutes.
[d] Arbogast *et al*.: retrospective study.
[e] Howard and Sanchez: not randomised.

TABLE 2 *Summary of studies of LH versus VH*

Author[a]	Number of cases		Operating time (minutes)		Length of stay (days)		Recovery time (weeks)		Complications (%)	
	LH	VH	LH	VH	LH	VH	LH	VH	LH	VH
Soriano *et al*., 2001[26]	40	40	160 ± 50	108 ± 35	5.7 ± 3.1	5.3 ± 2.1	–	–	32.5	15
Summitt *et al*., 1992[27 b]	29	24	120	65	–	–	–	–	8	8
Richardson *et al*., 1995[28]	22	23	131	37	3.2	3.3	6.4	5.7	36	30

[a] Bolded name indicates the study was available when the EVALUATE trial was being designed.
[b] Summitt *et al*.: all complications included.

TABLE 3 *Study of LH versus VH versus AH*

Author[a]	Number of cases			Operating time (minutes)			Length of stay (days)			Recovery time (weeks)			Complications (%)		
	LH	VH	AH	LH	VH	AH	LH	VH	AH	LH	VH	AH	LH	VH	AH
Ottosen *et al*., 2000[29 b]	40	40	40	102	81	68	3.1	2.8	3.7	19.7	21.3	28.1	2.5	7.5	2.5
Casey *et al*., 1994[30 c]	115	220	194	112	90	116	2.3	3.4	4.7	–	–	–	0	4	8.8
Boike *et al*., 1993[5 c]	50	50	50	240	176	163	2.5	3.8	163	–	–	–	12	6	26

[a] Bolded name indicates the study was available when the EVALUATE trial was being designed.
[b] Ottosen *et al*.: all complications have been recorded.
[c] Casey *et al*. and Boike *et al*.: not randomised.

fibroids or severe pelvic adhesions) must be included in the trial if it is to reflect the realities of clinical practice. Most gynaecologists would have excluded patients with major pelvic disease from trials involving VH, and this viewpoint would also preclude a single trial with a three-way randomisation protocol.

Hence neither a single trial of LH against AH nor a trial of LH against VH would have adequately defined the role of LH in gynaecological practice. Therefore, the EVALUATE trial design involved two parallel trials comparing LH with AH and LH with VH.

In terms of economic evaluation, the advent of laparoscopic approaches to hysterectomy offers the prospect of improved patient outcomes and gains in cost-effectiveness. This potential exists, in particular, through reduced severity in women's convalescence and reduced length of stay in hospital. However, with the exception of some observational studies[31–33] and some small randomised trials,[15,34] few data have emerged on the costs and cost-effectiveness of laparoscopic forms of hysterectomy relative to standard (abdominal and vaginal) approaches.

Chapter 2
Methods

Objectives

The EVALUATE trial proposed to:

1. Test the null hypothesis of no significant difference between LH and AH and between LH and VH with regard to each of the outcome measures of the trial.
2. Carry out an economic appraisal of the cost and the cost-effectiveness to the health service and the patients of AH, VH and LH.

Trial design

Two parallel, concurrently conducted, multi-centre randomised trials were designed: the abdominal trial comparing LH with AH and the vaginal trial comparing LH with VH. Both trials had the same management structure, eligibility criteria and outcome measures.

Eligibility

Inclusion and exclusion criteria were designed to produce a homogeneous group of patients on whom many gynaecologists could have performed any of the techniques under investigation.

Inclusion criteria

Women:

- with gynaecological symptoms that, in the opinion of the gynaecologist and the patient, justified hysterectomy
- who gave their informed consent to participate
- having previous failed medical or conservative treatments, such as endometrial ablative therapies.

Exclusion criteria

The following groups of conditions present specific problems and were excluded from the trial:

- confirmed or suspected malignant disease of any part of the genital tract
- second- or third-degree uterine prolapse
- uterine mass greater than the size of a 12-week pregnancy
- associated medical illness precluding laparoscopic surgery
- bladder or other pelvic support surgery required
- patients deemed unsuitable for randomisation by the consultant
- patients refusing consent for the trial.

Generalisability

The main limitation of the inclusion and exclusion criteria was the exclusion of patients having an indication for hysterectomy of fibroids of >12 weeks in size. This excludes a large number of indications for hysterectomy.

Conduct

Trial organisational structure

The Trial Steering Committee with an independent Chair (Appendix 2) was responsible for monitoring the conduct of the trial, according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.[35] A Data Monitoring and Ethics Committee (Appendix 3) provided independent monitoring of the data.

The Northern and Yorkshire Clinical Trials and Research Unit (NYCTRU), University of Leeds, was the main coordinating centre and was responsible for randomisation, data management, statistical monitoring and analysis of the trial.

The Centre for Health Economics, University of York, undertook the economic evaluation.

The Clinical Coordinators were responsible for the publicity of the trial, for queries about patient management within the trial and for interpretation of the results.

Gynaecologist participants

A total of 43 surgeons from 28 centres throughout the UK and two centres in South Africa took part in the study. Clinical practice in the South African centres reflected practice in the UK; the patients were predominantly Caucasian.

Each gynaecologist participating in the trial provided information about his experience with each of the techniques under investigation. To

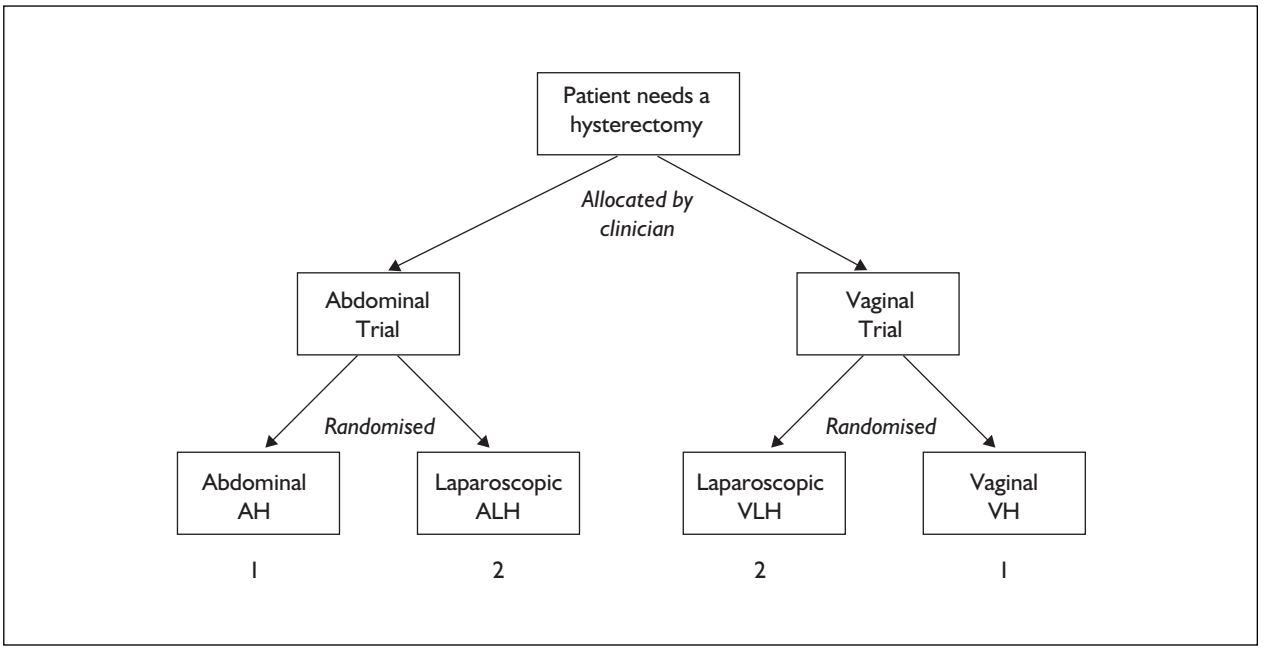

FIGURE 1 *Randomisation. ALH = LH arm of the AH trial; VLH = LH arm of the VH trial.*

exclude the effect of the early learning curve, only surgeons competent in all these procedures were eligible to participate in the trial. This was defined as a surgeon who had completed at least 25 of each technique. We did not specify whether these should be solo operations or under supervision; however, the assumption was that these were solo operations. At the time of designing this trial, 25 was an arbitrary figure (since the skills acquisition curve for this technique had not previously been measured) and was based on clinical experience of introducing previous new procedures. Subsequently a study from Finland has suggested that the risks of a major complication are higher in the first 30 cases than in subsequent procedures.[35]

Surgeons did not have to be of consultant grade and teaching cases were included, provided that the main assistant was the surgeon named at randomisation. The protocol emphasised that the surgeon named at randomisation either performed or directly assisted in the complete hysterectomy (i.e. from the first incision to the last suture). If for any reason that did not happen, the Trials Unit was informed but the patient remained in the trial.

Randomisation

At the initial clinic visit, a patient was selected for inclusion into the trial when she and her gynaecologist both considered that she had sufficient indication for a hysterectomy and the eligibility criteria were fulfilled. The patient was provided with an appropriate information sheet (Appendix 4), and then the gynaecologist allocated the patient to either the abdominal or the vaginal trial according to preferred clinical grounds. Informed consent was obtained and subsequent randomisation to either the selected conventional approach or LH was made by telephone. Depending upon the trial chosen, the patients were randomised to either LH, AH or VH via an independent, computerised programme produced and run by the NYCTRU.

Randomisation to the selected arm was stratified by the following parameters, which were based on commonly accepted clinical criteria that they would influence outcome:

- individual surgeon
- proposed trial (abdominal or vaginal)
- ovary removal ('none' or 'one or more' planned)
- patient body mass index (BMI ≤ 30 kg/m^2 and >30 kg/m^2).

Imbalanced randomisation was used in favour of LH in a ratio of 2:1 (LH:AH and LH:VH; see *Figure 1*).

Once selected and randomised, patients were placed on the routine operating waiting list and admitted to hospital for their operation.

Treatment details
Surgical procedures were as currently practised: there were four approaches to LH: LH, LAVH, laparoscopic supracervical hysterectomy (LSH) and TLH (see Appendix 1). All conversions were documented.

The following were standardised within each surgeon's practice, over all three techniques:

- pre-, peri- and postoperative prophylactic antibiotics/analgesia and anticoagulants
- anaesthetic care.

Standard postoperative instructions were given regarding resuming normal activities (see Appendix 5).

Ethical considerations
The trial received Multi-centre Research Ethics Committee approval and the appropriate Local Research Ethics Committee approval for each participating institution prior to their entry into the trial. Approval for recruitment in South Africa was obtained according to local practice. The trial complied with all aspects of the Data Protection Act.

Informed consent
The gynaecologist discussed the trial and its implications with the patient before recruitment. Potential participants received one of two possible information sheets depending on the clinician's preferred type of hysterectomy for that patient (Appendix 4) and the potential risks and benefits associated with each arm of the trial were explained. Informed, written consent was obtained from the patients prior to randomisation into the trial. Those who were unsure or who wished to delay a decision to allow further discussion were encouraged to do so, and were given a further appointment at a later date. The protocol emphasised the need to respect the right of the patient to refuse participation without giving reasons and that the patient must remain free to withdraw at any time from the trial without giving reasons and without prejudicing her further treatment.

Quality control
The NYCTRU worked to MRC Guidelines for Good Clinical Practice in Clinical Trials[36] and Unit standard operating procedures. Databases had in-built validation checks. One hundred per cent of the data were checked. Data were checked by a different trial coordinator from the one who entered them.

All missing or ambiguous data were chased until resolved. Postal questionnaires to patients were chased once (no more to ensure voluntariness of participation) and 'thank you' letters were sent upon receipt of completed questionnaires.

There was some source validation of data, including at one of the South African centres, to ensure data quality.

Assessments/data collection

The data collection structure is outlined in Appendix 6.

Initial clinic visit (collected by the surgeon/research nurse)
The following information was collected for all eligible patients in the trial:

1. consultant
2. patient address details
3. obstetric history (parity, vaginal deliveries after 24 weeks' gestation, Caesarean deliveries)
4. indications for hysterectomy
5. hysterectomy grading by clinical examination:
   (a) uterine size
   (b) uterine position
   (c) uterine mobility
   (d) uterine descent
   (e) vaginal capacity
   (f) palpable endometriosis
6. intended ovary removal
7. height, weight, smoking status
8. previous pelvic surgery
9. health questionnaires
   (a) EuroQol Instrument (EQ-5D)[37,38]
   (b) Short Form with 12 Items (SF-12) Health Survey questionnaire[39]
   (c) Body Image Scale (BIS) questionnaire[40]
   (d) Sexual Activity questionnaire (SAQ).[41]

Preoperative details (collected by the research nurse/patient)
The following questionnaires/information were collected prior to the operation (as close as possible to the operation date, usually following admission to hospital but prior to surgery):

1. health questionnaires
2. employment details
3. height and weight
4. smoking details
5. previous pelvic surgery (since initial clinic visit)
6. haematology (haemoglobin and haematocrit).

Intraoperative details (day 0) (collected by the surgeon/theatre nurse)

The following assessments were collected intraoperatively:

1. type of anaesthesia used
2. type of hysterectomy performed – abdominal, vaginal, laparoscopic
3. operative timings:
   (a) date of operation
   (b) time anaesthesia induced
   (c) time of first incision
   (d) time of last suture
   (e) time of leaving recovery room
4. problems encountered securing uterine artery
5. ovary removal
6. cervix retention
7. estimated blood loss
8. method of haemostasis
9. antibiotic prophylaxis used
10. urinary catheterisation
11. type of incision used (AH only)
12. type of LH carried out (LH only – see Appendix 1)
13. number of trocars used and associated incisions (LH only)
14. pneumoperitoneum details (LH only)
15. disposable items (LH only)
16. conversion from planned procedure and reason.

Pathology

1. gross description of uterus and adnexa (including weight of specimen)
2. microscopic description of uterus and adnexa
3. presence of endometriosis and leiomyomata
4. other pathology.

Intraoperative complications

1. whether or not patient experienced complications
2. if yes, whether:
   (a) trocar injury
   (b) major haemorrhage
   (c) bowel, ureteric or bladder injury
   (d) anaesthetic problems
   (e) other complications
   (f) death
   (g) blood transfused for the complication, and number of units
   (h) further details of complication and treatment.

Postoperative (from day 0 to discharge home) (collected by doctor/research nurse/patient)

The following assessments were collected postoperatively:

1. type of ward patient returned to postoperatively (general/high dependency/ intensive care)
2. prophylactic anticoagulants
3. postoperative haemoglobin – on day 2 postoperation
4. postoperative haematocrit – on day 2 postoperation
5. hospital daily diary (see Appendix 7) – administered from day 0 until discharge:
   (a) pain Visual Analogue Score (VAS) assessed twice daily (day 0 at ~9.00 p.m; subsequent days at ~9.00 a.m and 9.00 p.m)
   (b) analgesia/opiates taken
   (c) activities able to perform.

Postoperative complications (after leaving theatre, but prior to discharge)

1. whether or not patient experienced complications
2. type of complication and treatment
3. whether returned to theatre, and time in theatre
4. whether laparotomy performed
5. whether caused by trocar injury
6. whether blood transfused for the complication and number of units.

Hospital discharge

1. date and time of discharge from hospital
2. consultant judgement of appropriateness of length of hospital stay.

If the patient remained in hospital for longer than 1 week, a further hospital diary booklet was administered (see Appendix 8). At discharge the patient was given standard instructions for resuming normal activities from the research nurse/doctor (see Appendix 5). The patient was given another daily diary to fill in for 6 weeks following discharge from hospital. A stamped, addressed envelope was provided for the patient to return the diary to the Trials Unit.

Follow-up postoperation (collected from the patient)

1. day of discharge until end of 6 weeks – daily diary booklet:
   (a) pain VAS taken twice daily (at ~9.00 a.m and 9.00 p.m)
   (b) activities able to perform.

The following questionnaires/assessments were sent with an explanatory letter to the patient by the Trials Unit. They were completed and returned using the stamped addressed envelope enclosed.

1. at the end of 6 weeks:
   (a) health questionnaires
   (b) health resource use questions.
2. at the end of 4 months:
   (a) health questionnaires
   (b) health resource use questions.
3. at the end of 1 year:
   (a) health questionnaires
   (b) health resource use questions.

Follow-up clinic visit (collected by the surgeon)

At ~6 weeks after the operation, when the patient attended for her follow-up clinic visit, a general routine clinical examination was carried out, and any complications which had occurred and treatment carried out from the time of discharge until the patient attended for her appointment were documented.

Withdrawal

Prior to operation

If a patient was randomised into the trial and withdrew prior to her operation (i.e. between the initial clinic visit and before entering the operating theatre), then the withdrawal form was completed. No follow-up assessments were collected on the patient, although she was included in the intention-to-treat (ITT) analysis.

During and after the operation

During and after the operation, withdrawal from the trial might have occurred for the following reasons:

- transfer after operation to a centre not taking part in the trial
- patient decision to leave trial for other reasons
- death of the patient.

For these scenarios, the withdrawal form was completed. If a decision was made to withdraw the patient, provided consent was still maintained, the patient continued to be followed up and as much information (postoperation up to 1 year) as possible was collected.

End-points

Primary end-point

The primary end-point of the trial was the occurrence of a major complication or death. A gynaecologist, who was not recruiting to the trial, performed a blinded independent review of the complication forms to ensure accuracy of assessment. All major complications were regarded as life threatening and are therefore equally weighted.

All complications were classed in two categories:

- short term: all major complications that occurred while the patient was in hospital, prior to discharge
- long term: all major complications that occurred after the patient had been discharged from the hospital up to the 6-week postoperation follow-up visit.

Major complications were defined as:

1. major haemorrhage (requiring transfusion)
2. haematoma (requiring transfusion/surgical drainage)
3. bowel injury
4. ureteric injury
5. bladder injury
6. pulmonary embolus
7. major anaesthesia problems (defined by independent clinical review)
8. wound dehiscence
9. unintended laparotomy, defined as either:
   (a) intraoperative conversion (failure of the planned procedure)
   (b) return to theatre:
      (i) prior to discharge from hospital
      (ii) prior to 6-week postoperative follow-up visit.

Secondary end-points

Clinical outcomes

Minor complications

Minor complications were defined as:

- haemorrhage (not requiring transfusion)
- infection: chest, urinary, wound, pelvic, other/or pyrexia 38 °C on any single occasion
- haematoma (spontaneous drainage)
- deep vein thrombosis (DVT)
- cervical stump problems
- minor anaesthesia problems (defined by independent clinical review)
- other minor complication requiring treatment.

Blood loss (intraoperatively)

Blood loss was assessed in two ways:

1. Intraoperative blood loss was categorised by subjective assessment of the surgeon as less than average, average and more than average.

2. An indirect measure of blood loss was recorded as the change in haemoglobin and haematocrit from preoperative level to day 2 postoperative level.

Pain assessment
Pain was assessed in two ways:

- the pain VAS in the daily diary completed by the patient
- amount of opiates (milligrams) taken.

The amount of opiates was summarised from day 0 to day 2 postoperation (since most patients were likely to have pain during this time), and also from day 0 until discharge.

The pain VAS was summarised at days 2, 7, 21 and 42, as these were thought to be clinically important time points.

Sexual activity
Sexual activity was measured by the SAQ, which included subscales on pleasure, habit and discomfort. It was completed by the patient and was administered at baseline, at initial clinic visit (and also when admitted to hospital prehysterectomy, if there was more than 1 week between the two visits) and then at 6 weeks, 4 months and 1 year postoperatively.

Body image
This was assessed using the BIS at baseline (both at initial clinic visit and when admitted to hospital prehysterectomy) and then at 6 weeks, 4 months and 1 year postoperatively.

Health status
Health status was assessed using the SF-12 Health Survey questionnaire, and was completed by the patient at baseline, at initial clinic visit (and also when admitted to hospital prehysterectomy if there was more than 1 week between the two visits) and then at the end of 6 weeks, 4 months and 1 year. It scored the following areas: physical functioning, role functioning, bodily pain, mental health and emotional and social functioning.

Quality of life (QoL) was also assessed using the EQ-5D Instrument, which scored the areas of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

For the economic evaluation, the health outcomes of the alternative forms of hysterectomy were assessed in terms of quality-adjusted life-years (QALYs). QALYs were calculated, for each woman in the trial, on the basis of her responses to the EQ-5D at baseline and at up to three points postoperatively (6 weeks, 4 months and 1 year). The EQ-5D is a generic measure of health status, where health is characterised on five dimensions (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression).[38] At each point of follow-up, women were asked to indicate their level of health on each dimension using one of three levels: no problems, moderate problems and severe problems. Each response located a woman into one of 245 mutually exclusive health states, each of which had previously been valued on the 0 (equivalent to dead) to one (equivalent to good health) 'utility' scale based on interviews with a sample of 3395 members of the UK public.[42] Hence, each woman in the trial had a utility at up to four time points and, using area under the curve methods,[43] these observations were translated into QALYs over each woman's period of follow-up.

Resource use
Patient numbers
The economic analysis was undertaken on the 1346 women who did not drop out prior to surgery over a median follow-up of 52 weeks (range, 3–52 weeks).

Resource use measurement
Resource utilisation data were collected in all patients in the EVALUATE trial in case record forms, completed by clinical staff in trial centres, and in postal questionnaires completed and returned by patients. These data were collected at various stages.

Theatre. Using detailed case record forms, information on resource utilisation in theatre was collected, as completed by clinical medical staff. This included time in theatre and recovery room. Time in theatre was calculated as the time elapsed from the moment in which anaesthesia was induced to the time when the last suture was applied, increased by 5 minutes to allow for the time needed to prepare the patient in the operating theatre. Time in recovery room was calculated as the difference between the time at which the patient left the recovery room and the time of the last suture. Finally, time in the anaesthetic room was assumed to be 15 minutes. Data were also collected on type of hysterectomy undertaken, use of prophylactic antibiotics and anticoagulants, form of anaesthesia employed, method of haemostasis and use of specific consumables such as disposable trocars and scissors. Details of intraoperative complications

were also collected, including any need for blood transfusion. Any additional resource use associated with these complications (e.g. drugs or tests) was estimated by a clinical expert blinded to treatment allocated.

Main hospitalisation. Case record forms were also used to measure other resource utilisation during a woman's main hospitalisation, including length of stay in hospital, any time in an intensive care unit (ICU) or high-dependency ward (HDW) and the use of urinary catheterisation. Details of postoperative complications during hospitalisation were also collected, including any blood transfusion and whether a woman had to be returned to theatre. Again, any additional resource use (e.g. drugs or tests) associated with these complications was estimated by a clinical expert blinded to treatment allocation.

Follow-up. All women were invited to return to hospital for a follow-up visit ~6 weeks after their operation. During this visit, case record forms were used to collect data on the incidence of any complications, including whether further surgery or blood transfusion was required. Again, any additional resource use (e.g. drugs or tests) associated with these complications was estimated by a clinical expert blinded to treatment allocated. Patients also completed a questionnaire at this point in follow-up, which included questions on numbers of inpatient days and outpatient, day-case and GP visits made for any reason since leaving hospital. Patients were also asked to complete similar questionnaires at 4 months and 1 year after their operation.

Unit costs. UK unit costs at 1999–2000 prices were used to value the resource use measured in the trial. These were average costs and, where appropriate, both fixed and variable costs were considered. *Table 134* in Chapter 6 details the key unit costs, together with their sources. Data from the questionnaires on any inpatient days in hospital subsequent to the main hospitalisation were, on the basis of the reasons provided, allocated to a speciality by a clinical expert blinded to treatment allocation. These have been costed based on average inpatient costs per day from English hospitals.[44]

Statistical considerations

Sample size

The sample size for this trial was established using the hypothesis that LH has no effect in reducing the incidence of major complications, intra- and/or postoperatively (up to 6 weeks).

AH versus LH

It was expected that 9% of the AHs would have major complications.[30] If an incidence of 4.5% in the complication rates was to be observed in the LH group, that is, a difference of 50% between the two groups, this would be considered clinically relevant. In order to detect this difference, a sample size of ~487 patients per trial arm was required, using 80% power and a two-sided Type I error rate of 5%.

VH versus LH

It was expected that 4% of the VHs would have major complications.[30] If an incidence of 2% in the complication rates was to be observed in the LH group, that is, a difference of 50% between the two groups, this would be considered clinically relevant. In order to detect this difference, a sample size of ~1141 patients per trial arm was required, using 80% power and a two-sided Type I error rate of 5%.[45]

It was assumed that AH had the greater long-term implications, since it was associated with higher complication rates and more pain and incapacity.[4] The health effects of a change of practice would be potentially greater with respect to AH. The national proportion of AH to VH was 80% to 20%, but it was thought that surgeons in this trial would probably perform a greater proportion of their operations by the vaginal route and it was estimated that the proportion in the trial might be 60% to 40% (preliminary informed estimate from the trial group participants). Therefore, the sample size was set at 1800 patients in total. The AH trial had sufficient power to detect changes in major complications. The VH trial was not planned to have sufficient power to detect a statistically significant difference. However, it was considered that the database from this trial would be the largest collected from any randomised clinical trial, and later it might be amalgamated with data from other trials/studies (meta-analysis), which might ultimately produce a more precise estimate.

To allow for the ~2–3% conversion rate[46] from laparoscopic surgery to open surgery, and to enable as much information as possible to be collected on laparoscopic surgery, it was proposed that the randomisation for this trial be unbalanced at 2:1 (LH:AH and LH:VH). This imbalance should also ensure that surgeons, if not already at the top of their learning curve, gained as much

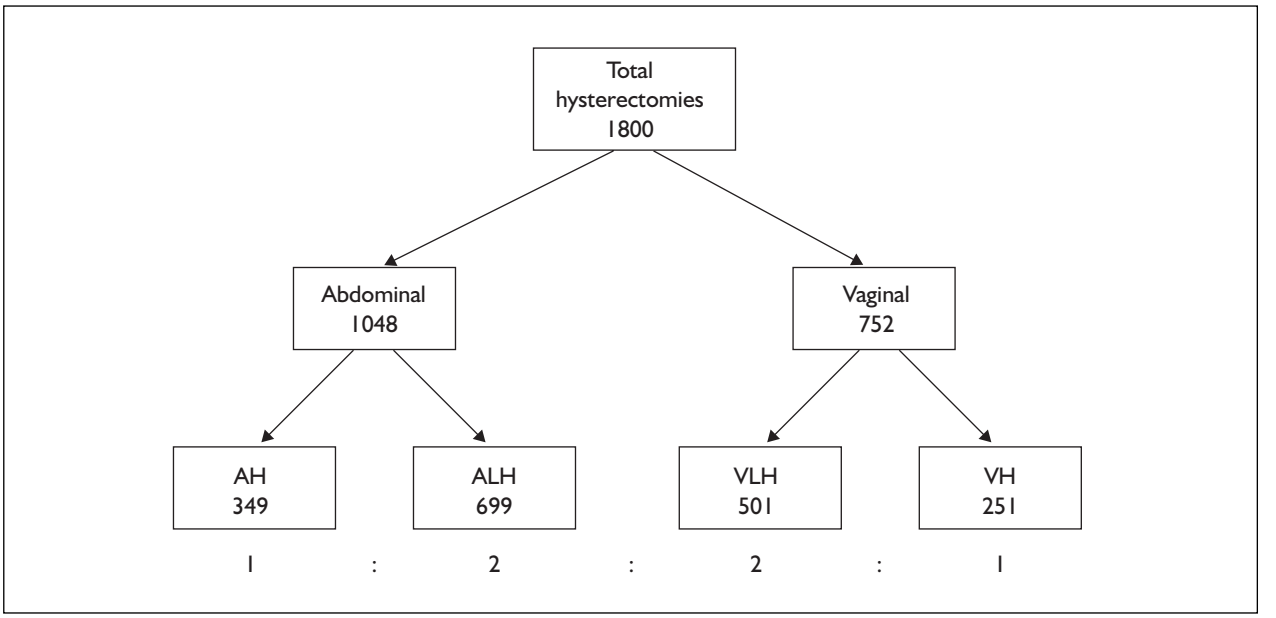

FIGURE 2 *Sample size. ALH = LH arm of the AH trial; VLH = LH arm of the VH trial.*

experience of laparoscopic surgery as quickly as possible. The 2:1 randomisation resulted in a relatively small reduction in power compared to a trial with balanced randomisation.

Taking into account the sample size calculation for the abdominal arm and also the imbalanced randomisation, the number of patients in each arm was planned as shown in *Figure 2*.

In practice, this sample size was not achieved. The trial had a 2-year extension, and achieving the target sample size would have required a further extension but recruitment was slowing. The Trial Steering Committee reached a decision to close the trial to recruitment in October 2000. This was endorsed by the Data Monitoring and Ethics Committee. The problems encountered with recruitment are discussed in Chapter 7.

Prior to randomisation, it was believed that surgeons would have preferences on clinical grounds for either the abdominal or vaginal approach, so the trial was therefore designed as two studies under one umbrella trial. However, until the clinical baseline data was summarised, these reasons were unknown. The baseline data demonstrate that patients were selected for the abdominal trial with the following clinical criteria:

- Caesarean deliveries
- palpable endometriosis
- more than one indication for hysterectomy
- no uterine descent
- intended oophorectomy.

Patients were selected for the vaginal trial with the following clinical criteria:

- more than one vaginal delivery
- freely mobile uterus.

Analysis

Clinical

The analysis of the complication rates was carried out using both ITT and per-protocol populations. The ITT population contained all randomised patients, whether they had an operation or not, and they were analysed according to the procedure to which they were randomised. The per-protocol population again contained all randomised patients including those who did not have an operation, but this time patients were analysed according to the type of operation that was actually started.

The primary end-point of the study was whether a patient experienced at least one major complication or not. A chi-squared test was used to compare the number of patients experiencing at least one major complication between AH and ALH within the abdominal trial and to compare VH and VLH within the vaginal trial. The complication rates, the difference in the rates and the 95% confidence interval (CI) were reported. The analysis was initially by ITT; a sensitivity analysis around the patients in the ITT population

that did not have an operation was used to assess the impact of using all randomised patients. This analysis and sensitivity analysis was repeated using the per-protocol population.

A logistic regression analysis was used to adjust for the stratification factors, BMI and intended ovary removal. Also, logistic regression was used to identify important variables in the prediction of major complications. This analysis was done within each type of procedure, that is, AH, VH and LH; the odds ratios (ORs) and 95% CIs around the odds ratios were reported.

The secondary end-points were minor complication rates, blood loss (intraoperatively), pain assessment, sexual activity, body image, health status and QoL. The previous analysis of the major complication rates was repeated for the minor complication rates.

Blood loss data were collected at the time of the procedure on the surgeon's subjective assessment as to whether blood loss had been 'less than average', 'average' or 'more than average'. A chi-squared test for trend was used to detect any differences between the procedures. Also, the patient's pre- and postoperative haemoglobin and haematocrit values were recorded. A *t*-test of the difference and 95% CIs around the change in haemoglobin and haematocrit pre- and postoperation were reported.

Analysis of covariance was used to analyse pain assessment. Pain scores are presented on days 0, 2, 7, 21 and 42. The numbers of patients using opiates are also reported. The adjusted mean pain scores are presented, adjusting for opiate use on day 0 and day 2.

A chi-squared test was used to assess any differences in the quantity of additional unexpected pathology that was found during the operation.

A more in-depth analysis using multilevel modelling was used to investigate a surgeon effect and to identify any potential patient-level factors that may be important in determining which patients were more likely to have had at least one major complication.

QoL was measured using the SF-12, the BIS and the SAQ. Data were collected at randomisation, preoperation, 6 weeks postoperation, 4 months postoperation and 1 year postoperation. The scores were calculated following the appropriate scoring manuals and analysed using the *t*-test of means. The mean difference and 95% CIs were reported.

Economic evaluation

A cost–utility analysis was performed using patient-level data collected alongside the EVALUATE trial. Costs were estimated from the perspective of the UK NHS and health benefits were expressed in terms of QALYs. The time horizon for this initial analysis was 1 year.

Statistical analysis was undertaken using Stata 6.0.[47] Due to differential follow-up, 11.7% of patients were not followed up for a full year. Estimates of mean costs and QALYs, over 12 months' follow-up, were therefore calculated using methods to adjust for censored data.[48] More specifically, censored cost data were handled using the method proposed by Lin and colleagues.[48] Under the assumption that censoring occurs completely at random (i.e. is not systematically related to any observed or unobserved variable), this method is implemented by partitioning the study period in a number of subperiods and calculating the average costs in each subperiod for the different arms of the trial and weighting these by the Kaplan–Meier survival probability. The mean total cost is, therefore, the sum of the adjusted costs in each subperiod. Given that the time horizon of the analysis was 1 year, total costs and QALYs remain undiscounted. Mean differential QALYs were estimated using ordinary least-squares regression with randomised treatment and baseline EQ-5D as covariates. The reason for using the second of these covariates was to adjust for the fact that the trial groups being compared are likely to have differences in mean baseline EQ-5D scores simply by chance, and this will influence the mean QALYs calculated in those groups.

To account for the skewed nature of the data, 95% CIs for the differential costs and QALYs were calculated using bias-corrected non-parametric bootstrapping.[49]

In some patients, resource use data and EQ-5D responses were wholly or partially missing. As they did not display a systematic pattern within treatment arms, missing data were imputed using a multivariate multiple imputation procedure. This procedure assumes that data were missing at random, that is, cases with incomplete data differ from cases with complete data, but the missing data pattern is fully predictable from other variables in the dataset.[50]

Cost-effectiveness analysis was undertaken to relate differential mean cost to differential mean QALYs associated with the alternative arms of the trial. Using these results, laparoscopic-assisted hysterectomy can be considered more cost-effective than standard hysterectomy if one of the following apply:

1. Laparoscopic-assisted hysterectomy generates higher mean QALYs with lower mean costs than standard (abdominal or vaginal) hysterectomy; in other words, it 'dominates' standard hysterectomy.
2. Laparoscopic-assisted hysterectomy generates higher mean QALYs than the standard procedure but at a higher mean cost, and each additional QALY produced by the laparoscopic procedure has an extra cost (the incremental cost-effectiveness ratio) which is less than the decision-makers' maximum willingness to pay.
3. Standard hysterectomy generates higher mean QALYs than laparoscopic-assisted hysterectomy but at a higher mean cost, and each additional QALY produced by standard hysterectomy has an extra cost (the incremental cost-effectiveness ratio) which is more than the decision-makers' maximum willingness to pay.

Mean differential costs and QALYs were calculated in order to assess whether any of these conditions were satisfied. Two comparisons are presented: (1) the cost-effectiveness of laparoscopic-assisted hysterectomy (ALH) relative to AH in women for whom the latter was the conventional procedure of choice and (2) the cost-effectiveness of the laparoscopic operation (VLH) relative to VH in women for whom the latter was the standard operation.

Mean costs and QALYs are estimated with uncertainty. Therefore, to account for uncertainty due to sampling variations, we plotted cost-effectiveness acceptability curves.[51,52] Given the data collected within the trial, this curve shows the probability of laparoscopic-assisted hysterectomy being more cost-effective than conventional hysterectomy for different maximum levels that the decision-maker may be willing to pay for an additional QALY. This is a Bayesian approach to the presentation of cost-effectiveness data,[53] although a full Bayesian analysis was not undertaken. The statistical approach used in the economic analysis therefore differs from that adopted for the clinical analysis. Rather than use the rules of statistical inference, the analysis reports incremental cost-effectiveness based on mean costs and QALYs, and then reports the error probabilities associated with a decision explicitly. In interpreting the cost-effectiveness analysis, therefore, decision-makers need to be clear about their willingness to pay for an additional QALY and to decide what error probability they are willing to accept in making their decision.

Chapter 3

Main clinical results

Sample size

A total of 1380 patients were randomised between November 1996 and September 2000: 292 AH, 584 ALH, 168 VH and 336 VLH; 51 surgeons had agreed to participate in the study but only 43 surgeons actually recruited patients (*Table 4*).

Figure 3 shows the wide range of recruitment rates by surgeon, from 1 to 115 patients. However, 51% (22/43) of surgeons recruited more than 20 patients each, that is, 89% (1233/1380) of patients. *Figure 3* shows the number of procedures undertaken per surgeon within the trials; data are not available on the number of procedures actually performed per surgeon per year.

Analysis populations

Intention-to-treat

The ITT population includes all randomised patients, even those who did not have an operation, and analyses them according to the type of operation to which they were randomised. There were 1380 randomised patients; the number of patients randomised to each type of operation is shown in *Table 4*.

Per protocol

The per-protocol population includes all randomised patients, analysing them according to the type of operation that was actually started. Patients not having an operation were included and a sensitivity analysis was performed, first

TABLE 4 *Number randomised*

Abdominal			Vaginal			Total
AH	ALH	Total	VH	VLH	Total	
292	584	876 (63.5%)	168	336	504 (36.5%)	1380

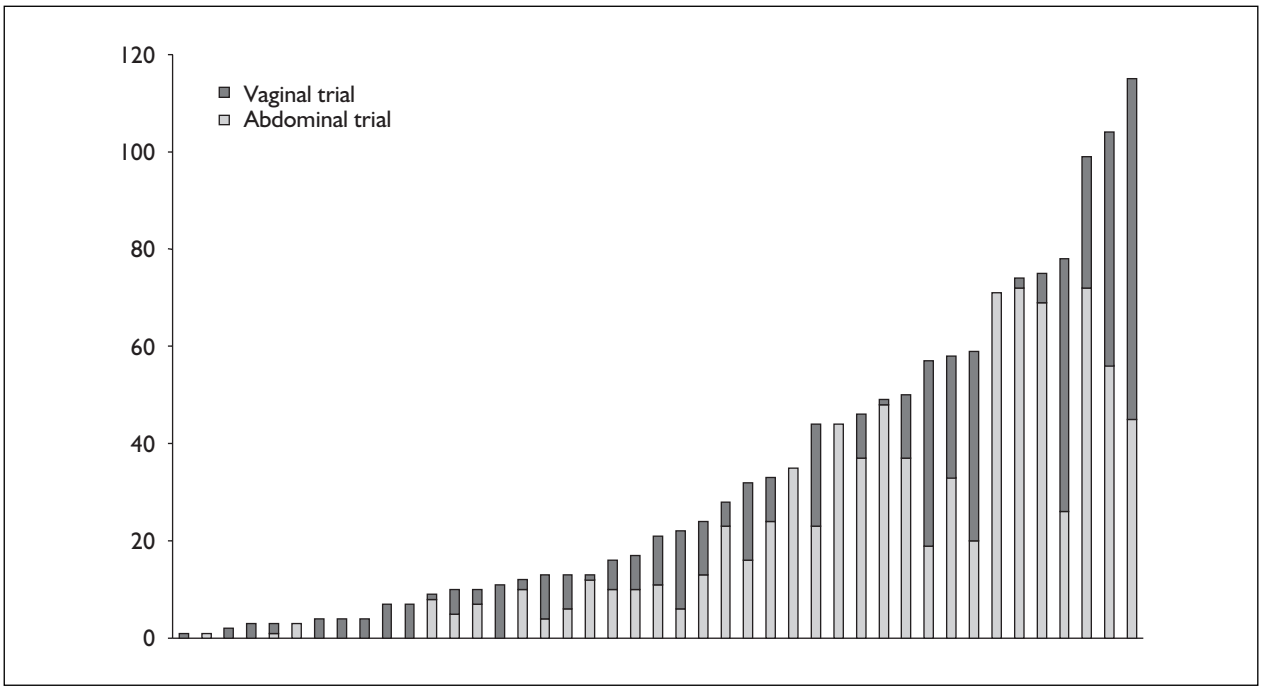

FIGURE 3 *Patients recruited by surgeon*

assuming that they had a major complication and then assuming no complication. There were 1380 randomised patients; the numbers analysed in each group were 289 AH, 587 ALH, 178 VH and 326 VLH.

Figure 4 shows the participant flow diagram; 876 patients were randomised to the abdominal trial and 504 to the vaginal trial. Within the abdominal trial, 292 were randomised to AH and 584 to ALH. Of the 292 AH patients, 18 converted preoperatively to another procedure and from the other procedures 15 patients converted to AH preoperatively; therefore, 268 had the allocated AH procedure, six withdrew and 18 converted = 292.

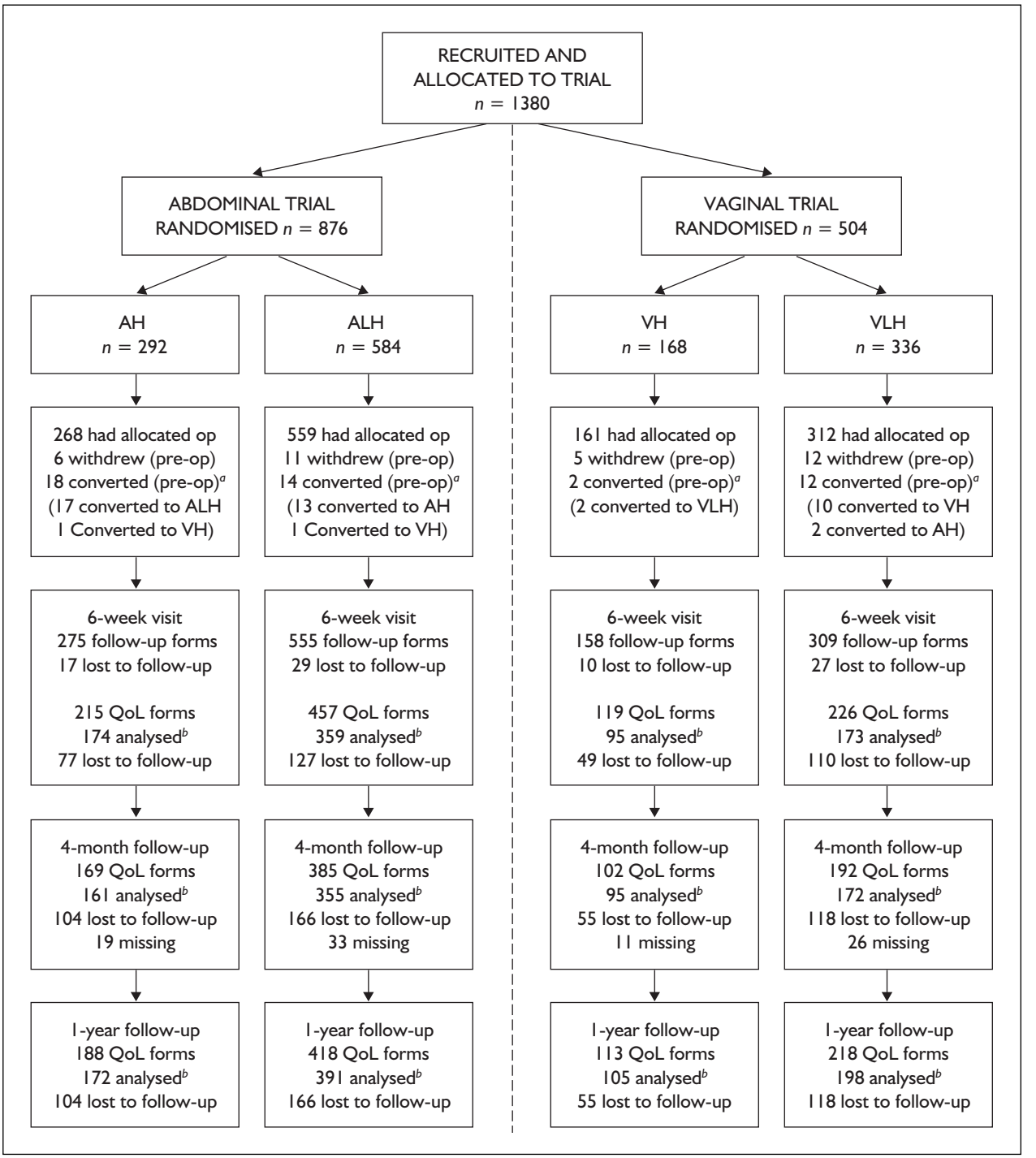

FIGURE 4 *Participant flow diagram.* [a] *283 had AH, 576 had ALH, 173 had VH and 314 had VLH operations.* [b] *Follow-up forms not received within the appropriate time frames were not included in the analysis. The time frames were ±14 days at 6 weeks and ±28 days at 4 months and 1 year.*

The figures used in the per-protocol analysis include those actually having an AH procedure, that is, 283 plus six withdrawals = 289.

Baseline data

Table 5 shows the (70) 5% of patients who withdrew from the study and the reasons for withdrawal. Amongst the 'other' reasons for withdrawing from the study were cancer found at surgery, adhesions that prevented the operation and one patient who died of non-trial-related reasons prior to the operation.

Of the 30 patients who cancelled their hysterectomy, three were pregnant and two simply did not attend for their operation; other reasons for cancelling operations included patients deciding not to go ahead with a hysterectomy. *Table 6* shows the reasons for patients not having a hysterectomy.

Table 7 shows that baseline data were in general well matched, within each trial, indicating that the randomisation process had worked within the two trials. There are differences between the trials; for example, >90% of the patients allocated to the vaginal trial had had one or more vaginal deliveries compared with <85% in the abdominal trial; this trend is reversed for the number of Caesarean deliveries. This indicates that surgeons have a tendency to allocate patients into one of the trials based on the patient's baseline characteristics. Only one of 30 patients with palpable endometriosis has been allocated to the vaginal trial, again indicating that surgeons have a preference towards the AH procedure rather than the VH procedure for these patients. Vaginal capacity was a clinical assessment and not a standard measure; ~95% were classed as normal.

Table 8 shows the number of times each indication for hysterectomy was reported, several patients having more than one indication for a hysterectomy. There were 117 different reasons classified as 'Other'. Four classifications have more than 40 patients and have been included in the table: dysmenorrhea, dyspareunia, menorrhagia and premenstrual syndrome. Again, the percentage of patients with each indication for hysterectomy was balanced within each of the randomised trials. However, there is a difference between the patients who were allocated to the abdominal and vaginal trials. *Table 8* shows that surgeons were reluctant to allocate patients with endometriosis or pelvic pain to the vaginal trial.

Table 9 shows the frequency of the number of indications for hysterectomy that patients have,

TABLE 5 *Patients withdrawn from the trial*

Reason	Abdominal				Vaginal				Total
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336		
Transfer to another centre	0	(0%)	0	(0%)	1	(0.6%)	2	(0.6%)	3
Cancelled hysterectomy	6	(2.1%)	11	(1.9%)	4	(2.4%)	9	(2.7%)	30
Lost to follow-up	4	(1.4%)	7	(1.2%)	2	(1.2%)	6	(1.8%)	19
Other	7	(2.4%)	8	(1.4%)	2	(1.2%)	1	(0.3%)	18
Total	17	(5.8%)	26	(4.5%)	9	(5.4%)	18	(5.4%)	70

TABLE 6 *Reasons why patients did not have a hysterectomy*

Reason	Abdominal				Vaginal				Total
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336		
Cancelled operation	6	(2.1%)	8	(1.4%)	3	(1.8%)	8	(2.4%)	25
Pregnant	0	(0%)	2	(0.3%)	0	(0%)	1	(0.3%)	3
Transferred to another centre/private operation	0	(0%)	0	(0%)	1	(0.6%)	2	(0.6%)	3
Died	0	(0%)	1	(0.2%)	0	(0%)	0	(0%)	1
Did not attend	0	(0%)	0	(0.0%)	1	(0.6%)	1	(0.3%)	2
Total	6	(2.1%)	11	(1.9%)	5	(2.9%)	12	(3.6%)	34

TABLE 7 *Baseline characteristics*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Age, mean (SD) (years)	41.17	(7.58)	41.68	(7.15)	40.82	(6.46)	40.89	(6.97)
BMI, mean (SD)	25.93	(5.42)	26.58	(5.06)	26.53	(4.75)	26.42	(5.09)
Parity								
Mode (min., max.) (% parous)	2 (0, 6)	(90.7%)	2 (0, 9)	(91.4%)	2 (0, 6)	(95.2%)	2 (0, 7)	(96.7%)
Missing	2	(0.7%)	2	(0.3%)	1	(0.6%)	3	(0.9%)
Vaginal deliveries								
Mode (min., max.) (% ≥ 1)	2 (0, 6)	(83.4%)	2 (0, 9)	(80.9%)	2 (0, 6)	(91.0%)	2 (0, 7)	(94.3%)
Missing	2	(0.7%)	2	(0.3%)	1	(0.6%)	3	(0.9%)
Caesarean deliveries								
Mode (min., max.) (% ≥ 1)	0 (0, 3)	(16.9%)	0 (0, 4)	(19.1%)	0 (0, 2)	(9.6%)	0 (0, 3)	(10.2%)
Missing	2	(0.7%)	2	(0.3%)	1	(0.6%)	3	(0.9%)
Vaginal capacity								
Narrow	14	(4.8%)	32	(5.5%)	8	(4.8%)	7	(2.1%)
Normal	275	(94.2%)	549	(94.0%)	157	(93.5%)	322	(95.8%)
Large	2	(0.7%)	2	(0.3%)	2	(1.2%)	4	(1.2%)
Missing	1	(0.3%)	1	(0.2%)	1	(0.6%)	3	(0.9%)
Palpable endometriosis	10	(3.4%)	19	(3.3%)	1	(0.6%)	0	(0.0%)
Missing	4	(1.4%)	9	(1.5%)	1	(0.6%)	3	(0.9%)
Current smoker	142	(48.6%)	242	(41.4%)	72	(43.1%)	131	(39.0%)
Missing	1	(0.3%)	1	(0.2%)	1	(0.6%)	3	(0.9%)
Previous pelvic surgery	185	(63.3%)	368	(63.40%)	102	(61.50%)	197	(58.6%)
Missing	2	(0.7%)	3	(0.6%)	2	(1.2%)	3	(0.9%)

TABLE 8 *Indications for hysterectomy*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
DUB	172	(58.9%)	361	(61.8%)	120	(71.9%)	221	(65.8%)
Fibroids	49	(16.8%)	107	(18.3%)	24	(14.4%)	55	(16.5%)
Endometriosis	41	(14.0%)	67	(11.5%)	5	(3.0%)	13	(3.9%)
Failed ablation	19	(6.5%)	35	(6.0%)	17	(10.2%)	33	(9.9%)
Other	62	(21.2%)	133	(22.8%)	39	(23.2%)	94	(27.9%)
Pelvic pain	45	(15.4%)	87	(15.1%)	6	(3.6%)	13	(3.9%)
Dysmenorrhea	21	(7.2%)	52	(8.9%)	9	(5.4%)	24	(7.2%)
Dyspareunia	9	(3.1%)	22	(3.8%)	7	(4.2%)	13	(3.9%)
Menorrhagia	10	(3.4%)	19	(3.3%)	6	(3.6%)	11	(3.3%)
Premenstrual syndrome	5	(1.7%)	27	(4.6%)	3	(1.8%)	7	(2.1%)
Missing	0	(0.0%)	1	(0.2%)	1	(0.6%)	3	(0.9%)

TABLE 9 *Number of indications for hysterectomy per patient*

Number	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
1	177	(60.6%)	348	(59.6%)	119	(70.9%)	233	(69.3%)
2	96	(32.9%)	165	(28.3%)	35	(20.8%)	62	(18.5%)
3	15	(5.1%)	54	(9.3%)	8	(4.8%)	27	(8.0%)
4	3	(1.0%)	12	(2.1%)	3	(1.8%)	11	(3.3%)
5	0	(0.0%)	4	(0.7%)	1	(0.6%)	0	(0.0%)
6	1	(0.3%)	0	(0.0%)	1	(0.6%)	0	(0.0%)
Missing	0	(0.0%)	1	(0.2%)	1	(0.6%)	3	(0.9%)

TABLE 10 *Haematology (preoperative)*

Number	Abdominal		Vaginal	
	AH	ALH	VH	VLH
Haemoglobin (g/dl)				
Preoperative	*n* = 271	*n* = 541	*n* = 154	*n* = 302
Mean (SD)	13.1 (1.2)	13.1 (1.3)	13.1 (1.1)	13.1 (1.4)
Missing/excluded	21	43	14	34
Haematocrit (%)				
Preoperative	*n* = 269	*n* = 541	*n* = 154	*n* = 299
Mean (SD)	38.9 (3.9)	39.0 (3.8)	38.9 (3.2)	39.0 (4.2)
Missing/excluded	23	43	14	37

18 patients have been excluded as their blood was taken more than 6 weeks preoperatively or were not done preoperatively.

TABLE 11 *Operative details*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Uterine position								
Anteverted	249	(85.3%)	496	(84.9%)	148	(88.1%)	282	(83.9%)
Retroverted	42	(14.4%)	86	(14.7%)	19	(11.3%)	50	(14.9%)
Missing	1	(0.3%)	2	(0.3%)	1	(0.6%)	4	(1.2%)
Uterine mobility								
Fixed	30	(10.3%)	45	(7.7%)	5	(3.0%)	11	(3.3%)
Freely mobile	261	(89.4%)	538	(92.1%)	162	(96.4%)	322	(95.8%)
Missing	1	(0.3%)	1	(0.2%)	1	(0.6%)	3	(0.9%)
Uterine descent								
No descent	234	(80.1%)	473	(81.0%)	106	(63.1%)	208	(61.9%)
1st degree	57	(19.5%)	109	(18.7%)	61	(36.3%)	125	(37.2%)
Missing	1	(0.3%)	2	(0.3%)	1	(0.6%)	3	(0.9%)
Uterine size (weeks)								
Median (min., max.)	6 (0, 12)		6 (0, 12)		6 (0, 12)		6 (0, 12)	
Missing	0	(0%)	4	(0.7%)	2	(1.2%)	5	(1.5%)

and again it can be seen that there was a tendency to allocate patients with only one indication for a hysterectomy to the vaginal trial, that is, 60% of AH patients compared with 70% of VH patients.

Eighteen patients were excluded from the analysis of the haematology data, as the preoperative blood measurements were not taken. *Table 10* shows that the preoperative haemoglobin and haematocrit levels across all procedures are very evenly balanced, as would have been expected.

Operative details

Table 11 shows the baseline operative information, that is, uterine size, position, mobility and descent. It can be seen that patients with a fixed uterus were more likely to be allocated to the abdominal trial, and therefore patients with a freely mobile uterus tended to be allocated to the vaginal trial, as were patients with first-degree uterine descent. This is further evidence of the selection criteria being used by surgeons when allocating patients to trials.

Table 12 shows the intended and completed oophorectomy rates. It can be seen that the number of completed oophorectomies was higher across all procedures than had been intended prior to theatre. There is evidence suggesting that the allocation of patients to the abdominal or vaginal trial is also dependent on the intended oophorectomy rate. It can also be seen that ~50%

TABLE 12 *Oophorectomy*

	Abdominal				Vaginal			
	AH		ALH		VH		VLH	
	Intended *n* = 292	Completed *n* = 278	Intended *n* = 584	Completed *n* = 559	Intended *n* = 168	Completed *n* = 159	Intended *n* = 336	Completed *n* = 317
No ovary removal	155 (53.1%)	137 (49.3%)	310 (53.1%)	260 (46.5%)	131 (78.0%)	122 (76.7%)	260 (77.4%)	229 (72.2%)
Ovary removal	137 (46.9%)	141 (50.7%)	274 (46.9%)	299 (53.5%)	37 (22.0%)	37 (23.3%)	76 (22.6%)	88 (27.8%)
Left only	6 (2.1%)	12 (4.3%)	15 (2.6%)	27 (4.8%)	2 (1.2%)	5 (3.1%)	1 (0.3%)	6 (1.9%)
Right only	10 (3.4%)	12 (4.3%)	11 (1.9%)	13 (2.3%)	0 (0.0%)	1 (0.6%)	3 (0.9%)	8 (2.5%)
Both	121 (41.4%)	117 (42.1%)	248 (42.5%)	259 (46.3%)	35 (20.8%)	31 (19.5%)	72 (21.4%)	74 (23.3%)
Missing	0	14	0	25	0	9	0	19

TABLE 13 *Length of stay [admission to discharge (days)]*

	Abdominal		Vaginal	
	AH *n* = 292	ALH *n* = 584	VH *n* = 168	VLH *n* = 336
Mean (SD)	5.11 (2.72)	3.95 (2.38)	4.32 (2.01)	4.29 (2.06)
Median (min., max.)	5 (1, 37)	4 (1, 38)	4 (2, 17)	4 (1, 20)
95% discharged	8	7	7	7
Missing	11	20	7	24

of the patients who have been allocated to the abdominal trial have an intended oophorectomy compared with <25% of the patients allocated to the vaginal trial.

The differences in the baseline data between the two trials demonstrate that the populations of patients are different within each of the trials. There is evidence that surgeons have a preferred trial for patients with certain baseline characteristics (parity, palpable endometriosis, endometriosis, pelvic pain, number of indications for hysterectomy, intended oopherectomy, uterine mobility and descent). This justifies the design of this study, in addition to verifying that the two trials contain different populations of patients. Patients have different baseline and clinical characteristics, indicating that the LH procedures may be more complex in one group than another; therefore, safety and efficacy of LH may be different within each subset, and hence the two groups should be analysed separately. In addition, comparisons across the trials are not valid.

Length of stay

Initially, the length of stay in hospital was calculated as the number of days from admission day to the patient being discharged from hospital. *Table 13* shows that patients having an AH procedure generally stay in hospital for ~1 day longer than patients having the other procedures (that is, 5 days compared with 4), with 95% of AH patients leaving hospital by day 8 compared with day 7 for the other procedures.

Table 14 shows that approximately three times as many ALH as AH patients have been discharged from hospital by day 2 (after admission); 40% of AH patients have been discharged from hospital by day 4 (after admission) compared with 70% of

TABLE 14 *Frequency of length of stay [admission to discharge (days)] (abdominal trial)*

Days in hospital	AH *n* = 292	%	Cumulative %	ALH *n* = 584	%	Cumulative %
1	1	0.3	0.3	3	0.5	0.5
2	17	5.8	6.1	103	17.6	18.1
3	34	11.6	17.7	151	25.9	44
4	64	21.9	39.6	152	26	70
5	69	23.6	63.2	88	15.1	85.1
6	58	19.9	83.1	32	5.5	90.6
7	18	6.2	89.3	19	3.3	93.9
>7	20	6.8	96.1	16	2.7	96.6
Missing	11	5.1	100	20	3.4	100

TABLE 15 *Frequency of length of stay [admission to discharge (days)] (vaginal trial)*

Days in hospital	VH *n* = 168	%	Cumulative %	VLH *n* = 336	%	Cumulative %
1	0	0	0	1	0.3	0.3
2	14	8.3	8.3	27	8	8.3
3	47	27.9	36.2	88	26.2	34.5
4	37	22	58.2	88	26.2	60.7
5	37	22	80.2	56	16.7	77.4
6	16	9.5	89.7	32	9.5	86.9
7	4	2.4	92.1	10	3	89.9
>7	6	3.6	95.7	10	3	92.9
Missing	7	4.2	100	24	7.1	100

TABLE 16 *Postoperative length of stay [operation day to discharge (days)]*

	Abdominal		Vaginal	
	AH *n* = 292	ALH *n* = 584	VH *n* = 168	VLH *n* = 336
Mean (SD)	4.43 (2.49)	3.4 (2.57)	3.55 (1.89)	3.49 (1.89)
Median (min., max.)	4 (1, 36)	3 (1, 36)	3 (1, 16)	3 (1, 19)
95% discharged	7	6	6	6
Missing	12	16	7	21

ALH patients. By day 7 following admission, ~90% of all patients have been discharged from hospital.

Table 15 shows that similar proportions of patients are being discharged from hospital on the same day for the VH and VLH procedures; for example, 60% of VH and VLH patients have been discharged from hospital by day 4 (after admission). Approximately 90% of all patients have been discharged from hospital by day 7 (following admission).

Different centres have different policies on when they admit patients preoperatively; some centres admit patients on operation day whereas in other centres patients are admitted 1 day prior to the operation. Therefore, length of stay was also calculated as the number of days postoperation (that is, number of days from operation day to the day the patient is discharged from hospital). *Table 16* shows that AH patients are in hospital ~1 day longer following the operation than for the other procedures.

TABLE 17 *Frequency of postoperative length of stay (abdominal trial)*

Days in hospital	AH *n* = 292	%	Cumulative %	ALH *n* = 584	%	Cumulative %
1	1	0.3	0.3	6	1.0	1.0
2	19	6.5	6.8	171	29.3	30.3
3	58	19.9	26.7	199	34.1	64.4
4	99	33.9	60.6	116	19.9	84.3
5	64	21.9	82.5	43	7.4	91.7
6	22	7.5	90	15	2.6	94.3
7	5	1.7	91.7	8	1.4	95.7
>7	12	4.1	95.8	10	1.7	97.4
Missing	12	4.1	99.9	16	2.7	100

TABLE 18 *Frequency of postoperative length of stay (vaginal trial)*

Days in hospital	VH *n* = 168	%	Cumulative %	VLH *n* = 336	%	Cumulative %
1	2	1.2	1.2	2	0.6	0.6
2	37	22	23.2	83	24.7	25.3
3	58	34.5	57.7	109	32.4	57.7
4	38	22.6	80.3	75	22.3	80
5	15	8.9	89.2	26	7.7	87.7
6	4	2.4	91.6	8	2.4	90.1
7	2	1.2	92.8	4	1.2	91.3
>7	5	2.9	95.7	8	2.4	93.7
Missing	7	4.8	100	21	6.3	100

Table 17 shows that four times as many ALH patients as AH patients have been discharged from hospital by day 2 (following surgery) and <30% of AH patients have been discharged from hospital by day 3 following their operation compared with >60% of ALH patients. By day 6 (following surgery), ~90% of all patients have been discharged from hospital.

Table 18 shows that very similar proportions of patients are being discharged from hospital on the same day following surgery; for example, ~60% of all patients in the vaginal trial have been discharged from hospital by day 3 (following surgery) and 90% of all patients have been discharged from hospital by day 6 (following surgery).

Tables 19 and *20* show that there is some indication that patients having had an infection may have had a slightly longer hospital stay than those patients not having an infection. However, some of these patients will also have had major complications and other minor complications, hence these data are not conclusive.

Length of procedure

Table 21 shows the length of procedure, calculated from the first incision to the last suture, and it can be seen that the LH procedure generally takes ~30 minutes longer than either of the conventional methods (~75 compared with ~45 minutes). The LH procedure also generally takes longer within the abdominal trial (84 compared with 72 minutes), although these may be more difficult cases.

Table 22 shows the length of the procedure by the year of operation. Recruitment for the EVALUATE trial was over 4 years; during this time the training methods for laparoscopic surgery may have changed and the technique improved. However, it appears that the length of the VLH procedure has increased over time, whereas the length of the other procedures has not changed over time.

Table 23 shows the average length of each of the procedures by the surgeon's year of recruitment (that is, if a surgeon began recruiting patients into the EVALUATE study in 1997, that would be his

TABLE 19 *Length of stay [admission to discharge (days)] (abdominal trial)*

	AH		ALH	
	Infection *n* = 46	**No infection *n* = 235**	**Infection *n* = 86**	**No infection *n* = 478**
Mean (SD)	5.8 (5.1)	5.0 (2.0)	4.3 (4.0)	3.9 (1.9)
Median (min., max.)	5 (2, 37)	5 (1, 17)	4 (2, 38)	4 (1, 30)

TABLE 20 *Length of stay [admission to discharge (days)] (vaginal trial)*

	VH		VLH	
	Infection *n* = 24	**No infection *n* = 137**	**Infection *n* = 36**	**No infection *n* = 276**
Mean (SD)	5.0 (3.0)	4.2 (1.8)	5 (2.8)	4.2 (1.9)
Median (min., max.)	4 (2, 17)	4 (2, 16)	5 (1, 15)	4 (2, 20)

TABLE 21 *Length of procedure [first incision to last suture (minutes)]*

	Abdominal		Vaginal	
	AH *n* = 292	**ALH *n* = 584**	**VH *n* = 168**	**VLH *n* = 336**
Median (min., max.)	50 (19, 155)	84 (10, 325)	39 (14, 168)	72 (21, 220)
Missing	16	32	11	23

TABLE 22 *Length of procedure by year of operation*

Year	**Abdominal**				**Vaginal**			
	AH		**ALH**		**VH**		**VLH**	
	n	**Median (min., max.)**	***n***	**Median (min., max.)**	***n***	**Median (min., max.)**	***n***	**Median (min., max.)**
1996	10	57.5 (38, 130)	21	85 (38, 270)	6	29 (18, 52)	12	43 (25, 90)
1997	106	50 (20, 136)	220	84 (30, 325)	48	40 (18, 168)	93	65 (21, 200)
1998	74	50 (19, 155)	146	85 (10, 209)	34	33.5 (18, 120)	67	65 (29, 180)
1999	52	46.5 (25, 145)	102	81.5 (39, 140)	52	41.5 (14, 135)	89	80 (30, 185)
2000	34	60 (20, 100)	63	85 (12, 190)	17	40 (25, 120)	52	90 (31, 220)

TABLE 23 *Length of procedure by surgeon's recruitment date*

Year	Abdominal				Vaginal			
	AH		ALH		VH		VLH	
	n	Median (min., max.)	*n*	Median (min., max.)	*n*	Median (min., max.)	*n*	Median (min., max.)
1	1 3 9	51 (20, 130)	296	85 (30, 270)	76	42 (18, 168)	152	75 (21, 200)
2	8 5	50 (19, 155)	160	81 (10, 325)	53	40 (14, 120)	106	71 (29, 220)
3	4 1	48 (20, 100)	79	75 (22, 209)	21	30 (18, 80)	43	60 (30, 170)
4	1 0	47.5 (28, 63)	17	80 (12, 168)	7	34 (25, 60)	12	73 (31, 170)

TABLE 24 *Destination after operation*

	Abdominal		Vaginal	
	AH *n* = 292	ALH *n* = 584	VH *n* = 168	VLH *n* = 336
Gynaecological	277 (94.9%)	553 (94.7%)	157 (93.5%)	307 (91.4%)
HDW	0 (0%)	2 (0.3%)	1 (0.6%)	2 (0.6%)
ICU	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)
Missing	15 (5.1%)	28 (4.8%)	10 (6.0%)	27 (8.0%)

first year of recruitment). This was to indicate any possible learning curve effect over the period of time that surgeons recruited into this study. It was difficult to see whether the length of procedure changed with experience.

Destination after operation

Table 24 shows that virtually all patients returned to the gynaecological ward after surgery.

Conversions

Overall 3.3% (46) of patients converted preoperatively, for the following reasons:

- 25 patient decisions
- 10 named surgeons not available
- 3 lack of time
- 3 included in a training workshop
- 2 obesity
- 2 anaesthetist unhappy (1 obesity, 1 heart problem)
- 1 decision made preoperatively (no reason given).

Some 1.8% (25) of patients changed their minds about their procedure preoperatively. This could have been due to the length of the waiting time, which provided the opportunity for a change of decision. The mean waiting times for each procedure were 75.6 days (AH), 74.6 days (ALH), 68.9 days (VH) and 71.7 days (VLH). *Table 25* shows the mean, SD, median, interquartile range (IQR), minimum and maximum waiting times. *Table 26* shows these preoperative conversions, detailing the number of patients that converted from each procedure to which procedure.

One patient was randomised to an AH procedure and converted preoperatively (patient's decision) to ALH; during the procedure, the surgeon converted again from an ALH back to an AH procedure. This patient's data were analysed according to the ITT definition, and she was therefore analysed as an AH patient. Approximately 3% of all procedures were converted during the operation, for the following reasons:

TABLE 25 *Days between randomisation and operation day*

	AH *n* = 292	ALH *n* = 584	VH *n* = 168	VLH *n* = 336
Mean (SD)	75.6 (100.2)	74.6 (96)	68.9 (101.5)	71.7 (111.7)
Median	47	48	27	32
IQR	8, 82	8, 92	1, 90	1, 85
Min., max.	0, 511	0, 785	0, 475	0, 731
Withdrew	6	11	5	12
Missing[a]	3	2	0	1

[a] Missing operation dates; 3 patients have operation dates before randomisation date.

TABLE 26 *Summary of conversions (preoperatively)*

Conversion from	Conversion to				Total
	VH	VLH	ALH	AH	
VH		2	0	0	2
VLH	10		0	2	12
ALH	1	0		13	14
AH	1	0	17		18
Total	12	2	17	15	46

TABLE 27 *Summary of conversions (intraoperatively)*

Conversion from	Conversion to				Total
	VH	VLH	ALH	AH	
VH		5	0	2	7
VLH	0		0	9	9
ALH	0	0		23	23
AH	0	0	0	1	1
Total	0	5	0	35	40

- 20 additional pathology (adhesions, endometriosis, large fibroid, cancer of endometrium)
- 7 access (high cervix, uterus larger than expected, no descent of cervix, frozen pelvis, narrow vagina)
- 5 unable to complete hysterectomy
- 4 complication/injury
- 2 conversion after completion of operation
- 2 reason not given.

Table 27 shows these intraoperative conversions.

Primary end-point

The primary end-point of the study was whether a patient had at least one major complication (see Chapter 2) or not; the analysis is based on the number of subjects having at least one major complication.

The Trial Steering Committee agreed the major and minor complications in the protocol prior to the start of recruitment. Prior to analysis an independent clinical review was undertaken of the major complications. Major haemorrhage requiring a blood transfusion had been defined as a major complication; however, surgeons had reported major haemorrhage when in fact a blood transfusion had not occurred, and these were regarded as minor complications. Haematomas that required surgical drainage were regarded as major complications. Anaesthetic problems had been recorded for patients covering a wide range of clinical reasons, which ranged from "Anaphylactic reaction, 10 hours postoperatively due to morphine" to "postoperatively patient

TABLE 28 *Number of major complications per patient (ITT population)*

No. of major complications per patient	Abdominal				Vaginal					
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336		Total *n* = 1380	
1	16	(5.5%)	50	(8.6%)	15	(8.9%)	26	(7.7%)	107	(7.8%)
2	2	(0.7%)	13	(2.2%)	1	(0.6%)	5	(1.5%)	21	(1.5%)
3	0	(0%)	2	(0.3%)	0	(0%)	1	(0.3%)	3	(0.2%)
4	0	(0%)	0	(0%)	0	(0%)	1	(0.3%)	1	(0.07%)
Total	18	(6.2%)	65	(11.1%)	16	(9.5%)	33	(9.8%)	132	(9.6%)

drowsy, given Norcan". These were independently reviewed and categorised as major or minor complications.

Table 28 shows the number of major complications experienced by patients (ITT population); *Table 32* shows the number of each major complication (per protocol population).

The major complication rates within the abdominal trial were 6.2% (AH), 11.1% (ALH), with a difference of –4.9% (95% CI –9.1 to –0.9%, p = 0.02). The 95% CI of the difference does not span zero, therefore the complication rate for AH patients is statistically significantly lower than for ALH patients; however, the true difference between the complication rates could lie between 0.9 and 9.1%. If the true difference is at the lower end of this range, it may not be a clinically important difference. The major complication rates within the vaginal trial are 9.5% (VH), 9.8% (VLH), with a difference of –0.3% (95% CI –5.8 to 5.2%, p = 0.92). The difference between the complication rates for VH and VLH patients is very close to zero; the 95% CI ranges ±5%, that is, the true difference between the procedures may in fact be 5%, which may be a clinically important difference. There was an overall major complication rate of 9.6%.

A chi-squared test was used to identify a statistically significant difference between the types of operation within the two trial arms. As the ITT population includes all patients, even though some did not have an operation, a sensitivity analysis was used to assess the extremes of the effect that including these patients could have on the analysis.

Abdominal trial

- Assuming that all the patients who did not have an operation would not have had a major complication, the chi-squared test gives a test statistic of 5.59 on one degree of freedom (p = 0.02), which is statistically significant at the 5% level.
- Assuming that all patients who did not have an operation would have had a major complication, the chi-squared test gives a test statistic of 4.43 on one degree of freedom (p = 0.04), which is still statistically significant at the 5% level.

This indicates that the ALH procedure has a statistically significantly higher major complication rate than the AH procedure.

Vaginal trial

- Assuming that all the patients who did not have an operation would not have had a major complication, the chi-squared test gives a test statistic of 0.11 on one degree of freedom (p = 0.92), which is not statistically significant.
- Assuming that all patients who did not have an operation would have had a major complication, the chi-squared test gives a test statistic of 0.08 on one degree of freedom (p = 0.78), which is still not statistically significant at the 5% level.

This indicates that there is not a significant difference in the major complication rates between the VH and VLH procedure.

The sensitivity analysis did not change the significance of the results, indicating that the impact of including all 1380 patients in the analysis (even though some did not have an operation and could not have had a major complication) does not affect the significance of the results in either trial.

Major complications were reported in both the short and long term. The short term was defined as intraoperatively and/or up to discharge from hospital; the long term was defined as after discharge but prior to 6 weeks follow-up. *Table 29* shows the number of each of the major complications that were reported in the short term. The number of each of the long-term major complications is shown in *Table 30*.

TABLE 29 *Short-term major complications (short term being prior to discharge)*

Complication	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Major haemorrhage	7[a]	(2.4%)	27[a]	(4.6%)	5	(2.9%)	17	(5%)
Bowel injury	3	(1%)	1	(0.2%)	0	(0%)	0	(0%)
Ureteric injury	0	(0%)	3	(0.5%)	0	(0%)	0	(0%)
Bladder injury	3	(1%)	12[a]	(2.1%)	2	(1.2%)	3	(0.9%)
Pulmonary embolus	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Anaesthesia problems	0	(0%)	5[a]	(0.8%)	0	(0%)	2	(0.6%)
Unintended laparotomy								
Intra-op. conversion	1	(0.3%)	23	(3.9%)	7	(4.2%)	9	(2.7%)
Return to theatre	1	(0.3%)	0	(0%)	0	(0%)	0	(0%)
Wound dehiscence	1	(0.3%)	1	(0.2%)	0	(0%)	1	(0.3%)
Haematoma	1	(0.3%)	2	(0.5%)	0	(0%)	3	(0.9%)
Other complications	0	(0%)	0	(0%)	1	(0.6%)	0	(0%)

[a] These patients actually converted procedure prior to the operation: 1 AH patient converted to an ALH and had a major haemorrhage; 2 ALH patients converted to an AH and had a major haemorrhage; 1 ALH patient converted to an AH and had a major anaesthetic problem; 1 ALH patient converted to an AH and had a bladder injury.

TABLE 30 *Long-term major complications (long term after discharge and prior to 6 weeks follow-up)*

Complication	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Major haemorrhage	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Bowel injury	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Ureteric injury	0	(0%)	2	(0.3%)	0	(0%)	1	(0.3%)
Bladder injury	0	(0%)	3[a]	(0%)	0	(0%)	0	(0%)
Pulmonary embolus	2	(0.7%)	1	(0.2%)	0	(0%)	2	(0.6%)
Unintended laparotomy								
Return to theatre	0	(0%)	3	(0.5%)	0	(0%)	1	(0.3%)
Wound dehiscence	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Haematoma	1	(0.3%)	2	(0.3%)	2	(1.2%)	4	(1.2%)
Other complications	0	(0%)	0	(0%)	0	(0%)	0	(0%)

[a] 3 bladder injuries were reported at 6 weeks follow-up but had already been recorded as short-term complications.

It can be seen from *Tables 29* and *30* that major complications tended to occur before patients were discharged from hospital. *Table 31* includes the number of each type of major complication regardless of short or long term.

The formal analysis was based on the number of patients experiencing at least one major complication and did not take into account whether these occurred in the long or short term, or how many major complications each patient had.

Analysis of per-protocol population

The data were also analysed using a per-protocol population. In this analysis, patients were analysed according to the type of operation that was actually started: 46 patients had converted procedure preoperatively, the 34 patients who did not have an operation have remained in the analysis, and a sensitivity analysis around those patients was carried out. *Table 32* shows the major complication rates using a per-protocol population. The major complication rates compared with the ITT population have increased in the AH and VLH arms (7.3%, 10.1% respectively) and decreased in the ALH and VH arms (10.6%, 9% respectively); clearly the overall rate remains at 9.6%.

Again a chi-squared test was used to identify a statistically significant difference between the types

TABLE 31 *Major complications*

Complication	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Major haemorrhage	7	(2.4%)	27	(4.6%)	5	(2.9%)	17	(5.1%)
Bowel injury	3	(1%)	1	(0.2%)	0	(0%)	0	(0%)
Ureteric injury	0	(0%)	5	(0.9%)	0	(0%)	1	(0.3%)
Bladder injury	3	(1%)	15[a]	(2.1%)	2	(1.2%)	3	(0.9%)
Pulmonary embolus	2	(0.7%)	1	(0.2%)	0	(0%)	2	(0.6%)
Anaesthesia problems	0	(0%)	5	(0.9%)	0	(0%)	2	(0.6%)
Unintended laparotomy								
Intra-op. conversion	1	(0.3%)	23	(3.9%)	7	(4.2%)	9	(2.7%)
Return to theatre	1	(0.3%)	3	(1%)	0	(0%)	1	(0.3%)
Wound dehiscence	1	(0.3%)	1	(0.2%)	0	(0%)	1	(0.3%)
Haematoma	2	(0.7%)	4	(0.9%)	2	(1.2%)	7	(2.1%)
Other complications	0	(0%)	0	(0%)	1	(0.6%)	0	(0%)

[a] 3 bladder injuries have been recorded as short- and long-term complications.

TABLE 32 *Number of major complications per patient (per protocol population)*

No. of major complications per patient	Abdominal				Vaginal				Total	
	AH *n* = 289		ALH *n* = 587		VH *n* = 178		VLH *n* = 326		*n* = 1380	
1	19	(6.6%)	47	(8.0%)	15	(8.4%)	26	(8.0%)	107	(7.8%)
2	2	(0.7%)	13	(2.2%)	1	(0.6%)	5	(1.5%)	21	(1.5%)
3	0	(0%)	2	(0.3%)	0	(0%)	1	(0.3%)	3	(0.2%)
4	0	(0%)	0	(0%)	0	(0%)	1	(0.3%)	1	(0.07%)
Total	21	(7.3%)	62	(10.6%)	16	(9.0%)	33	(10.1%)	132	(9.6%)

of operation within the two trial arms. There was no statistically significant difference between the AH and ALH procedures within the abdominal trial ($p = 0.11$), or between the VH and VLH procedures within the vaginal trial ($p = 0.68$). Neither of these results was affected by the sensitivity analysis.

When the per-protocol population is used for the analysis instead of the ITT population, the significance of the result in the abdominal trial is affected. There is no longer a significant difference between the major complication rates for the AH and ALH procedures. However, the direction of the difference between the two procedures does not change, suggesting that there is a difference in the major complication rates between the two procedures in the abdominal trial. The difference between the procedures remains non-significant within the vaginal trial.

The per-protocol analysis is important as it reflects the complication rates for the procedures that were actually started; it represents the results from a safety point of view. It does not change the direction of the result and therefore supports the evidence of the main ITT analysis. No conclusions have been or would be changed as a result of this analysis. The ITT analysis is the primary analysis.

Adjusted comparison of major complications

Patients had been randomised within each trial according to the stratification factors: intended ovary removal, BMI ≤30 or >30 and surgeon. The analysis was adjusted for two of these stratification factors: intended ovary removal and BMI.

Table 33 shows the frequency of patients with a BMI of ≤30 compared with those with a BMI of >30 by the occurrence or not of a major complication. Approximately 80% of patients in all groups have a BMI of ≤30. Whether a patient had a major complication or not does not appear to be influenced by her BMI.

TABLE 33 *Frequency of BMI at randomisation by major complication*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Complication	**BMI ≤30**	**BMI >30**	**BMI ≤30**	**BMI >30**	**BMI ≤30**	**BMI >30**	**BMI ≤30**	**BMI >30**
Yes	14 (6.0%)	4 (6.6%)	46 (10.1%)	19 (14.9%)	12 (9.2%)	4 (10.5%)	25 (9.4%)	8 (11.6%)
No	218 (93.9%)	56 (93.3%)	411 (89.9%)	108 (85%)	118 (90.8%)	34 (89.5%)	242 (90.6%)	61 (88.4%)
Total	232 (79.5%)	60 (20.5%)	457 (78.3%)	127 (21.7%)	130 (77.4%)	38 (22.6%)	267 (79.5%)	69 (20.5%)

TABLE 34 *Frequency of intended ovary removal by major complication*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
	Intended ovary removal		Intended ovary removal		Intended ovary removal		Intended ovary removal	
Complication	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Yes	8 (5.8%)	10 (6.5%)	32 (11.7%)	33 (10.6%)	4 (10.8%)	12 (9.2%)	6 (7.9%)	27 (10.4%)
No	129 (94.2%)	145 (93.5%)	242 (88.3%)	277 (89.4%)	33 (89.2%)	119 (90.8%)	70 (92.1%)	233 (89.6%)
Total	137 (46.9%)	155 (53.1%)	274 (46.9%)	310 (53.1%)	37 (22%)	131 (77.9%)	76 (22.6%)	260 (77.4%)

TABLE 35 *Odds ratios and 95% confidence intervals for stratification factors*

Variable (comparison)	Abdominal			Vaginal		
	p	OR	95% CI	*p*	OR	95% CI
Type of operation (conv. vs lap.)	0.02	0.53	0.3 to 0.9	0.9	0.97	0.5 to 1.8
BMI (≤30 vs >30)	0.15	0.7	0.4 to 1.1	0.54	0.8	0.4 to 1.6
Intended ovary removal (yes vs no)	0.84	1.1	0.7 to 1.7	0.7	0.86	0.2 to 1.8

Table 34 shows the frequency of patients where ovary removal had been intended prior to surgery by the occurrence or not of a major complication. Approximately 50% of patients in the abdominal trial had intended ovary removal compared with <25% in the vaginal trial. However, the complication rate does not appear to be influenced by intended ovary removal.

Logistic regression was used to adjust the major complication rates for type of operation by the two stratification factors BMI and intended ovary removal.

Using the data from the abdominal trial initially, BMI and intended ovary removal were not significant in the analysis. *Table 35* shows the

TABLE 36 *Frequency of type of incision (abdominal hysterectomy)*

Type of incision	Major complication		Total
	Yes	No	
Pfannenstiel	15 (5.9%)	239 (94.1%)	254 (86.9%)
Others	3 (13.6%)	19 (86.4%)	22 (7.5%)
Missing			16 (5.5%)
Total	18 (6.2%)	258 (88.4%)	292 (100%)

TABLE 37 *Frequency of previous pelvic surgery (abdominal hysterectomy)*

Previous pelvic surgery	Major complication		Total
	Yes	No	
Yes	13 (7%)	172 (93%)	185 (63.4%)
No	5 (4.8%)	100 (95.2%)	105 (35.9%)
Missing			2 (0.7%)
Total	18 (6.2%)	272 (93.2%)	292 (100%)

TABLE 38 *Frequency of uterine mobility (abdominal hysterectomy)*

Uterine mobility	Major complication		Total
	Yes	No	
Fixed	3 (10%)	27 (90%)	30 (10.3%)
Freely mobile	15 (5.7%)	246 (94.3%)	261 (89.4%)
Missing			1 (0.34%)
Total	18 (6.2%)	273 (93.5%)	292 (100%)

unadjusted OR for type of operation, The OR indicates that patients having an ALH procedure are approximately twice as likely to have a major complication as patients having an AH procedure.

Using the data from the vaginal trial, BMI, intended ovary removal and type of operation were not significant in the model. *Table 35* shows the unadjusted OR for type of operation. The OR is almost one, indicating that the odds of a patient experiencing a major complication are the same for VH as for VLH patients.

Prediction of major complications

Logistic regression was used to identify any important variables that may influence whether a patient was likely to have a major complication or not. Variables to be considered in the logistic regression were decided by the Trial Steering Committee. The variables were different for each type of procedure. This analysis was carried out within each type of procedure.

AH

The variables thought to be potentially important in the prediction of the occurrence of a major complication for patients having an AH procedure were type of incision, previous pelvic surgery, uterine mobility, vaginal capacity, palpable endometriosis, uterine descent and uterine size. Vaginal capacity was a clinical assessment and was categorised as 'narrow/normal/large'; there are no standard definitions. It was expected that 'narrow' would reflect more difficult access. *Tables 36–42* show the frequency of each of these variables by occurrence or not of a major complication.

Table 36 shows that almost 87% of AH operations used the Pfannenstiel type of incision. The frequency of the midline and the paramedian incision were so sparse that they were re-categorised and added to the 'other' category for this analysis. Of the 22 patients who had an 'other' type of incision, three (almost 14%) had a major complication.

Table 37 shows that ~63% of patients who had an AH operation had had previous pelvic surgery. Of these, 7% had a major complication compared with 5% who had not had previous pelvic surgery.

TABLE 39 *Frequency of vaginal capacity (abdominal hysterectomy)*

Vaginal capacity	Major complication		Total
	Yes	No	
Narrow	1 (7.1%)	13 (92.9%)	14 (4.8%)
Normal	16 (5.8%)	259 (94.2%)	275 (94.2%)
Large	1 (50%)	1 (50%)	2 (0.7%)
Missing			1 (0.34%)
Total	18 (6.2%)	273 (3.5%)	292 (100%)

TABLE 40 *Frequency of palpable endometriosis (abdominal hysterectomy)*

Palpable endometriosis	Major complication		Total
	Yes	No	
Yes	0 (0%)	10 (100%)	10 (3.4%)
No	18 (6.5%)	260 (93.5%)	278 (95.2%)
Missing			4 (1.4%)
Total	18 (6.2%)	270 (92.5%)	292 (100%)

TABLE 41 *Frequency of uterine descent (abdominal hysterectomy)*

Uterine descent	Major complication		Total
	Yes	No	
No descent	14 (6%)	220 (94%)	234 (80.1%)
1st degree	4 (7%)	53 (93%)	57 (19.5%)
Missing			1 (0.34%)
Total	18 (6.2%)	273 (93.5%)	292 (100%)

TABLE 42 *Frequency of uterine size (abdominal hysterectomy)*

Uterine size (weeks)	Major complication		Total
	Yes	No	
0	4 (5.8%)	64	68 (23.3%)
1–4	2 (4.8%)	40	42 (14.4%)
5 + 6	6 (7.5%)	73	79 (27.1%)
7 + 8	4 (7.8%)	47	51 (17.5%)
9 + 10	2 (5.7%)	33	35 (11.9%)
11 + 12	0 (0%)	17	17 (5.8%)
Missing	0		0 (0%)
Total	18 (6.2%)	274	292 (100%)

TABLE 43 *Frequency of training procedures (abdominal hysterectomy)*

Training procedure	Major complication		Total
	Yes	No	
Yes	4 (4.3%)	88 (95.7%)	92 (31.5%)
No	14 (7.6%)	171 (92.4%)	185 (63.4%)
Missing			15 (5.1%)
Total	18 (6.2%)	259 (88.7%)	292 (100%)

TABLE 44 *Odds ratios and 95% confidence intervals for predictive variables (abdominal hysterectomy)*

Variable (comparison)	*p*	OR	95% CI
Type of incision (Pfannenstiel vs rest)	0.21	0.39	0.11 to 1.49
Previous pelvic surgery (yes vs no)	0.43	1.5	0.5 to 4.4
Uterine mobility (fixed vs freely mobile)	0.39	1.82	0.49 to 6.7
Vaginal capacity			
Narrow vs large	0.22	0.08	0.002 to 2.39
Normal vs large		0.06	0.004 to 1.03
Palpable endometriosis		No convergence	
Uterine descent (no descent vs 1st degree)	0.78	0.84	0.26 to 2.66
Uterine size (per additional week)	0.85	0.99	0.87 to 1.13
Training procedure (yes vs no)	0.29	0.5	0.18 to 1.74

TABLE 45 *Frequency of previous pelvic surgery (vaginal hysterectomy)*

Previous pelvic surgery	Major complication		Total
	Yes	No	
Yes	6 (5.9%)	96 (94.1%)	102 (60.7%)
No	10 (15.6%)	54 (84.4%)	64 (38.1%)
Missing			2 (1.2%)
Total	16 (9.5%)	150 (89.3%)	168 (100%)

Table 38 shows that almost 90% of AH patients had a freely mobile uterus. Of the 30 patients who had a fixed uterus, three (10%) had a major complication.

Table 39 shows that almost 95% of AH patients had a 'normal' vaginal capacity. The data in the narrow and large categories are so sparse it is difficult to draw any conclusions from these data.

Table 40 shows that only 10 (3.4%) of AH patients had palpable endometriosis, and none of these patients experienced a major complication.

Table 41 shows that ~80% of AH patients had no uterine descent; of these, 6% had a major complication compared with 7% of patients with first-degree uterine descent.

Table 42 shows the frequency of the uterine size in terms of weeks of pregnancy for AH patients. The frequency of patients in each category is similar and the complication rates within each category range from 4.8 to 7.8%.

Table 43 shows the frequency of the operations that were training procedures for AH patients. Approximately one-third of operations were training procedures; the complication rate is lower amongst the training procedures (4.3 compared with 7.6%).

Table 44 shows the *p*-value, OR and 95% CI for each of the variables in the model. The model containing palpable endometriosis did not converge, as there were only 10 patients with palpable endometriosis, none of whom had a major complication.

None of these variables (type of incision, previous pelvic surgery, uterine mobility, vaginal capacity, palpable endometriosis, uterine descent, uterine size or training procedure) were important predictors of major complications in AH patients.

VH

The variables thought to be potentially important in the prediction of the occurrence of a major complication for patients having a VH procedure were previous pelvic surgery, uterine size, uterine descent, uterine mobility, palpable endometriosis and vaginal capacity. *Tables 45–52* show the frequency of each of these variables by occurrence or not of a major complication.

Table 45 shows that ~61% of patients having a VH operation had had previous pelvic surgery. Of these, 6% had a major complication compared with 16% of those not having previous pelvic surgery.

Table 46 shows that ~96% of all VH patients had a freely mobile uterus; 15 of the 16 patients who had a major complication had a freely mobile uterus.

TABLE 46 *Frequency of uterine mobility (vaginal hysterectomy)*

Uterine mobility	Major complication		Total
	Yes	No	
Fixed	1 (20%)	4 (80%)	5 (2.9%)
Freely mobile	15 (9.3%)	147 (90.7%)	162 (96.4%)
Missing			1 (0.6%)
Total	16 (9.5%)	151 (89.9%)	168 (100%)

TABLE 47 *Frequency of vaginal capacity (vaginal hysterectomy)*

Vaginal capacity	Major complication		Total
	Yes	No	
Narrow	1 (12.5%)	7 (87.5%)	8 (4.8%)
Normal	15 (9.6%)	142 (90.4%)	157 (93.5%)
Large	0 (0%)	2 (100%)	2 (1.2%)
Missing			1 (0.6%)
Total	16 (9.5%)	151 (89.9%)	168 (100%)

TABLE 48 *Frequency of palpable endometriosis (vaginal hysterectomy)*

Palpable endometriosis	Major complication		Total
	Yes	No	
Yes	0 (0%)	1 (100%)	1 (0.6%)
No	16 (9.6%)	150 (90.4%)	166 (98.8%)
Missing			1 (0.6%)
Total	16 (9.5%)	151 (89.9%)	168 (100%)

TABLE 49 *Frequency of uterine descent (vaginal hysterectomy)*

Uterine descent	Major complication		Total
	Yes	No	
No descent	12 (11.3%)	94 (88.7%)	106 (63.1%)
1st degree	4 (6.6%)	57 (93.4%)	61 (36.3%)
Missing			1 (0.6%)
Total	16 (9.5%)	151 (89.9%)	168 (100%)

Table 47 shows that >90% of all VH patients had a 'normal' vaginal capacity; 15 of the 16 who had a major complication had a 'normal' vaginal capacity.

Table 48 shows that only one patient who had a VH had palpable endometriosis and she did not have a major complication.

Table 49 shows that ~63% of VH patients had no uterine descent; 12 (11.3%) of these did have a major complication compared with 4 (6.6%) of the 61 patients who had first-degree uterine descent.

Table 50 shows that the frequency of VH patients within each of the categories for uterine size in weeks of pregnancy is normally distributed with similar numbers in each category; however, only eight patients are in the 11- and 12-week category. The major complication rate varies from 4.8 to 12.5% across the size categories.

TABLE 50 *Frequency of uterine size (vaginal hysterectomy)*

Uterine size (weeks)	Major complication		Total
	Yes	No	
0	4 (11.8%)	30 (88.2%)	34 (20.2%)
1–4	1 (5%)	19 (95%)	20 (11.9%)
5 + 6	5 (11.1%)	40 (88.9%)	45 (26.8%)
7 + 8	3 (7.9%)	35 (92.1%)	38 (22.6%)
9 + 10	1 (4.8%)	20 (95.2%)	21 (12.5%)
11 + 12	1 (12.5%)	7 (87.5%)	8 (4.8%)
Missing	1 (50%)	1 (50%)	2 (1.2%)
Total	16 (9.5%)	152 (90.5%)	168 (100%)

TABLE 51 *Frequency of training procedures (vaginal hysterectomy)*

Training procedure	Major complication		Total
	Yes	No	
Yes	7 (13.7%)	44 (86.3%)	51 (30.4%)
No	9 (8.3%)	99 (91.7%)	108 (64.3%)
Missing			9 (5.4%)
Total	16 (9.5%)	143 (85.1%)	168 (100%)

TABLE 52 *Odds ratios and 95% confidence intervals for predictive variables (vaginal hysterectomy)*

Variable (comparison)	*p*	OR	95% CI
Previous pelvic surgery (yes vs no)	0.04	0.34	0.12 to 0.98
Uterine mobility (fixed vs freely mobile)	0.47	2.45	0.25 to 23.4
Vaginal capacity		No convergence	
Palpable endometriosis		No convergence	
Uterine descent (no descent vs 1st degree)	0.30	1.82	0.56 to 5.91
Uterine size (per additional week)	0.64	0.96	0.83 to 1.12
Training procedure (yes vs no)	0.30	1.7	0.61 to 5

Table 51 shows the frequency of the operations that were training procedures for VH patients. Approximately one-third of operations were training procedures and the complication rate is higher amongst the training procedures (13.7% compared with 6.3%).

Table 52 shows the *p*-values, the ORs and 95% CIs for each variable. The models containing vaginal capacity and palpable endometriosis did not converge; none of the 10 patients who did not have a 'normal' vaginal capacity had a major complication, nor did the one patient that had palpable endometriosis.

From *Table 52*, it can be seen that only previous pelvic surgery was significantly important in predicting major complications for VH patients; if a patient had not had previous pelvic surgery, she was three times more likely to experience a major complication.

LH – combined

As the LH procedure is the same in both of these trials, the two groups of LH patients can be combined for this analysis. This group is representative of all patients who have an LH procedure.

The variables that were thought to be important in the prediction of major complications for the LH procedure were previous pelvic surgery, uterine size, uterine descent, uterine mobility, palpable endometriosis, vaginal capacity, size of trocars, number of abdominal incisions, type of laparoscopic incision, haemostasis of the ovarian and uterine pedicles and maximum intraoperative CO_2 pressure (mmHg) (*Tables 53–68*).

Table 53 shows that just over 60% of LH patients had had previous pelvic surgery, of whom 10% had a major complication compared with 11.5% of those who had not had previous pelvic surgery.

TABLE 53 *Frequency of previous pelvic surgery (laparoscopic hysterectomy)*

Previous pelvic surgery	Major complication		Total
	Yes	No	
Yes	57 (10.1%)	508 (89.9%)	565 (61.4%)
No	40 (11.5%)	309 (88.5%)	349 (37.9%)
Missing	1 (16.7%)	5 (83.3%)	6 (0.7%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 54 *Frequency of uterine mobility (laparoscopic hysterectomy)*

Uterine mobility	Major complication		Total
	Yes	No	
Fixed	7 (12.5%)	49 (87.5%)	56 (6.1%)
Freely mobile	90 (10.5%)	770 (89.5%)	860 (93.5%)
Missing	1 (25%)	3 (75%)	4 (0.4%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 55 *Frequency of vaginal capacity (laparoscopic hysterectomy)*

Vaginal capacity	Major complication		Total (%)
	Yes	No	
Narrow	7 (17.9%)	32 (82.1%)	39 (4.2%)
Normal	90 (10.3%)	781 (89.7%)	871 (94.7%)
Large	0 (0%)	6 (100%)	6 (0.6%)
Missing	1	3 (75%)	4 (0.4%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 56 *Frequency of palpable endometriosis (laparoscopic hysterectomy)*

Palpable endometriosis	Major complication		Total
	Yes	No	
Yes	4 (21%)	15 (78.9%)	19 (2.1%)
No	92 (10.3%)	797 (89.7%)	889 (96.6%)
Missing	2 (16.7%)	10 (83.3%)	12 (1.3%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 57 *Frequency of uterine descent (laparoscopic hysterectomy)*

Uterine descent	Major complication		Total
	Yes	No	
No descent	81 (11.9%)	600 (88.1%)	681 (74%)
Ist degree	16 (6.8%)	218 (93.2%)	234 (25.4%
Missing	1 (20%)	4 (80%)	5 (0.5%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

Table 54 shows that >90% of LH patients had a freely mobile uterus, of whom 10% had a major complication compared with 12.5% of patients who had a fixed uterus.

Table 55 shows that ~95% of VH patients had a 'normal' vaginal capacity, of whom 10% had a major complication compared with almost 18% of those with a 'narrow' vaginal capacity.

Table 56 shows that 19 (2.1%) of LH patients had palpable endometriosis; of these, four (21%) had a major complication compared with 10% of those who did not have palpable endometriosis.

TABLE 58 *Frequency of type laparoscopic incision (laparoscopic hysterectomy)*

Type of laparoscopic incision	Major complication		Total
	Yes	No	
Laparoscopic	12 (6.1%)	184 (93.9%)	196 (21.3%)
Laparoscopic-assisted vaginal	52 (9.5%)	497 (90.5%)	549 (59.7%)
Total laparoscopic	3 (5.3%)	55 (94.8%)	58 (6.3%)
Other laparoscopic	2 (5.7%)	33 (94.3%)	35 (3.8%)
Missing	29 (35.4%)	53 (64.6%)	82 (8.9%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 59 *Frequency of number of abdominal incisions (laparoscopic hysterectomy)*

Number of abdominal incisions	Major complication		Total
	Yes	No	
1–3	48 (9.4%)	465 (90.6%)	513 (55.8%)
4–6	28 (8.8%)	292 (91.2%)	320 (34.8%)
Missing	22 (25.3%)	65 (74.7%)	87 (9.5%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 60 *Frequency of size 12-mm trocars used (laparoscopic hysterectomy)*

Size 12-mm trocars	Major complication		Total
	Yes	No	
No	32 (7.9%)	407 (92.7%)	439 (47.7%)
Yes	44 (11.1%)	351 (88.9%)	395 (42.9%)
Missing	22 (25.6%)	64 (74.4%)	86 (9.3%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 61 *Frequency of size 10-mm trocars used (laparoscopic hysterectomy)*

Size 10-mm trocars	Major complication		Total
	Yes	No	
No	20 (8.8%)	208 (91.2%)	228 (24.8%)
Yes	57 (9.4%)	551 (90.6%)	608 (66.1%)
Missing	21 (25%)	63 (75%)	84 (9.1%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

Table 57 shows that ~75% of LH patients had no uterine descent; of these, 11.9% had a major complication compared with 6.8% of those with first-degree uterine descent.

Table 58 shows that ~60% of LH procedures used the 'laparoscopic-assisted vaginal' type of incision; of these, 9.5% had a major complication. Unfortunately, for 29 of the 98 patients who had a major complication, the data for the type of laparoscopic incision are missing.

Table 59 shows that ~56% of LH procedures had 1–3 incisions; of these, 9.4% of patients experienced a major complication compared with 8.8% of patients who had 4–6 incisions. The data for the number of incisions are missing for 22 (22.4%) of the patients who had a major complication.

It was expected that major complications were more likely to occur in procedures where larger trocars had been used. *Table 60* shows that almost 43% of LH procedures did use 12-mm trocars; 11.1% of these patients had a major complication compared with 7.9% of patients where 12-mm trocars had not been used; data are missing for 22/98 (22.4%) of the patients who had a major complication. Although procedures that used 12-mm trocars did have a slightly higher complication rate, it is not significant.

TABLE 62 *Frequency of size 5-mm trocars used (laparoscopic hysterectomy)*

Size 5-mm trocars	Major complication		Total
	Yes	No	
No	27 (9.6%)	254 (90.4%)	281 (30.5%)
Yes	49 (8.9%)	504 (91.1%)	553 (60.1%)
Missing	22 (25.6%)	64 (74.4%)	86 (9.3%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 63 *Frequency of size of trocar used (laparoscopic hysterectomy)*

Trocars used	Major complication		Total
	Yes	No	
5-mm only	1 (20%)	4 (80%)	5 (0.5%)
10-mm only	4 (8.3%)	44 (91.7%)	48 (5.2%)
12-mm only	3 (3.4%)	85 (96.6%)	88 (9.6%)
5- and 10-mm	28 (7.2%)	361 (92.8%)	389 (42.3%)
5- and 12-mm	17 (12.4%)	120 (87.6%)	137 (14.9%)
10- and 12-mm	20 (13.7%)	126 (86.3%)	146 (15.9%)
5-, 10- and 12-mm	4 (17.4%)	19 (82.6%)	23 (2.5%)
Missing	21 (25%)	63 (75%)	84 (9.1%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 64 *Frequency of uterine size (laparoscopic hysterectomy)*

Uterine size	Major complication		Total
	Yes	No	
0	13 (7.6%)	159 (92.4%)	172 (18.7%)
1–4	17 (12.8%)	116 (87.2%)	133 (14.5%)
5 + 6	22 (9.5%)	210 (90.5%)	232 (25.2%)
7 + 8	20 (10.9%)	164 (89.1%)	184 (20%)
9 + 10	18 (13.7%)	113 (86.3%)	131 (14.2%)
11 + 12	7 (11.9%)	52 (88.1%)	59 (6.4%)
Missing	1 (11.1%)	8 (88.9%)	9 (0.9%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

Table 61 shows that ~66% of LH procedures used 10-mm trocars; of these patients, 9.4% had a major complication compared with 8.8% of patients where a 10-mm trocar was not used.

Table 62 shows that ~60% of LH procedures used a 5-mm trocar; of these patients, 8.9% had a major complication compared with 9.6% of patients where a 5-mm trocar was not used.

Table 63 shows the combination of the size of trocars that were used for LH procedures. For example, only five operations used 5-mm trocars and 23 operations used 5-, 10- and 12-mm trocars. *Table 63* indicates that the most popular approach is to use 5- and 10-mm trocars (42% of operations). Data are missing for 21 of the 98 patients who had a major complication. The complication rate varies from 3.4% (12 mm only) to 20% (5 mm only); however, for the 5-mm group there are only five patients. Some 17.4% of patients had a major complication when all three sizes of trocars were used.

Table 64 shows the distribution of patients across all categories of uterine size measured in weeks of pregnancy; this is relatively evenly distributed, the complication rates varying from 7.6% (0 weeks) to 13.7% (9 and 10 weeks).

Table 65 shows that more than half of all LH procedures use a maximum CO_2 pressure from 11 to <20 mmHg. The complication rates are very similar in these three categories, ranging from 6.3 to 9.7%.

TABLE 65 *Frequency of maximum intraoperative CO_2 pressure (mmHg) (laparoscopic hysterectomy)*

Maximum CO_2 pressure (mmHg)	Major complication		Total
	Yes	No	
≤ 10	2 (6.3%)	30 (93.8%)	32 (3.5%)
11–<20	56 (9.7%)	523 (90.3%)	579 (62.9%)
≥ 20	18 (8.1%)	204 (91.9%)	222 (24.1%)
Missing	22 (25.3%)	65 (74.7%)	87 (9.5%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 66 *Frequency of haemostasis: ovarian pedicle (laparoscopic hysterectomy)*

Ovarian pedicle	Major complication		Total
	Yes	No	
Bipolar	46 (8.6%)	486 (91.4%)	532 (57.8%)
Linear stapler	24 (10.9%)	196 (89.1%)	220 (23.9%)
Suture	24 (35.3%)	44 (64.7%)	68 (7.4%)
Other	4 (7.1%)	52 (92.9%)	56 (6.1%)
Missing	0 (0%)	44 (100%)	44 (4.8%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 67 *Frequency of haemostasis: uterine pedicle (laparoscopic hysterectomy)*

Uterine pedicle	Major complication		Total
	Yes	No	
Bipolar	13 (8.2%)	146 (91.8%)	159 (17.3%)
Linear stapler	10 (7.4%)	125 (92.6%)	135 (14.7%)
Suture	73 (13.5%)	468 (86.5%)	541 (58.8%)
Other	2 (5.1%)	37 (94.9%)	39 (4.2%)
Missing	0 (0%)	46 (100%)	46 (5%)
Total	98 (10.7%)	822 (89.3%)	920 (100%)

TABLE 68 *Frequency of training procedures (laparoscopic hysterectomy)*

Training procedure	Major complication		Total
	Yes	No	
Yes	32 (9.6%)	301 (90.4%)	333 (36.2%)
No	65 (12.1%)	472 (87.9%)	537 (58.4%)
Missing			50 (5.4%)
Total	97 (10.5%)	773 (84%)	920 (100%)

Table 66 shows that more than half of LH procedures use the bipolar method of haemostasis (which uses electrical current to seal blood vessels) on the ovarian pedicle. Of these patients, 46 (8.6%) have a major complication compared with 24 (35.3%) of patients where the suturing method was used. This accounts for 24 of the 98 patients who had a major complication, almost 25% of all major complications for LH patients.

Table 67 shows that more than half of LH procedures used suturing for the uterine pedicle; of these patients, 13.5% experienced a major complication.

Table 68 shows the frequency of the operations that were training procedures for LH patients. Approximately one-third of operations were training procedures and the complication rate is lower amongst the training procedures (9.6% compared with 12.1%).

TABLE 69 *Odds ratios and 95% confidence intervals for predictive variables (laparoscopic hysterectomy)*

Variable (comparison)	*p*	OR	95% CI
Previous pelvic surgery (yes vs no)	0.51	0.87	0.56 to 1.33
Uterine mobility (fixed vs freely mobile)	0.64	1.22	0.54 to 2.78
Vaginal capacity (narrow vs normal, large)	0.16	1.91	0.82 to 4.45
Palpable endometriosis (yes vs no)	0.18	2.31	0.75 to 7.11
Uterine descent (no descent vs 1st degree)	0.02	1.84	1.05 to 3.21
Type of lap incision			
Laparoscopic vs other		1.08	0.23 to 5.03
LH vs other	0.32	1.72	0.40 to 7.4
Total laparoscopic vs other		0.9	0.14 to 5.67
Number of incisions (1–3 vs 4–6)	0.77	1.08	0.66 to 1.75
Uterine size (per additional week)	0.15	1.05	0.98 to 1.11
Max. intraoperative CO_2 pressure (mmHg)			
≤ 10 vs ≥ 20	0.74	0.91	0.19 to 4.14
11–<20 vs ≥ 20)		1.21	0.69 to 2.11
Haemostasis: uterine pedicle			
Bipolar vs other		1.65	0.36 to 7.6
Linear stapler vs other	0.04	1.48	0.31 to 7.1
Suture vs other		2.89	0.68 to 12.2
Haemostasis: ovarian pedicle			
Bipolar vs other		1.23	0.43 to 3.56
Linear stapler vs other	<0.001	1.59	0.53 to 4.79
Suture vs other		7.09	2.29 to 21.99
Training procedure (yes vs no)	0.25	0.77	0.49 to 1.21

Table 69 details the *p*-value, the OR and 95% CI for each variable. *Table 69* shows that uterine descent and haemostasis of both the uterine pedicle and the ovarian pedicle are significantly important variables in the prediction of major complications. The OR for uterine descent indicates that patients with no descent are approximately twice as likely to have a major complication as those with first-degree descent. Patients who were sutured on the uterine pedicle were almost three times as likely to have a major complication than patients where an 'other' method of haemostasis is used. Patients who were sutured on the ovarian pedicle were seven times more likely to have a major complication than patients where an 'other' method is used.

Secondary end-points

The secondary end-points of this study are minor complications, blood loss (intraoperatively), pain assessment, sexual activity, body image, health status and QoL.

Minor complications

The Trial Steering Committee agreed the major and minor complications in the protocol prior to the start of recruitment. Pulmonary embolus was regarded as a major complication with DVT being its precursor. DVT in itself is considered a minor complication, although it is recognised that it can develop into a more serious complication.

The analysis of the minor complication rates used the same statistical methods as the analysis of the major complications. *Table 70* shows the frequency of the minor complications that were experienced by patients. The minor complications within the abdominal trial were 27.1% AH and 25.2% ALH with a difference of –1.9% (95% CI –8.0 to 4.3%, $p = 0.55$). The minor complication rates within the vaginal trial were 27.9% VH and 23.2% VLH with a difference of –4.8% (95% CI –12.8 to 3.3%, $p = 0.24$). There was an overall minor complication rate of 25.4%.

Table 70 shows the number of minor complications that were experienced per patient. Approximately 75% of patients who did have a minor complication only had one. However, one patient had five minor complications. The analysis is based on whether a patient had a minor complication or not, and does not use the frequency of minor complications.

TABLE 70 *Number of minor complications per patient*

No. of minor complications per patient	Abdominal				Vaginal					
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336		Total *n* = 1380	
1	62	(21.2%)	112	(19.2%)	35	(20.8%)	61	(18.2%)	270	(19.6%)
2	15	(5.1%)	27	(4.6%)	7	(4.2%)	12	(3.6%)	61	(4.4%)
3	2	(0.7%)	7	(1.2%)	3	(1.8%)	2	(0.6%)	14	(1%)
4	0	(0%)	0	(0%)	2	(1.2%)	3	(0.9%)	5	(0.4%)
5	0	(0%)	1	(0.2%)	0	(0%)	0	(0%)	1	(0.07%)
Total	79	(27.1%)	147	(25.2%)	47	(27.9%)	78	(23.2%)	351	(25.4%)

A chi-squared test was used to identify a statistically significant difference between the types of operation within the two trial arms. As the ITT population includes all patients, even though some did not have an operation, a sensitivity analysis was used to assess the extremes of the effect that including these patients could have on the analysis.

Abdominal trial

- Assuming that all patients who did not have an operation would not have a minor complication, the chi-squared test gives a test statistic of 0.36 on one degree of freedom ($p = 0.55$), which is not statistically significant.
- Assuming that all patients who did not have an operation would have had a minor complication, the chi-squared test gives a test statistic of 0.48 on one degree of freedom ($p = 0.49$), which is still not statistically significant.

This indicates that there is not a significant difference in the minor complication rates between the AH and ALH procedures.

Vaginal trial

- Assuming that all patients who did not have an operation would not have a minor complication, the chi-squared test gives a test statistic of 1.36 on one degree of freedom ($p = 0.24$), which is not statistically significant.
- Assuming that all patients who did not have an operation would have had a minor complication, the chi-squared test gives a test statistic of 0.72 on one degree of freedom ($p = 0.40$), which is still not statistically significant.

Again the sensitivity analysis did not change the significance of these results, indicating that the impact of including all 1380 randomised patients (although some patients did not have an operation and could not have had a minor complication) did not affect the significance of the results in either trial.

Minor complications were reported in both the short and long term. *Table 71* shows the number of each of the minor complications that were reported in the short term. It can be seen that pyrexia is one of the most frequently reported minor complications in the short term.

Table 72 shows that of the long-term minor complications, infection is the most commonly reported in both trial arms following a patient's discharge from hospital.

Table 73 shows all minor complications reported in both the short and long term. It can be seen that infection is the most commonly reported of the minor complications within each trial arm. Approximately 15% of all patients had an infection; approximately half of the patients having a minor complication had an infection. The table shows that almost 30% of patients having an ALH procedure had an infection.

Per-protocol analysis

The analysis of the minor complications was repeated using the per-protocol population. *Table 74* shows the number of patients experiencing a minor complication according to the procedure that was actually started. The minor complication rates for the per-protocol population show slight differences from the ITT population. The rates are increased for AH and VLH to 29.1 and 23.3%, respectively, and decreased for ALH and VH to 24.2 and 27.5%, respectively.

A chi-squared test was used to identify a statistically significant difference between the types

TABLE 71 *Short-term minor complications (short term being prior to discharge)*

Complication	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Haemorrhage	3	(1%)	6	(0.9%)	2	(1.2%)	8	(2.4%)
Anaesthesia problems	0	(0%)	2	(0.3%)	1	(0.6%)	3	(0.9%)
Pyrexia	6	(2.1%)	20	(3.4%)	9	(5.4%)	15	(4.5%)
Infection	15	(5.1%)	16	(2.7%)	4	(2.4%)	7	(2.1%)
Haematoma	7	(2.4%)	3	(0.5%)	4	(2.4%)	3	(0.9%)
DVT	0	(0%)	1	(0.2%)	0	(0%)	0	(0%)
Other complications	11	(3.8%)	22	(3.8%)	10	(5.9%)	18	(5.4%)

TABLE 72 *Long-term minor complications (long term after discharge and prior to 6 weeks' follow-up)*

Complication	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Haemorrhage	0	(0%)	2	(0.3%)	0	(0%)	0	(0%)
Pyrexia	3	(1%)	9	(1.5%)	3	(1.8%)	3	(0.9%)
Infection	32	(11.0%)	70	(11.9%)	20	(11.9%)	29	(8.6%)
Haematoma	10	(3.4%)	22	(3.8%)	6	(3.6%)	11	(3.3%)
DVT	0	(0%)	1	(0.2%)	0	(0%)	0	(0%)
Other complications	11	(3.8%)	18	(3.1%)	7	(4.2%)	6	(1.8%)

TABLE 73 *All minor complications*

Complication	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Haemorrhage	3	(1%)	8	(1.4%)	2	(1.2%)	8	(2.4%)
Anaesthesia problems	0	(0%)	2	(0.3%)	1	(0.6%)	3	(0.9%)
Pyrexia	9	(3.1%)	29	(5.0%)	12	(7.1%)	18	(5.4%)
Infection	47	(16.1%)	86	(14.7%)	24	(14.3%)	36	(10.7%)
Haematoma	17	(5.8%)	25	(4.3%)	10	(5.9%)	14	(4.2%)
DVT	0	(0%)	2	(0.3%)	0	(0%)	0	(0%)
Other complications	22	(7.5%)	40	(6.8%)	17	(10.1%)	24	(7.1%)

of operation within the two trial arms. As the per-protocol population also includes all patients who did not have an operation, a sensitivity analysis to assess the extremes of the effect that including these patients could have on the analysis was also carried out. There was no statistically significant difference between the minor complication rates for the AH and ALH procedures within the abdominal trial ($p = 0.12$) nor between the VH and VLH procedures within the vaginal trial ($p = 0.30$). This result was not affected by the sensitivity analysis.

Analysis using the per-protocol population was consistent with results from the ITT population.

Adjusted comparison of minor complications

The analysis of the minor complication rates was

TABLE 74 *Frequency of minor complications per patient*

Frequency	Abdominal				Vaginal					
	AH *n* = 289		ALH *n* = 587		VH *n* = 178		VLH *n* = 326		Total *n* = 1380	
1	67	(23.2%)	107	(18.2%)	37	(20.8%)	59	(18.1%)	270	(19.6%)
2	15	(5.2%)	27	(4.6%)	7	(3.9%)	12	(3.7%)	61	(4.4%)
3	2	(0.7%)	7	(1.2%)	3	(1.7%)	2	(0.6%)	14	(1.0%)
4	0	(0%)	0	(0%)	2	(1.1%)	3	(0.9%)	5	(0.4%)
5	0	(0%)	1	(0.1%)	0	(0%)	0	(0%)	1	(0.07%)
Total	84	(29.1%)	142	(24.2%)	49	(27.5%)	76	(23.3%)	351	(25.4%)

TABLE 75 *Frequency of BMI at randomisation by minor complication*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Complication	BMI ≤30	BMI >30	BMI ≤30	BMI >30	BMI ≤30	BMI >30	BMI ≤30	BMI >30
Yes	65 (28%)	15 (25%)	113 (24.7%)	35 (27.6%)	39 (30%)	10 (26.3%)	65 (24.3%)	14 (20.3%)
No	167 (71.9%)	45 (75%)	344 (75.3%)	92 (72.4%)	91 (70%)	28 (73.7%)	202 (75.7%)	55 (79.7%)
Total	232 (79.5%)	60 (20.5%)	457 (78.3%)	127 (21.7%)	130 (77.4%)	38 (22.6%)	267 (79.5%)	69 (20.5%)

adjusted for the stratification factors of BMI and intended ovary removal.

Table 75 shows the frequency of patients with a BMI of ≤30 compared with those with a BMI >30 by minor complication. Whether patients had a minor complication or not does not appear to be influenced by the patient's BMI.

Table 76 shows the frequency of patients where ovary removal had been intended prior to surgery by minor complication. Complication rates are higher within each type of operation where ovary removal was not intended.

Logistic regression was used to adjust the minor complication rates for type of operation and the stratification factors of BMI and intended ovary removal. *Table 77* shows the OR and the 95% CI around that OR.

Using the data from the abdominal trial, intended ovary removal was significant, indicating that patients where ovary removal had been intended were less likely to have a minor complication than those where it was not intended. Type of operation and BMI were not significant in the model.

Table 77 shows the OR for type of operation adjusted for BMI and intended ovary removal. This OR indicates that the odds of having a minor complication were almost the same for AH and ALH patients.

Using the data from the vaginal trial, intended ovary removal was significant in the model, again indicating that patients where ovary removal had been intended were less likely to have a minor complication than those where it was not intended. Type of operation and BMI were not important in this model. *Table 78* shows the adjusted OR and the 95% CI around that OR.

Tables 79 and *80* show that the maximum length of stay for patients having an infection was longer than for those not having an infection. However, some of these patients will have had other major/minor complications; some patients having an infection went home within the first few days. The median time for patients being discharged from hospital was the same (except for VLH) for patients whether they had an infection or not. There is no evidence to suggest that having an infection increased length of stay.

TABLE 76 *Frequency of intended ovary removal by minor complication*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
	Intended ovary removal		Intended ovary removal		Intended ovary removal		Intended ovary removal	
Complication	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Yes	29 (21.2%)	51 (32.9%)	65 (23.7%)	83 (26.8%)	6 (16.2%)	43 (32.8%)	14 (18.4%)	65 (25%)
No	108 (78.8%)	104 (67.1%)	209 (76.3%)	227 (73.2%)	31 (83.8%)	88 (67.2%)	62 (81.6%)	195 (75%)
Total	137 (46.9%)	155 (53.1%)	274 (46.9%)	310 (53.1%)	37 (22%)	131 (77.9%)	76 (22.6%)	260 (77.4%)

TABLE 77 *Odds ratios and 95% confidence intervals for stratification factors (abdominal trial)*

Variable (comparison)	*p*	Adjusted OR	95% CI
Type of operation (AH vs ALH)	0.55	1.14	0.82 to 1.57
Intended ovary removal (yes vs no)	0.04	0.71	0.52 to 0.97
BMI (≤30 vs >30)	0.74	0.96	0.66 to 1.40

TABLE 78 *Odds ratios and 95% confidence intervals for stratification factors (vaginal trial)*

Variable (comparison)	*p*	Adjusted OR	95% CI
Type of operation (VH vs VLH)	0.25	1.34	0.88 to 2.03
Intended ovary removal (yes vs no)	0.01	0.57	0.33 to 0.97
BMI (≤30 vs >30)	0.37	1.21	0.73 to 2.01

Blood loss intraoperatively

Blood loss data were collected on the surgeon's assessment of blood loss (i.e. 'less than average', 'average' and 'more than average'), and also by pre- and postoperative haematocrit and haemoglobin measurements.

Table 81 shows the frequency of each of the categories of blood loss according to the surgeon's assessment. Within the abdominal trial 60% of procedures have 'average' blood loss, compared with ~45–50% in the vaginal trial. A Mantel–Haenszel chi-square test for trend for ordered categorical data was used to test the data within the abdominal trial. A test statistic of 3.7 on one degree of freedom ($p = 0.06$) is not statistically significant but suggests that there may be a trend for surgeons to report more than average blood loss for ALH patients than AH patients. The same test for the data within the vaginal trial gave a test statistic of 10.8 on one degree of freedom ($p < 0.01$). This is highly statistically significant and indicates that according to the surgeons' own assessment of blood loss, there is evidence to suggest greater blood loss with the VLH procedure than with the VH procedure.

Haemoglobin and haematocrit blood measurements were taken pre- and postoperatively. Thirty-four patients were excluded from this analysis; 18 did not have preoperative blood taken within 6 weeks prior to the operation; one patient did not have postoperative blood taken and 15 patients had their postoperative blood taken more than 4 days after their operation. The change in

TABLE 79 *Length of stay for patients having an infection [admission to discharge (days)]*

Complication	Abdominal		Vaginal	
	AH ***n* = 47**	**ALH** ***n* = 86**	**VH** ***n* = 24**	**VLH** ***n* = 36**
Mean (SD)	5.85 (5.1)	4.3 (4)	5 (3)	5 (2.8)
Median (min., max.)	5 (2, 37)	4 (2, 38)	4 (2, 17)	5 (1, 15)
95% discharged	10	7	9	14
Missing	1	0	0	0

TABLE 80 *Length of stay for patients not having an infection [admission to discharge (days)]*

Complication	Abdominal		Vaginal	
	AH ***n* = 235**	**ALH** ***n* = 478**	**VH** ***n* = 137**	**VLH** ***n* = 276**
Mean (SD)	5 (2)	3.89 (1.9)	4.2 (1.78)	4.2 (1.9)
Median (min., max.)	5 (1, 17)	4 (1, 30)	4 (2, 16)	4 (2, 20)
95% discharged	8	7	7	7
Missing	10	20	7	24

TABLE 81 *Surgeons' assessment of blood loss (abdominal trial)*

Surgeons' assessment	Abdominal				Vaginal			
	AH ***n* = 292**		**ALH** ***n* = 584**		**VH** ***n* = 168**		**VLH** ***n* = 336**	
Less than average	69	(23.6%)	115	(19.7%)	68	(40.5%)	91	(27.1%)
Average	176	(60.3%)	358	(61.3%)	77	(45.8%)	176	(52.4%)
More than average	30	(10.3%)	83	(14.2%)	14	(8.3%)	49	(14.6%)
Missing	17	(5.8%)	28	(4.8%)	9	(5.4%)	20	(5.9%)

haemoglobin and haematocrit was calculated, and a *t*-test within each trial was used to assess any difference between the change in blood measurements for each type of operation.

Tables 82 and *83* show the mean change in haemoglobin and haematocrit (pre- to postoperation), the mean difference, the 95% CI around the means, the standard error of the means and the minimum and maximum values and the *p*-values for the *t*-test. None of the *t*-tests were statistically significant, indicating that there is no difference in the change (pre- to postoperation) in haemoglobin or haematocrit measurements between the types of operation within the abdominal or the vaginal trial. The haemoglobin measurements decrease by ~1.7 g/dl postoperatively and the haematocrit decreases by ~5% postoperatively.

Table 84 shows the units of blood that were transfused by type of operation. Approximately 90% of all patients did not have a blood transfusion; the proportion of patients who had at least one unit of blood transfused ranges from 3.1% for AH patients to 6% for VLH patients.

Additional pathology

Data were also collected on additional unexpected pathology that was found intraoperatively, that is, that had not been expected prior to the procedure. *Table 85* indicates that considerably more unexpected pathology was found in the ALH patients than for the AH patients, and also for the VLH patients compared with the VH patients.

The types of additional pathology that were found are reported in *Table 86*; additional pathology was coded into 121 different categories, the main

TABLE 82 *Change in haemoglobin (g/dl)*

	Abdominal			Vaginal		
	AH	**ALH**	**Difference**	**VH**	**VLH**	**Difference**
n	251	516		138	276	
Mean	1.88	1.76	0.11	1.58	1.76	–0.18
95% CI	1.71 to 2.05	1.66 to 1.86	–0.08 to 0.31	1.38 to 1.77	1.60 to 1.92	–0.45 to 0.08
Std error	0.09	0.06	0.1	0.10	0.08	0.13
Minimum	–4.1	7.8		–0.3	7.6	
Maximum	7.8	7.6		–2.3	8.7	
p			0.27			0.17

TABLE 83 *Change in haematocrit (%)*

	Abdominal			Vaginal		
	AH	**ALH**	**Difference**	**VH**	**VLH**	**Difference**
n	248	505		136	268	
Mean	5.6	5.16	0.43	5.01	5.11	–0.1
95% CI	5.06 to 6.11	4.81 to 5.5	–0.19 to 1.04	4.25 to 5.76	4.57 to 5.64	–1.02 to 0.82
Std error	0.27	0.17	0.31	0.38	0.27	0.47
Minimum	–3.3	23.9		–4.1	–14.5	
Maximum	–10.8	24.9		30.9	25.6	
p			0.17			0.83

TABLE 84 *Units of blood transfused*

Units	**Abdominal**				**Vaginal**					
	AH *n* **= 292**		**ALH** *n* **= 584**		**VH** *n* **= 168**		**VLH** *n* **= 336**		**Total** *n* **= 1380**	
0	270	(92.5%)	530	(90.8%)	154	(91.7%)	297	(88.4%)	1251	(90.7%)
≥ 1	9	(3.1%)	30	(5.1%)	6	(3.6%)	20	(6%)	65	(4.7%)
Missing	13	(4.5%)	24	(4.1%)	8	(4.8%)	19	(5.7%)	64	(4.6%)

three were adhesions (78 patients), endometriosis (45 patients) and fibroids (22 patients).

A chi-squared test was used to identify a statistically significant difference between the types of operation within the two trial arms with respect to whether additional pathology was found. As the ITT population includes all patients, even though some did not have an operation, a sensitivity analysis to assess the extremes of the effect that including these patients could have on the analysis was also carried out.

There was a highly statistically significant difference between the AH and ALH procedures within the abdominal trial; the chi-squared test statistic was 12.3 ($p = 0.0004$). This was also highly statistically significant within the vaginal trial between VH and VLH [chi-squared test statistic 13.8 ($p = 0.0002$)]. These results were not affected by the sensitivity analysis. This indicates that significantly more additional pathology was found when the ALH and VLH procedures were used compared with the AH and VH procedures, respectively.

Tables 87–91 show the additional unexpected pathology that was found during the procedure for subgroups of patients, by each of the indications for hysterectomy: dysfunctional uterine bleeding, fibroids, endometriosis, failed ablation and 'other' indication.

TABLE 85 *Additional pathology – was unexpected pathology found?*

Additional pathology found	Abdominal				Vaginal				Total
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336		*n* = 1380
Yes	37	(12.7%)	132	(22.6%)	8	(4.8%)	55	(16.4%)	232
No	240	(82.2%)	424	(72.6%)	151	(89.8%)	259	(77.1%)	1074
Missing	15	(5.1%)	28	(4.8%)	9	(5.4%)	22	(6.5%)	74

TABLE 86 *Additional pathology found*

Additional pathology found	Abdominal				Vaginal				Total
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336		*n* = 1380
Adhesions	5	(1.7%)	55	(9.4%)	5	(2.9%)	13	(3.9%)	78
Endometriosis	10	(3.4%)	23	(3.9%)	2	(1.2%)	10	(2.9%)	45
Fibroids	2	(0.7%)	13	(2.2%)	1	(0.6%)	6	(1.8%)	22
Other	28	(9.6%)	78	(26.7%)	3	(1.8%)	35	(10.4%)	144

Tables 87, 88, 90 and *91* indicate that if dysfunctional uterine bleeding or fibroids or failed or ablation or 'other' are indications for hysterectomy, then the LH procedure appears to find more unexpected additional pathology than do the other two conventional procedures. No additional unexpected pathology was found when the VH procedure was used for patients with failed ablation.

Table 89 indicates that if endometriosis is an indication for hysterectomy, no additional pathology was found within the vaginal trial, and similar amounts of additional pathology are found in the abdominal trial.

Pain assessment

The level of pain was a secondary end-point for this trial. The level of pain is a very important patient outcome following surgery, but it is notoriously difficult data to collect and to assess, as it is a very subjective, soft end-point. Nevertheless, in a randomised clinical trial this effect is balanced across the treatment groups. At first it was considered whether or not all analgesia use should be included, but the many different regimes precluded a meaningful analysis; hence, the use of opiate was focused upon as this is the most commonly used group of agents.

Patients had been asked to complete a daily diary card whilst they were in hospital and another one following discharge (i.e. at home). Both of these diaries contained a visual analogue scale that patients had been asked to record their level of pain on, at 9 a.m. and again at 9 p.m. This scale ranged from 0 to 10, with 0 being 'no pain' and 10 being 'pain as bad as it could possibly be'. The patient-completed hospital diary (Appendix 7) requested patients to record the medications they had taken each day. Due to the wide range of practices used to administer pain relief (i.e. in the form of injections or medication) and the wide range of treatments used, it was difficult to assess the dosage of opiate administered to each patient. However, a consistent analgesia treatment protocol was in place across the procedures. Therefore, these data were used simply to report whether a patient had taken an opiate on each day or not.

From *Tables 92* and *93*, it can be seen that some patients had only used a non-opiate on some days, whereas other patients may have taken an opiate, with or without a non-opiate or another medication that was actually a mix of opiate and non-opiate. From *Table 92*, it can be seen that 74% of AH patients had used at least one opiate on day 0, compared with 65% of ALH patients. By day 4 only 10% of ALH patients were taking at least one opiate compared with 24% of AH patients. The number of patients taking any medication declined rapidly from day 4; this was to be expected as most patients would have been discharged from hospital by this time point.

TABLE 87 *Indication for hysterectomy – dysfunctional uterine bleeding*

Additional pathology found	Abdominal				Vaginal				
	AH *n* = 172		ALH *n* = 361		VH *n* = 120		VLH *n* = 221		Total *n* = 874
Yes	15	(8.7%)	80	(22.2%)	6	(5%)	33	(14.9%)	134
No	152	(88.4%)	263	(72.8%)	108	(90%)	177	(80%)	700
Missing	5	(2.9%)	18	(4.9%)	6	(5%)	11	(4.9%)	40

TABLE 88 *Indication for hysterectomy – fibroids*

Additional pathology found	Abdominal				Vaginal				
	AH *n* = 49		ALH *n* = 107		VH *n* = 24		VLH *n* = 55		Total *n* = 235
Yes	6	(12.2%)	27	(25.2%)	1	(4.2%)	8	(14.5%)	42
No	42	(85.7%)	77	(71.9%)	21	(87.5%)	42	(76.4%)	182
Missing	1	(2%)	3	(2.8%)	2	(8.3%)	5	(9%)	11

TABLE 89 *Indication for hysterectomy – endometriosis*

Additional pathology found	Abdominal				Vaginal				
	AH *n* = 41		ALH *n* = 67		VH *n* = 5		VLH *n* = 13		Total *n* = 126
Yes	7	(17.1%)	10	(14.9%)	0	(0%)	0	(0%)	17
No	28	(68.3%)	57	(85.1%)	5	(100%)	13	(100%)	103
Missing	6	(14.6%)	0	(0%)	0	(0%)	0	(0%)	6

TABLE 90 *Indication for hysterectomy – failed ablation*

Additional pathology found	Abdominal				Vaginal				
	AH *n* = 19		ALH *n* = 35		VH *n* = 17		VLH *n* = 33		Total *n* = 104
Yes	4	(21.1%)	10	(28.6%)	0	(0%)	9	(27.3%)	23
No	14	(73.7%)	23	(65.7%)	16	(94.1%)	20	(60.6%)	73
Missing	1	(5.3%)	2	(5.7%)	1	(5.9%)	4	(12.1%)	8

TABLE 91 *Indication for hysterectomy – other indication*

Additional pathology found	Abdominal				Vaginal				
	AH *n* = 114		ALH *n* = 241		VH *n* = 48		VLH *n* = 114		Total *n* = 517
Yes	16	(14%)	66	(27.4%)	3	(6.3%)	20	(17.5%)	105
No	94	(82.3%)	164	(68%)	44	(91.7%)	87	(76.3%)	389
Missing	4	(3.5%)	11	(4.6%)	1	(2.1%)	7	(6.1%)	23

TABLE 92 *Use of opiates and non-opiates up to day of discharge (abdominal trial)*

Day	AH *n* = 292						ALH *n* = 584					
	Opiate ± non-opiate		Non-opiate (only)		Total		Opiate ± non-opiate		Non-opiate (only)		Total	
0	215	(73.6%)	2	(0.7%)	217	(74.3%)	379	(64.9%)	30	(5.1%)	409	(70%)
1	203	(69.5%)	29	(9.9%)	232	(79.5%)	381	(65.2%)	61	(10.5%)	442	(75.7%)
2	144	(49.3%)	77	(26.4%)	221	(75.7%)	231	(39.6%)	165	(28.3%)	396	(67.8%)
3	113	(38.7%)	82	(28.18%)	195	(66.8%)	142	(24.3%)	109	(18.7%)	251	(42.9%)
4	69	(23.6%)	62	(21.2%)	131	(44.9%)	62	(10.6%)	58	(9.9%)	120	(20.5%)
5	35	(11.9%)	34	(11.6%)	69	(23.6%)	16	(2.7%)	21	(3.6%)	37	(6.3%)
6	18	(6.2%)	10	(3.4%)	28	(9.6%)	8	(1.4%)	8	(1.4%)	16	(2.7%)
7	6	(2.1%)	5	(1.7%)	11	(3.8%)	6	(1.0%)	0	(0%)	6	(1.0%)
>7	2	(0.7%)	1	(0.3%)	3	(1.0%)	3	(0.5%)	1	(0.2%)	4	(0.7%)

TABLE 93 *Use of opiates and non-opiates up to day of discharge (vaginal trial)*

Day	VH *n* = 168						VLH *n* = 336					
	Opiate ± non-opiate		Non-opiate (only)		Total		Opiate ± non-opiate		Non-opiate (only)		Total	
0	112	(66.7%)	2	(1.2%)	114	(67.8%)	183	(54.5%)	12	(3.6%)	195	(58%)
1	103	(61.3%)	15	(8.9%)	118	(70.2%)	181	(53.9%)	34	(10.1%)	215	(63.9%)
2	64	(38.1%)	41	(24.4%)	105	(62.5%)	110	(32.7%)	87	(25.9%)	197	(58.6%)
3	44	(26.2%)	29	(17.3%)	73	(43.5%)	59	(17.6%)	61	(18.2%)	120	(35.7%)
4	17	(10.1%)	14	(8.3%)	31	(18.5%)	23	(6.8%)	28	(8.3%)	51	(15.2%)
5	8	(4.8%)	6	(3.6)	14	(8.3%)	7	(2.1%)	10	(3.0%)	17	(5.1%)
6	3	(1.8%)	3	(1.8%)	6	(3.6%)	1	(0.3%)	5	(1.5%)	6	(1.8%)
7	0	(0%)	2	(1.2%)	2	(1.2%)	0	(0%)	4	(1.2%)	4	(1.2%)
>7	1	(0.6%)	0	(0%)	1	(0.6%)	1	(0.3%)	1	(0.3%)	2	(0.6%)

From *Table 93*, it can be seen that 66% of VH patients had used at least one opiate on day 0, compared with 55% of VLH patients. By day 4 only 7% of ALH patients were taking at least one opiate compared with 10% of VH patients. The number of patients taking any medication declined rapidly from day 3; this was to be expected as most patients would have been discharged from hospital by this time point.

At least one opiate was used by 234 (80%) of AH, 442 (76%) of ALH, 119 (71%) of VH and 209 (62%) of VLH patients. Slightly more AH patients used at least one opiate than for the other procedures. This was as expected as the AH procedure is a more invasive operation than the other procedures.

Table 94 shows the median and the IQR for the pain scores, recorded on days 0, 2, 7, 21 and 42 with day 0 being the operation day. It can also be seen from *Table 94* that there were more data available on day 2 following the operation while patients were still in hospital than on operation day (day 0), when some patients would have been too ill to complete their diaries, or from day 7 once patients had been discharged from hospital.

Immediately following the operation and while patients remained in hospital, they would receive pain relief, which will undoubtedly have affected the level of pain they recorded. Therefore, the pain scores for day 0 (operation) and day 2 have been adjusted for the use of opiates on that day. As most patients would have been discharged from hospital around day 3 or 4, adjusting pain scores for opiate use after this time is not appropriate. However, patients may have taken pain relief once they were at home; this has not been recorded.

Analysis of covariance was used to adjust the pain score by the use of an opiate on days 0 and 2. Pain had been recorded on the VAS twice per day so the average pain per day was therefore used as that day's pain score.

TABLE 94 *Pain assessment – VAS pain scores*

Day	Abdominal						Vaginal					
	AH			ALH			VH			VLH		
	n	Median	IQR	*n*	Median	IQR	*n*	Median	IQR	*n*	Median	IQR
0	224	6	4, 8	411	5.36	3.1, 7.1	112	6.3	3.8, 8	193	6	4, 8
2	234	4	2.1, 6	484	3	1.6, 5	130	2.5	1, 4.5	243	3	1.7, 4.6
7	196	2.3	1, 4.5	388	2	0.4, 3.5	106	1.5	0.2, 3	205	2	0.5, 3.2
21	187	1	0.1, 2	374	0.5	0, 2	102	0.1	0, 1.5	196	0.5	0, 1.4
42	165	0.1	0, 0.8	308	0	0, 0.5	79	0	0, 0.2	146	0	0, 0.3

TABLE 95 *Pain score adjusted for opiate use – abdominal trial*

	Day 0 – operation day (*n* = 709)		Day 2 – after operation day (*n* = 718)	
	Adjusted mean (95% CI)	*p*	Adjusted mean (95% CI)	*p*
AH	5.57 (5.22 to 5.92)		4.0 (3.73 to 4.29)	
ALH	5.07 (4.82 to 5.32)		3.37 (3.18 to 3.57)	
Difference	0.5 (0.07 to 0.93)	0.02	0.64 (0.3 to 0.97)	0.0003

TABLE 96 *Pain score adjusted for opiate use – vaginal trial*

	Day 0 – operation day (*n* = 365)		Day 2 – after operation day (*n* = 373)	
	Adjusted mean (95% CI)	*p*	Adjusted mean (95% CI)	*p*
VH	5.09 (4.6 to 5.59)		2.96 (2.59 to 3.32)	
VLH	5.39 (5.03 to 5.76)		3.31 (3.05 to 3.58)	
Difference	–0.3 (–0.9 to 0.3)	0.38	–0.36 (–0.81 to 0.09)	0.11

Tables 95–96 show the mean pain score adjusted for opiate use, the 95% CI, plus the difference in means and 95% CI around that difference, for each trial on days 0 and 2. This is statistically significantly different in the abdominal trial, showing that ALH patients have significantly less pain on operation day and 2 days following the procedure than AH patients. This is not statistically significantly different in the vaginal trial.

Training procedures

A proportion of the operations were training procedures, supervised by the named surgeon. *Table 97* shows the proportion of all procedures that were in fact training operations (i.e. between 30 and 40% of operations). Slightly more of the VLH procedures appear to have been used as training procedures than the others.

Table 98 shows the length of the procedure (from first incision time to last suture time in minutes) for training and non-training procedures. It can be seen that the length of the procedure is generally longer if it is a training operation, as would have been expected.

Table 99 shows the major complication rate for operations that were used as training procedures. The overall complication rates for the ITT population were 6.2% AH, 11.1% ALH, 9.5% VH and 9.8% for VLH. The proportion of patients with at least one major complication for the subset of patients who had training procedures is lower for all procedures, with the exception of the VH procedure.

TABLE 97 *Proportion of operations that were used for training*

Training procedure	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
Yes	92	(31.5%)	197	(33.7%)	51	(30.4%)	136	(40.4%)
No	185	(63.4%)	358	(61.3%)	108	(64.3%)	179	(53.3%)
Missing	15	(5.1%)	29	(4.9%)	9	(5.3%)	21	(6.3%)

TABLE 98 *Length of procedure by training operation and type of operation (minutes)*

	Abdominal				Vaginal			
	AH *n* = 292		ALH *n* = 584		VH *n* = 168		VLH *n* = 336	
	Training *n* = 92	Surgeon *n* = 183	Training *n* = 196	Surgeon *n* = 352	Training *n* = 50	Surgeon *n* = 107	Training *n* = 134	Surgeon *n* = 178
Median	57	47	85	81	40	38	79	66
Min., max.	25, 128	19, 155	10, 175	12, 325	18, 145	14, 168	25, 170	21, 220
95%	100	100	138	140	110	110	130	135
Missing	17		36		11		24	

TABLE 99 *Major complications by training procedure*

Major complications	Abdominal				Vaginal			
	AH *n* = 92		ALH *n* = 197		VH *n* = 51		VLH *n* = 136	
Yes	4	(4.3%)	19	(9.6%)	7	(13.7%)	13	(9.6%)
No	88	(95.7%)	178	(90.4%)	44	(86.3%)	123	(90.4%)

Summary

The baseline characteristics of patients within the abdominal and vaginal trials vary, indicating that clinicians have preferred clinical criteria for the abdominal or vaginal approach to hysterectomy. The preferred surgical approach varies for patients with certain baseline characteristics (parity, palpable endometriosis, endometriosis, pelvic pain, number of indications for hysterectomy, intended oophorectomy, uterine mobility and descent). This justifies the design of this study, in addition to verifying that the two trials contain different populations of patients. These different baseline and clinical characteristics indicate that the LH procedures may be more complex in one group than another, and therefore safety and efficacy of LH may be different within each subset, hence the two groups need to be analysed separately. In addition, comparisons across the trials are not valid.

Dysfunctional uterine bleeding is the most common indication for patients having a hysterectomy. Patients having an abdominal hysterectomy generally stay in hospital for 1 day longer than patients having an alternative operation. The operative time is ~30 minutes longer for the laparoscopic procedure than for the conventional procedures.

A statistically significant difference was found in the rate of major complications within the abdominal trial between AH and ALH. A statistically significant difference in the major complication rate was not found within the vaginal

trial; however, this trial was under-powered. There were no significant differences found in either trial in the rate of minor complications or blood loss.

A statistically significant difference was found in the level of additional unexpected pathology that was observed; in both trials more unexpected pathology was found using the laparoscopic approach to hysterectomy. Within the abdominal trial, the AH procedure was statistically significantly more painful than the ALH procedure. There was insufficient evidence of a difference within the vaginal trial.

Chapter 4

Statistical analysis of the potential impact of surgeon on patient outcome

Introduction

This chapter considers the analysis of the potential of a surgeon effect on the outcome of the operation for patients. One of the original aims of the trial was also to investigate the impact of surgeon experience on the results. However, in error, data surrounding experience were not collected during the trial and it has proved very difficult to collect reliable data on this retrospectively. It is therefore not possible to undertake the analysis investigating impact of surgeon experience in terms of either baseline experience or learning curve. This chapter therefore concentrates only on effect of surgeon *per se*.

Forty-three surgeons recruited and allocated 1380 patients on clinical grounds to either the abdominal or the vaginal trial; they were then randomised to one of the surgical procedures. The number of operations carried out by one surgeon ranged from one to 115; five surgeons only recruited patients into the abdominal trial; nine surgeons only recruited patients into the vaginal trial.

As this is a surgical trial, although the procedures are essentially the same for all patients there is a potential source of variation added by surgeons. Therefore, patients operated on by the same surgeon are likely to have a more similar outcome than those treated by different surgeons. Hence there are two levels of variation associated with patient outcomes: variation between patients within the same surgeon and variation between surgeons. Therefore, this data set has a hierarchical structure, with patients 'nested' within surgeons (i.e. a multilevel structure). In the same way, surgeons could have been grouped within centres, and centre would have been the highest level of variation. In this trial, the majority of surgeons were operating alone in centres, and centre was considered to be synonymous with surgeon.

The primary end-point of the trial was a binary response. Overall approximately 10% of patients did have at least one major complication, hence the outcome variable is sparse.

Methods

A linear mixed logistic regression model (with logit link function) was used to model the probability of a major complication, with 'surgeon' fitted as a random effect. For example, let Y_{ij} denote the outcome for the ith patient operated on by the jth surgeon, and U_j the surgeon random effect for the jth surgeon. It is assumed $Y_{ij}|U_j \sim$ binomial(1, π_{ij}) independently. The probability of a major complication, π_{ij}, is given by

$$\text{logit}(\pi_{ij}) = \beta_0 + \beta_1 x_{1ij} + \ldots + \beta_p x_{pij} + U_j$$

where x_{1ij} to x_{pij} are patient-level attributes and $U_j \sim N(0, \sigma_u^2)$ independently. For a general introduction to logistic regression and a summary of the use of random effects see Collett.[54] All mixed models were fitted using the method of maximum likelihood in the SAS Guide, using the NLMIXED procedure.[55]

The 'surgeon' effect could potentially be modelled as a fixed or random effect. Fitting 'surgeon' as a random effect and type of operation as a fixed effect generates a mixed model. Mixed models take account of the covariance structure or interdependence of the data. More conventional fixed effects models assume that all observations are independent. Mixed modelling is therefore more appropriate for this trial design as patients nested within the same surgeon are not independent. In addition, 'surgeon' and the surgeon–treatment interaction were fitted as random effects so that possible differences in the size of the 'type of operation' effect across surgeons could be assessed. Using a random effect has the advantage of enabling the results of the trial to be generalised to the population of surgeons, unlike the fixed-effect approach, which restricts any conclusions to this particular sample of 43 surgeons.

In addition to allowing more general conclusions, treating 'surgeon' as a random effect allows a more

parsimonious model to be fitted to the data, and introduces a correlation structure between patients within the same surgeon. A further effect, the 'type of operation' across 'surgeon' interaction, was also fitted as a random effect to allow possible differences in the size of the 'type of operation' effect across surgeons to be assessed.

This data set had a complex structure: it was hierarchical, contained mixed effects and had a sparse binary outcome variable. Initially, using the NLMIXED procedure, a model containing the interaction effect between 'surgeon' and 'type of operation' was fitted. Models containing 'surgeon' only and 'type of operation' only and both terms were then fitted. Using likelihood ratio tests, only 'type of operation' in the abdominal trial was significant at the 5% level ($p = 0.01$), and neither term was significant in the vaginal trial. However, in order to investigate the effect of 'surgeon' or 'type of operation' on our conclusions, both 'surgeon' and 'type of operation' were retained in both models.

Other variables that were considered to be potentially important in determining whether a patient had a major complication or not were included in the model. These were patient demographic data, plus many of the variables that had been included in the logistic regression analysis to identify operative variables that were predictive of a major complication for each type of surgery. The following were included:

1. Age, centred (i.e. the overall mean age was subtracted from the variable age).
2. Indication for hysterectomy:
   (a) dysfunctional uterine bleeding
   (b) fibroids
   (c) endometriosis
   (d) failed ablation
   (e) other indication for hysterectomy.
3. The number of indications for hysterectomy: this was re-categorised to 'one indication' versus 'more than one indication'.
4. Parity.
5. Current smoker.
6. Previous pelvic surgery.
7. Uterine size.
8. Uterine position.
9. Uterine mobility.
10. Uterine descent.
11. Completed oophorectomy; this was re-categorised to 'at least one ovary removed' versus 'no ovaries removed'.
12. Training procedure.
13. Use of disposable equipment.

In the abdominal trial, whether or not disposable equipment was used reflected whether the operation was laparoscopic or conventional; therefore, this variable was dropped in the abdominal trial. In the vaginal trial, only 18 patients had endometriosis as an indication for hysterectomy, so this variable was dropped in the vaginal trial.

Prior to the model-fitting process, exploration into correlation between potential covariates was undertaken. If any two variables were highly correlated, only the variable considered to be the most clinically important was retained for further consideration in the model-fitting process. None of the variables were found to be highly correlated. In total there were 17 potentially important covariates, as discussed previously, that may influence whether a patient had a major complication or not.

A manual forward selection method was used to identify important covariates to be included in a final model. Each of the 17 covariates was fitted individually as fixed effects in addition to 'surgeon' and 'type of operation' into a model. Likelihood ratio tests were used to assess their importance. Covariates were considered to be statistically significant with a p-value of <0.05; the covariate that was the most statistically significantly important was retained in the model and the remaining covariates were added in turn to that model until no variables were statistically significant.

The same manual forward selection method was used to identify important variables in a model in the vaginal trial, which already contained 'type of operation' as a fixed effect and 'surgeon' as a random effect. However, as there were relatively few convergence problems in this trial, PROC NLMIXED in SAS was used to identify the important variables.

Results

Surgeon effect

The initial model-building process demonstrated that the 'surgeon' across 'type of operation' interaction effect was not significant in either trial. The 'type of operation' term was highly significant in the abdominal trial but not in the vaginal trial. The 'surgeon' term was not significant in either trial when it was fitted as a random effect. For the abdominal trial, the estimated variance for the 'surgeon' random effect was 0.074, standard error

TABLE 100 *Final model for abdominal trial*

Fixed effect	Parameter estimate (95% CI)	OR (95% CI)
Type of operation (ALH vs AH)	0.7 (0.1 to 1.3)	2.0 (1.1 to 3.5)
Uterine position (retroverted vs anteverted)	–0.9 (–1.8 to –0.02)	0.4 (0.2 to 0.9)
Training procedure (no vs yes)	0.4 (–0.1 to 1.0)	1.5 (0.9 to 2.6)
Dysfunctional uterine bleeding (no vs yes)	0.5 (0.05 to 1.0)	1.7 (1.1 to 2.8)

TABLE 101 *Final model for vaginal trial*

Fixed effect	Parameter estimate (95% CI)	OR (95% CI)
Type of operation (VLH vs VH)	–0.03 (–0.7 to 0.6)	0.9 (0.5 to 1.8)
Current smoker (no vs yes)	1.0 (0.2 to 1.8)	2.7 (1.2 to 6)
Uterine descent (1st degree vs no descent)	–1.0 (–1.8 to –0.2)	0.4 (0.2 to 0.8)
Number of indications (>1 vs 1)	1.0 (0.3 to 1.7)	2.7 (1.3 to 5.5)
Previous pelvic surgery (no vs yes)	0.8 (0.2 to 1.5)	2.2 (1.2 to 4.5)

(SE) = 0.11, for the vaginal trial it was 0.005, SE = 0.13. The variance estimates are small, suggesting there may not be much variation to detect; however, the SEs are larger, indicating that the precision of the variance estimates may be questionable.

Surgeons recruiting patients to this study had to have completed 25 of each type of procedure before they were allowed to randomise patients. There were 43 surgeons recruiting patients; some surgeons only recruited patients into one trial and there was a wide range of number of patients recruited by surgeons. It is highly likely that the statistical test did not have the power to detect a surgeon effect and it is also possible that the trial design removed enough of the variation between surgeons for there not to be a surgeon effect. This analysis did not find a surgeon effect, but it is difficult to conclude that there was not a difference between surgeons in the trial as the power was not sufficient to do so.

Abdominal trial

Uterine position, training procedure and dysfunctional uterine bleeding were identified as independent predictors of major complications. Age had appeared to be important during the model-building process, but when more 'significant' variables were fitted first it became less significant.

Table 100 shows the variables selected in the final model, with the parameter estimates and 95% CIs. The ORs and 95% CIs illustrate the effect of each variable across 'surgeon'.

The ORs show that patients having an ALH are twice as likely to have a major complication as patients having an AH; this result reflects the previous analysis that does not adjust for the surgeon effect, indicating that adjusting for surgeon does not influence the type of operation effect. Patients with a retroverted uterus are less than half as likely to have a major complication than patients with an anteverted uterus. Patients with dysfunctional uterine bleeding as a prior indication for hysterectomy are also less likely to have a major complication than those who did not have dysfunctional uterine bleeding. There is evidence to suggest that patients having an operation as part of a training procedure are also less likely to have a major complication, although this is of borderline significance.

Vaginal trial

Current smoker, uterine descent, number of indications for hysterectomy and previous pelvic surgery were independent predictors of a major complication.

Table 101 shows the variables selected in the final model, with the parameter estimates and 95% CIs. The ORs and 95% CIs illustrate the effect of each variable across 'surgeon'.

The OR is almost one, showing that the type of operation (VLH versus VH) does not affect the

occurrence of a major complication; this result reflects the previous analysis in Chapter 3, indicating that adjusting for surgeon does not impact on the effect of type of operation. Patients with first-degree uterine descent are less likely to have a major complication than those with no descent. Patients who have not had previous pelvic surgery are approximately twice as likely to have a major complication as those who have had previous surgery. Patients with more than one indication for a hysterectomy are almost three times more likely to have a major complication than patients with one indication for a hysterectomy, as are current non-smokers.

The finding that current non-smokers are three times more likely to have a major complication than current smokers is an interesting result. Data were only collected on whether patients were current smokers or not. Data were not collected on smoking history, such as the number of years of smoking, quantity per day, previously smoked or for how long they had they stopped. It is difficult, therefore, to interpret this variable. It may be, for example, that some current non-smokers may have stopped only recently.

Two-way interactions with treatment were not taken into account in the model, but there is some evidence of a 'type of operation' and 'smoking' interaction. Smokers who had a VLH procedure appear less likely to have a major complication than if they had a VH procedure. This is reversed for non-smokers (i.e. non-smokers having a VH procedure appear less likely to have a major complication than if they had a VLH procedure). This may help to explain the significance of being a current smoker in the above model. It may also be that another important factor has not been identified by the model-building process, that is in fact confounded with smoking and has not been reported in this trial. There is no clinical explanation for why non-smokers would have more chance of a major complication than smokers within the vaginal trial; this may simply be a chance finding.

Conclusion

The aim of this analysis was to identify a potential surgeon effect and estimate the impact of this on results and then to identify any important factors in identifying patients who are more likely to have a major complication. A surgeon effect was not identified, nor was a surgeon and type of operation interaction effect. However, as had been expected from the previous main clinical results, type of operation was found to be significantly important in the abdominal trial but not in the vaginal trial.

Although the 'surgeon' term was not important in the model, it was retained in the model building, and important patient-level variables were selected in identifying which patients were likely to have a major complication.

Within the abdominal trial, patients were more likely to have a major complication if they had the ALH operation, had an anteverted uterus, the procedure was not a training procedure and they did not have dysfunctional uterine bleeding as their indication for a hysterectomy.

Within the vaginal trial, patients were more likely to have a major complication if they were non-smokers, had no uterine descent, had more than one indication for hysterectomy and had not had previous pelvic surgery.

These factors should be considered and validated in future studies.

Discussion

Some of the 43 surgeons only recruited patients into one of the trials; also, there was a wide range in the number of patients recruited by surgeons (1–115). Therefore, it is probable that the statistical test lacked sufficient power to detect a surgeon effect if one existed. Also, the likelihood ratio test for such random effects is not strictly correct, owing to the variance parameter being tested at a boundary point of the permissible parameter space (i.e. 0). Hence the test results should only be used as a rough guide for decision-making. It is also possible that, by insisting that recruiting surgeons had previously undertaken 25 procedures, the trial design itself may have removed enough of the variation between surgeons for there not to be a surgeon effect.

The analysis did not find a surgeon effect, but it is difficult to conclude that there was not a difference between surgeons in the trial. The variance estimates are small, suggesting there may not be much variation to detect; however, the larger SEs of these estimates indicate their precision may be questionable.

The aim of this analysis was to identify a potential surgeon effect and then to identify any important factors in identifying patients that are more likely to have a major complication after allowing for 'surgeon' and 'type of operation'. A surgeon effect was not identified, nor was a type of operation across surgeon interaction effect. However, as had been expected from the previous main clinical results, type of operation was found to be significantly important in the abdominal trial but not in the vaginal trial.

It seems reasonable to assume in a surgical trial that surgical skill and expertise will have a potential impact on the outcome for patients. However, although there is a clear additional source of variation added by surgeons, the variation between surgeons appears not to have an impact on the outcome for patients. There has been very little research in this area in other surgical trials, hence further validation of surgeon effect in other similar studies would be interesting.

Chapter 5

Quality of life results

Introduction

Quality of life (QoL) was measured using the SF-12 Health Survey questionnaire,[39] Body Image Scale (BIS) questionnaire,[40] the Sexual Activity questionnaire (SAQ)[41] and the EuroQoL Instrument (EQ-5D).[37,38]

The QoL data were completed by patients at randomisation, preoperatively and then by postal questionnaire at 6 weeks, 4 months and 1 year. The questionnaires were used according to their validated instructions and were designed to assess patients' views for the preceding month.

Data were collected at randomisation and preoperation as in many cases patients waited several months and in some cases more than 1 year for their operation following randomisation. The randomisation questionnaire was used as baseline data for the analysis, as these data should not be biased by the patient's knowledge of the procedure to which they were randomised; also, the overall mean scores at randomisation and preoperation are similar.

Data are presented and analysed using a ±28-day window around the expected date for the 4-month and 1-year forms and a ±14-day window around the 6-week form, and patients who completed preoperative forms after their operation have been removed from the analysis. The questionnaires were administered by post.

As recruitment was lower than had been expected, the Trial Steering Committee decided that the time that had been allocated for QoL follow-up would be better used on continuing recruitment. In order to keep to the time schedule and in view of the fact that sufficient 4-month and 1-year data had been collected to provide ample power for the QoL analysis, it was decided to cease collection of the 4-month and 1-year QoL form from October 1999. However, as preliminary analyses were conducted, it became apparent that the 1-year QoL data may be important and, for this reason, collection of the 1-year data was reinstated prior to any follow-ups being missed. Therefore, all patients received follow-up questionnaires at 6 weeks and 1-year but only patients randomised before October 1999 received a 4-month follow-up questionnaire.

Baseline characteristics

The median time from randomisation to operation was similar within each trial but different between the trials. Within the abdominal trial, for the AH group it was 47 days (range 0–511/days) and for the ALH group it was 48 days (range 0–637/days). Within the vaginal trial, for the VH group it was 27 days (range 0–475/days) and for the VLH group it was 32 days (range 0–731/days).

As the data in Chapter 3 demonstrate, the baseline characteristics between the two trials are different; therefore, each trial is analysed separately as in the main clinical analysis.

Assessment of missing data/compliance

Missing completion dates were calculated as the date the form was received, minus 7 days to allow for postage.

Table 102 gives the number of forms that were expected at each time point (i.e. the number of patients who were still in the study).

Table 103 indicates that compliance with questionnaire return was good, ranging from 68 to 95%.

A number of questionnaires were completed outside the required time frames, resulting in

TABLE 102 *Number of questionnaires expected*

Time	AH	ALH	VH	VLH	Total
Randomisation	292	584	168	336	1380
Preop.	280	567	161	323	1331
6 weeks	278	565	161	318	1322
4 months	227	469	130	249	1075
1 year	275	558	159	318	1310

TABLE 103 *Number of questionnaires received (% of expected)*

Time	AH	ALH	VH	VLH	Total
Randomisation	276 (94.5%)	550 (94.2%)	149 (88.7%)	303 (90.1%)	1278 (92.6%)
Preop.	260 (92.8%)	517 (91.2%)	143 (88.8%)	265 (82.0%)	1185 (89.0%)
6 weeks	215 (77.3%)	457 (80.9%)	119 (73.9%)	226 (71.1%)	1017 (76.9%)
4 months	169 (74.4%)	385 (82.1%)	102 (78.5%)	192 (77.1%)	848 (78.9%)
1 year	188 (68.4%)	418 (74.9%)	113 (71.1%)	218 (68.6%)	937 (71.5%)

TABLE 104 *Number of questionnaires received within time windows (% of expected)*

Time	AH	ALH	VH	VLH	Total
Randomisation	275 (94.2%)	548 (93.8%)	149 (88.7%)	302 (89.9%)	1274 (92.3%)
Preop.	260 (92.8%)	517 (91.2%)	143 (88.8%)	265 (82.0%)	1185 (89.0%)
6 weeks	174 (62.6%)	359 (63.5%)	95 (59.0%)	173 (54.4%)	801 (60.6%)
4 months	161 (70.9%)	355 (75.7%)	95 (73.1%)	172 (69.1%)	783 (72.8%)
1 year	172 (62.5%)	391 (70.1%)	105 (66.0%)	198 (62.3%)	866 (66.1%)

54–95% of expected forms eligible for analysis, as shown in *Table 104*.

Data summary and treatment comparisons at each time point

The data have an approximately normal distribution at baseline, 6 weeks and 1 year; however, the 4-month data are highly skewed. As the distributions in the two treatment groups for these scales were very similar and bounded by 0 and 100, it seemed reasonable to summarise the data for comparison purposes using the mean and standard deviation. The *p*-values for *t*-tests were calculated since the *t*-test is robust to violations of the associated assumptions and there were >30 observations in each group (Central Limit Theorem). In addition, the high number of ties meant that the assumptions for the Wilcoxon rank sum test were violated.

SF-12 questionnaire analysis

Missing data items

Plots of the mean scores for each of the summary scales by type of procedure at each time point grouped by the timing of the last assessment indicate that missing forms are missing at random.

Following the scoring manual for the SF-12, all out-of-range values are recoded as missing and if one item is missing then the summary scale score is missing. *Table 105* shows the frequency of missing responses for each of the 12 questions over time. The questions most often missed at all time points were 'Limited in the kind of work or other activities', 'Climbing several flights of stairs' and 'Didn't do work or other activities as carefully as usual'.

Table 106 shows that, for the majority of questionnaires that did have a missing response, only one or two questions had been omitted.

The SF-12 is scored using the third edition of the scoring manual, creating a mental component summary scale and a physical component summary scale. Each of the summary scales is made up of six of the 12 questions.

Unfortunately, due to a printing error in the questionnaires, question 12 had an additional response box, 'a good bit of the time', creating six response categories rather than five. For the analysis, this additional response box was combined with 'some of the time' to create five response categories. Four items are reverse scored (following the scoring manual) so that a higher score indicates better health than a lower score. Questions 1, 2, 3, 4, 5 and 8 make up the physical component summary score. Questions 6, 7, 9, 10, 11 and 12 make up the mental component summary score.

SF-12 results

The means, SDs and *p*-values for the physical and mental component summary scores within the abdominal and vaginal trials are given in *Tables 107* and *108*.

A high score represents a better QoL.

TABLE 105 *Missing items: number of missing responses at each time point*

Question on SF-12	Time questionnaire completed			
	Baseline *n* = 1274	**6 weeks *n* = 801**	**4 month *n* = 783**	**1 year *n* = 866**
1. General health	6 (0.5%)	3 (0.4%)	14 (1.8%)	14 (1.6%)
2. Moderate activities	16 (1.3%)	6 (0.7%)	16 (2%)	14 (1.6%)
3. Climbing several flights of stairs	72 (5.6%)	35 (4.4%)	59 (7.5%)	57 (6.6%)
4. Accomplished less than would like (physical health)	43 (3.4%)	25 (3.1%)	27 (3.4%)	27 (3.1%)
5. Limited in work or other activities (physical health)	97 (7.6%)	48 (5.9%)	43 (5.5%)	44 (5.1%)
6. Accomplished less than would like (emotional health)	47 (3.7%)	20 (2.5%)	14 (1.8%)	19 (2.2%)
7. Didn't do work or other activities as carefully as usual	96 (7.5%)	50 (6.2%)	35 (4.5%)	42 (4.8%)
8. How much did pain interfere with normal work?	14 (1.1%)	5 (0.6%)	9 (1.1%)	10 (1.1%)
9. Have you felt calm and peaceful?	27 (2.1%)	8 (0.9%)	10 (1.3%)	9 (1.0%)
10. Did you have a lot of energy?	31 (2.4%)	9 (1.1%)	11 (1.4%)	13 (1.5%)
11. Have you felt downhearted and low?	16 (1.3%)	10 (1.3%)	13 (1.7%)	15 (1.7%)
12. How much have physical or emotional problems interfered with social activities?	17 (1.3%)	6 (0.7%)	10 (1.3%)	9 (1.0%)
Summary score	219 (17.2%)	118 (14.7%)	111 (14.2%)	121 (14.0%)

TABLE 106 *Frequency of number of missing items per incomplete questionnaire*

Missing responses per questionnaire	Time questionnaire completed			
	Baseline *n* = 1274	**6 weeks *n* = 801**	**4 months *n* = 783**	**1 year *n* = 866**
1	92 (7.2%)	62 (7.8%)	60 (7.7%)	65 (7.5%)
2	68 (5.3%)	39 (4.9%)	21 (2.7%)	26 (3.0%)
3	30 (2.4%)	5 (0.6%)	9 (1.1%)	7 (0.8%)
4	13 (1.0%)	4 (0.5%)	0 (0%)	3 (0.4%)
5	7 (5.5%)	3 (0.4%)	9 (1.1%)	10 (1.2%)
6	0 (0%)	0 (0%)	2 (0.3%)	2 (0.2%)
7	4 (0.3%)	2 (0.2%)	9 (1.1%)	5 (0.6%)
8	1 (0.1%)	2 (0.2%)	0 (0%)	1 (0.1%)
9	1 (0.1%)	1 (0.1%)	0 (0%)	2 (0.2%)
10	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)
11	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12	1 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)

TABLE 107 *Mean (SD) and difference at each time point (abdominal trial)*

	Baseline *n* = 668	**6 weeks *n* = 449**	**4 months *n* = 438**	**1 year *n* = 478**
Physical component summary (PCS-12)				
AH	*n* = 221 45.6 (11.5)	*n* =148 41.7 (9.7)	*n* = 134 51.6 (8.6)	*n* = 148 52.7 (9.3)
ALH	*n* = 447 44.9 (11.7)	*n* = 301 46.8 (10.1)	*n* = 304 52.6 (8.6)	*n* = 330 53.6 (8.4)
Difference (95% CI)	0.6 (–1.2 to 2.5)	**–5.1 (–7.1 to –3.2)**	–1.0 (–2.8 to 0.7)	–0.9 (–2.5 to 0.8)
p		**<0.001**	0.25	0.32
Mental component summary (MCS-12)				
AH	*n* = 221 45.3 (11.3)	*n* = 148 51.9 (10.8)	*n* = 134 51.8 (9.5)	*n* = 148 51.9 (10.2)
ALH	*n* = 447 45.8 (11.7)	*n* = 301 50.0 (11.4)	*n* = 304 50.9 (10.5)	*n* = 330 50.7 (10.7)
Difference (95% CI)	–0.5 (–2.4 to 1.4)	1.8 (–0.4 to 4.0)	0.8 (–1.3 to 2.9)	1.1 (–0.9 to 3.2)
p		0.11	0.44	0.27

TABLE 108 *Mean (SD) and difference at each time point (vaginal trial)*

	Baseline *n* = 387	6 weeks *n* = 234	4 months *n* = 234	1 year *n* = 267
Physical component summary (PCS-12)				
VH	*n* = 127 47.0 (11.3)	*n* = 84 46.3 (9.6)	*n* = 82 53.5 (6.7)	*n* = 94 53.7 (7.3)
VLH	*n* =2 60 47.4 (11.1)	*n* = 150 46.2 (9.6)	*n* = 152 53.9 (6.7)	*n* = 173 54.6 (6.3)
Difference (95% CI)	–0.4 (–2.7 to 2.0)	0.1 (–2.5 to 2.7)	–0.4 (–2.2 to 1.4)	–0.9 (–2.5 to 0.8)
p		0.94	0.64	0.32
Mental component summary (MCS-12)				
VH	*n* = 127 45.1 (12.1)	*n* = 84 53.2 (9.1)	*n* = 82 53.1 (8.1)	*n* = 94 51.7 (11.4)
VLH	*n* = 260 47.9 (10.7)	*n* = 150 52.5 (10.4)	*n* = 152 51.6 (9.8)	*n* = 173 52.3 (9.9)
Difference (95% CI)	–2.9 (–5.2 to –0.5)	0.7 (–1.9 to 3.4)	1.4 (–1.1 to 3.9)	–0.7 (–3.3 to 1.9)
p		0.60	0.26	0.62

Analysis of covariance was used to adjust the 6-week, 4-month and 1-year scores for the baseline score. The baseline score was important in each of the models in determining the SF-12 scores at each time point. Having adjusted for the baseline score, there remains a highly significant difference at 6 weeks between AH and ALH on the physical component summary score of the SF-12. The adjusted means are AH 41.4. and ALH 47.2, with a difference of –5.8 (95% CI –7.9 to –3.7). However, due to missing data that prevent the summary scale score from being calculated, this analysis is based on 384 patients; more than half of the data are in fact missing, which makes interpretation very difficult.

Boxplots of the mean component summary score and the physical component summary score (*Figures 9–12*) are given in Appendix 9. The boxes represent the IQR data, asterisks denote outlying values and the median is denoted by a line across the box. The mean and approximate 95% CIs are superimposed on the boxplots as lines.

The boxplots show very little difference in the means or medians between operation types at any time point, but a gradual increase over time for all operation types. The physical component summary score data become more skewed with a large number of outliers at 4 months and 1 year.

Body image scale (BIS)

The BIS questionnaire[40] was used as an assessment of the patients' own perceptions of their body image. This scale had been validated previously only in cancer patients. Two questions were modified slightly, by adding a 'not applicable' option. We have now validated the BIS questionnaire in non-cancer patients,[56] following Hopwood and colleagues' method of validation.[40]

Missing data items

Plotting the mean score by type of procedure at each time point, grouped by the timing of the last assessment, demonstrated that missing forms are in fact missing at random.

Following Hopwood and colleagues,[40] the average score for completed questions is imputed for missing items. Two questions, 'Have you been feeling the treatment has left your body less whole?' and 'Have you been dissatisfied with the appearance of your scar?', were 'not applicable' for patients preoperation and for VH patients. This was an amendment to Hopwood and colleagues' BIS questionnaire. The percentage score of the completed questions was calculated and then imputed as the BIS score.

Table 109 shows the number of missing responses at each time point for each question.

Four questions were clearly difficult for patients to complete at baseline. These questions refer to the patient's treatment and therefore were simply missed out by many patients. At follow-up all 10 questions had responses from over 97% of those patients who returned the questionnaire within the time window.

TABLE 109 *Missing items: number of missing responses at each time point*

Question	Time questionnaire completed			
	Baseline ***n*** **= 1274**	**6 weeks** ***n*** **= 801**	**4 months** ***n*** **= 783**	**1 year** ***n*** **= 866**
Have you been feeling self-conscious about your appearance?	27 (2.1%)	11 (1.4%)	18 (2.3%)	20 (2.3%)
Have you felt less physically attractive as a result of your disease or treatment?	64 (5.0%)	9 (1.1%)	15 (1.9%)	21 (2.4%)
Have you been dissatisfied with your appearance when dressed?	38 (3.0%)	11 (1.4%)	15 (1.9%)	19 (2.2%)
Have you been feeling less feminine as a result of your disease or treatment?	62 (4.9%)	6 (0.7%)	14 (1.8%)	17 (2.0%)
Did you find it difficult to look at yourself naked?	48 (3.8%)	12 (1.5%)	17 (2.2%)	21 (2.4%)
Have you been feeling less sexually attractive as a result of disease or treatment?	69 (5.4%)	9 (1.1%)	16 (2.0%)	27 (3.1%)
Did you avoid people because of the way you felt about your appearance?	46 (3.6%)	7 (0.9%)	18 (2.3%)	17 (2.0%)
Have you been feeling the treatment has left your body less whole?	114 (8.9%)	5 (0.6%)	16 (2.0%)	17 (2.0%)
Have you been dissatisfied with your body?	100 (7.8%)	8 (1.0%)	15 (1.9%)	18 (2.1%)
Have you been dissatisfied with the appearance of your scar?	217 (17.0%)	6 (0.7%)	20 (2.6%)	25 (2.9%)

TABLE 110 *Frequency of number of missing items per incomplete questionnaire*

Missing responses per questionnaire	**Baseline** ***n*** **= 1274**	**6 weeks** ***n*** **= 801**	**4 months** ***n*** **= 783**	**1 year** ***n*** **= 866**
1	199 (15.6%)	16 (2%)	21 (2.7%)	21 (2.4%)
2	53 (4.2%)	1 (0.1%)	3 (0.4%)	4 (0.5%)
3	35 (2.7%)	4 (0.5%)	1 (0.1%)	0 (0%)
4	11 (0.9%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
5	5 (0.4%)	2 (0.2%)	0 (0%)	1 (0.1%)
6	6 (0.5%)	0 (0%)	0 (0%)	0 (0%)
7	5 (0.4%)	0 (0%)	0 (0%)	0 (0%)
8	10 (0.8%)	0 (0%)	0 (0%)	0 (0%)
9	5 (0.4%)	0 (0%)	0 (0%)	0 (0%)
10	11 (0.9%)	4 (0.5%)	13 (1.7%)	16 (1.8%)

Table 110 shows that again patients had difficulty in responding to all questions at baseline, but at follow-up the majority of questionnaires missing a response had only one or two missing.

Results of body image scale

Tables 111 and *112* show the mean, SD, difference between the means and the 95% CI of the difference, along with the *p*-value at each time point within the abdominal and vaginal trials.

A low score represents a better body image.

Analysis of covariance was used to adjust the 6-week, 4-month and 1-year scores for the baseline score. The baseline score was important in each of the models in determining the BIS score at each time point. Having adjusted for the baseline score, there remains a highly significant difference at 6 weeks between AH and ALH, and there is strong evidence to suggest a difference at 4 months.

The adjusted means at 6 weeks are AH 5.2 and ALH 3.7, with a difference of 1.5 (95% CI 0.6 to 2.4), and at 4 months AH 4.3 and ALH 3.4, with a

TABLE 111 *Unadjusted mean (SD) and difference at each time point (abdominal trial)*

	Baseline ***n* = 813**	**6 weeks** ***n* = 529**	**4 months** ***n* = 505**	**1 year** ***n* = 555**
AH	*n* = 270 9.0 (7.9)	*n* = 172 5.2 (5.9)	*n* = 159 4.4 (6.3)	*n* = 168 4.1 (5.7)
ALH	*n* = 540 8.8 (8.1)	*n* = 357 3.7 (4.9)	*n* = 346 3.3 (4.9)	*n* = 387 3.4 (5.2)
Difference (95% CI)	0.2 (–0.9 to 1.4)	1.5 (0.5 to 2.4)	1.1 (0.06 to 2.1)	0.7 (–0.2 to 1.7)
p		**0.005**	**0.06**	0.13

TABLE 112 *Unadjusted mean (SD) and difference at each time point (vaginal trial)*

	Baseline ***n* = 445**	**6 weeks** ***n* = 268**	**4 months** ***n* = 265**	**1 year** ***n* = 295**
VH	*n* = 146 8.4 (7.4)	*n* = 95 3.0 (3.5)	*n* = 94 3.1 (4.9)	*n* = 102 3 (4.8)
VLH	*n* = 298 7.8 (7.8)	*n* = 173 3.4 (4.6)	*n* = 171 2.9 (3.9)	*n* = 193 2.8 (4.9)
Difference (95% CI)	0.5 (–0.9 to 2)	–0.4 (–1.5 to 0.6)	0.2 (–0.9 to 1.3)	0.2 (–0.9 to 1.4)
p		0.38	0.73	0.76

difference of 0.8 (95% CI –0.2 to 1.8). Due to missing data, these analyses are based on 516 and 488 patients, respectively, hence interpretation is difficult.

Boxplots of the mean score are given in *Figures 13* and *14*. The boxes represent the IQR data, asterisks denote outlying values and the median is denoted by a line across the box. The mean and approximate 95% CI are superimposed on the boxplots as a line.

Plots (*Figures 15–54*, Appendix 9) of each individual question over time, and by treatment group, do not indicate any major differences between treatment groups on any of the individual questions. The question 'Have you been dissatisfied with the appearance of your scar?' should have been answered by all patients at baseline as 'N/A' and by the majority of VH patients; almost 40% of all patients answered this question at baseline and 40–50% of all VH patients answered this question at follow-up. Approximately 50% of patients answered the question 'Have you been feeling the treatment has left your body less whole?' at baseline, whereas 'N/A' would have been expected in all cases.

Sexual activity questionnaire (SAQ)

Missing data items

No advice is given in the scoring manual to score missing items. In this analysis, if one item is missing then the score will be missing. *Table 113* shows the frequency of missing responses for each of the questions over time. Whereas 97% of patients completed question 1 of Section 1, only 94% felt comfortable responding to 'Have you changed your partner?' and 'Do you engage in sexual activity?'. Section 2, referring to reasons for inactivity, is virtually 100% complete in all questionnaires completed at follow-up, by patients who are not currently sexually active. The percentage of missing data is much higher at baseline. Section 3 has some missing data for all responses at all time points.

Table 114 shows that for the majority of questionnaires that have a missing response, only one or two questions had actually been missed.

Data summary and treatment comparisons at each time point

Following the scoring manual, the SAQ is in three sections. Section 1 identifies the patients who are

TABLE 113 *Missing items: number of missing responses at each time point*

Question on SAQ	Time questionnaire completed			
	Baseline ***n* = 1274**	**6 weeks** ***n* = 801**	**4 months** ***n* = 783**	**1 year** ***n* = 866**
SECTION 1	*n* = 1274	*n* = 801	*n* = 783	*n* = 866
Are you currently married or having an intimate relationship with someone?	14 (1.1%)	14 (1.7%)	22 (2.8%)	21 (2.4%)
Have you changed your sexual partner in the last 6 months?	34 (2.7%)	37 (4.6%)	51 (6.5%)	55 (6.4%)
Do you engage in sexual activity with anyone at the moment?	40 (3.1%)	35 (4.3%)	47 (6%)	44 (5.1%)
SECTION 2	*n* = 302	*n* = 301	*n* = 136	*n* = 139
I do not have a partner at the moment	16 (5.3%)	1 (0.3%)	0 (0%)	1 (0.7%)
I am too tired	13 (4.3%)	1 (0.3%)	0 (0%)	1 (0.7%)
My partner is too tired	17 (5.6%)	1 (0.3%)	0 (0%)	1 (0.7%)
I am not interested in sex	13 (4.3%)	1 (0.3%)	0 (0%)	1 (0.7%)
My partner is not interested in sex	15 (4.9%)	1 (0.3%)	0 (0%)	1 (0.7%)
I have a physical problem, which makes sexual relations difficult or uncomfortable	12 (3.9%)	1 (0.3%)	0 (0%)	1 (0.7%)
My partner has a physical problem, which makes sexual relations difficult or uncomfortable	17 (5.6%)	1 (0.3%)	0 (0%)	1 (0.7%)
SECTION 3	*n* = 972	*n* = 500	*n* = 647	*n* = 727
Was 'having sex' an important part of your life this month?	16 (1.7%)	18 (3.9%)	9 (1.5%)	17 (2.5%)
Did you enjoy sexual activity this month?	17 (1.8%)	23 (4.9%)	11 (1.8%)	15 (2.2%)
In general, were you too tired to have sex?	18 (1.9%)	20 (4.3%)	12 (2%)	20 (2.9%)
Did you desire to have sex with your partner(s) this month?	19 (2%)	16 (3.4%)	11 (1.8%)	17 (2.5%)
During sexual relations, how frequently did you notice dryness of your vagina this month?	29 (3.1%)	45 (9.7%)	10 (1.7%)	18 (2.6%)
Did you feel pain or discomfort during penetration this month?	30 (3.2%)	47 (10.1%)	10 (1.7%)	24 (3.5%)
In general, did you feel satisfied after sexual activity this month?	34 (3.6%)	39 (8.4%)	9 (1.5%)	21 (3.1%)
How often did you engage in sexual activity this month?	10 (1.1%)	11 (2.4%)	5 (0.8%)	12 (1.8%)
How did this frequency of sexual activity compare with what is usual for you?	27 (2.9%)	16 (3.4%)	8 (1.3%)	14 (2%)
Were you satisfied with the frequency of sexual activity this month?	21 (2.2%)	23 (4.9%)	6 (1%)	13 (1.9%)

TABLE 114 *Frequency of number of missing items per incomplete questionnaire*

Missing responses per questionnaire	**Baseline** ***n* = 1274**	**6 weeks** ***n* = 801**	**4 months** ***n* = 783**	**1 year** ***n* = 866**
1	87 (6.8%)	36 (4.5%)	29 (3.7%)	48 (5.5%)
2	30 (2.3%)	28 (3.5%)	33 (4.2%)	27 (3.1%)
3	15 (1.2%)	24 (2.9%)	22 (2.8%)	20 (2.3%)
4	5 (0.4%)	6 (0.7%)	0 (0%)	1 (0.1%)
5	5 (0.4%)	4 (0.5%)	0 (0%)	1 (0.1%)
6	9 (0.7%)	4 (0.5%)	0 (0%)	0 (0%)
7	9 (0.7%)	3 (0.4%)	0 (0%)	1 (0.1%)
8	1 (0.08%)	0 (0%)	0 (0%)	0 (0%)
9	0 (0%)	2 (0.2%)	0 (0%)	0 (0%)
10	5 (0.4%)	8 (1%)	5 (0.6%)	12 (1.4%)

TABLE 115 *Number of patients in a relationship*

	Baseline	6 weeks	4 months	1 year
AH	249/275 (90.5%)	162/174 (93.1%)	146/161 (90.7%)	160/172 (93%)
ALH	481/548 (87.8%)	316/359 (88.0%)	306/355 (86.2%)	348/391 (89%)
VH	133/149 (89.3%)	84/95 (88.4%)	81/95 (85.3%)	96/105 (91.4%)
VLH	271/302 (89.7%)	151/173 (87.3%)	155/172 (90.1%)	178/198 (89.9%)
Overall	1134/1274 (89.0%)	713/801 (89.0%)	688/783 (87.9%)	782/866 (90.3%)

TABLE 116 *Currently sexually active*

	Baseline	6 weeks	4 months	1 year
AH	198/275 (72.0%)	105/174 (60.3%)	126/161 (78.3%)	134/172 (77.9%)
ALH	391/548 (71.4%)	203/359 (56.5%)	265/355 (74.6%)	301/391 (76.9%)
VH	112/149 (75.2%)	53/95 (55.8%)	75/95 (78.9%)	87/105 (82.9%)
VLH	231/302 (76.5%)	104/173 (60.1%)	134/172 (77.9%)	161/198 (81.3%)
Overall	932/1274 (73.2%)	465/801 (58.1%)	600/783 (76.6%)	683/866 (78.9%)

TABLE 117 *Currently sexually active and in a relationship*

	Baseline	6 weeks	4 months	1 year
AH	196/249 (78.7%)	105/162 (64.8%)	125/146 (85.6%)	134/160 (83.8%)
ALH	387/481 (80.5%)	203/316 (64.2%)	263/306 (85.9%)	301/348 (86.5%)
VH	111/133 (83.5%)	52/84 (61.9%)	75/81 (92.6%)	86/96 (89.6%)
VLH	230/271 (84.9%)	104/151 (68.9%)	134/155 (86.5%)	160/178 (89.9%)
Overall	924/1134 (81.5%)	464/713 (65.1%)	597/688 (86.8%)	681/782 (87.1%)

TABLE 118 *Patients sexually inactive*

	Baseline	6 weeks	4 months	1 year
AH	64/275 (23.3%)	61/174 (35.1%)	25/161 (15.5%)	26/172 (15.1%)
ALH	146/548 (26.6%)	139/359 (38.7%)	62/355 (17.5%)	67/391 (17.1%)
VH	29/149 (19.5%)	40/95 (42.1%)	17/95 (17.9%)	17/105 (16.2%)
VLH	63/302 (20.9%)	61/173 (35.3%)	32/172 (18.6%)	29/198 (14.6%)
Overall	302/1274 (23.7%)	301/801 (37.6%)	136/783 (17.4%)	139/866 (16.1%)

sexually active, and is used mainly to stratify the data set into sexually active/inactive patients. *Table 115* shows the number and percentage of patients who were in a relationship. Approximately 90% of patients were in a relationship throughout the trial.

Table 116 shows that >70% of patients were sexually active at baseline; this dropped dramatically at 6 weeks to ≤60% and increased to >75% at 4 months and to almost 80% at 1 year follow-up.

Table 117 shows that of the patients who were sexually active and in a relationship, there was a drop at 6 weeks but an increase again at 4 months and 1 year to a higher level than at baseline.

Section 2 is completed only by sexually inactive patients and looks at the reasons for inactivity; it is useful for comparing frequencies between the groups and is not scored as such. *Table 118* shows the number and percentage of patients who were sexually inactive at each time point.

Reasons for inactivity

Tables 119–126 show the number and percentage of patients who were sexually inactive for the reasons given. Of the population of patients not sexually active at baseline, the main reasons for inactivity are 'no partner', 'patient has a physical problem', 'patient is too tired' and 'patient has no interest in sex'. Only 5% of patients report that their partner is 'too tired', 'not interested' or 'has a physical problem'. At 6 weeks, the major reason for inactivity

TABLE 119 *I do not have a sexual partner at the moment*

	Baseline	6 weeks	4 months	1 year
AH	24/64 (37.5%)	10/61 (16.4%)	8/25 (32%)	7/26 (26.9%)
ALH	58/146 (39.7%)	28/139 (20.1%)	26/62 (41.9%)	24/67 (35.8%)
VH	11/29 (37.9%)	9/40 (22.5%)	12/17 (70.6%)	7/17 (41.2%)
VLH	23/63 (36.5%)	19/61 (31.1%)	15/32 (46.9%)	14/29 (48.3%)
Overall	116/302 (38.4%)	66/301 (21.9%)	61/136 (44.9%)	52/139 (37.4%)

TABLE 120 *I am too tired*

	Baseline	6 weeks	4 months	1 year
AH	21/64 (32.8%)	14/61 (22.9%)	4/25 (16%)	6/26 (23.1%)
ALH	50/146 (34.2%)	29/139 (20.9%)	14/62 (22.6%)	17/67 (25.4%)
VH	9/29 (31.0%)	10/40 (25%)	2/17 (11.8%)	3/17 (17.6%)
VLH	13/63 (20.6%)	10/61 (16.4%)	2/32 (6.3%)	4/29 (13.8%)
Overall	93/302 (30.8%)	63/301 (20.9%)	22/136 (16.2%)	30/139 (21.6%)

TABLE 121 *My partner is too tired*

	Baseline	6 weeks	4 months	1 year
AH	1/64 (1.6%)	2/61 (3.3%)	1/25 (4%)	3/26 (11.5%)
ALH	10/146 (6.8%)	4/139 (2.9%)	4/62 (6.5%)	7/67 (10.4%)
VH	2/29 (6.9%)	1/40 (2.5%)	1/17 (5.9%)	3/17 (17.6%)
VLH	2/63 (3.2%)	3/61 (4.9%)	1/32 (3.1%)	2/29 (6.9%)
Overall	15/302 (4.9%)	10/301 (3.3%)	7/136 (5.1%)	15/139 (10.8%)

TABLE 122 *I am not interested in sex*

	Baseline	6 weeks	4 months	1 year
AH	25/64 (39.1%)	20/61 (32.8%)	118/25 (44%)	14/26 (53.8%)
ALH	44/146 (30.1%)	35/139 (25.2%)	20/62 (32.2%)	25/67 (37.3%)
VH	9/29 (31.0%)	11/40 (27.5%)	2/17 (11.8%)	5/17 (29.4%)
VLH	10/63 (15.9%)	15/61 (24.6%)	6/32 (18.8%)	6/29 (20.7%)
Overall	88/302 (29.1%)	81/301 (26.9%)	39/136 (28.7%)	50/139 (36%)

TABLE 123 *My partner is not interested in sex*

	Baseline	6 weeks	4 months	1 year
AH	2/64 (3.1%)	2/61 (3.3%)	3/25 (12%)	4/26 (15.4%)
ALH	9/146 (6.2%)	8/139 (5.8%)	7/62 (11.3%)	11/67 (16.4%)
VH	1/29 (3.4%)	0/40 (0%)	0/17 (0%)	2/17 (11.8%)
VLH	5/63 (7.9%)	3/61 (4.9%)	4/32 (12.5%)	7/29 (24.1%)
Overall	17/302 (5.6%)	13/301 (4.3%)	14/136 (10.3%)	24/139 (17.3%)

TABLE 124 *I have a physical problem which makes sexual relations difficult or uncomfortable*

	Baseline	6 weeks	4 months	1 year
AH	27/64 (42.2%)	12/61 (19.7%)	4/25 (16%)	5/26 (19.2%)
ALH	54/146 (36.9%)	22/139 (15.8%)	8/62 (12.9%)	5/67 (7.5%)
VH	5/29 (17.2%)	5/40 (12.5%)	1/17 (5.9%)	1/17 (5.9%)
VLH	22/63 (34.9%)	5/61 (8.2%)	1/32 (3.1%)	0/29 (0%)
Overall	108/302 (35.8%)	44/301 (14.6%)	14/136 (10.3%)	11/139 (7.9%)

TABLE 125 *My partner has a physical problem which makes sexual relations difficult or uncomfortable*

	Baseline	6 weeks	4 months	1 year
AH	4/64 (6.3%)	3/61 (4.9%)	0/25 (0%)	2/26 (7.7%)
ALH	6/146 (4.1%)	7/139 (5.0%)	6/62 (9.7%)	7/67 (10.4%)
VH	0/29 (0%)	2/40 (5.0%)	0/17 (0%)	1/17 (5.9%)
VLH	5/63 (7.9%)	1/61 (1.6%)	2/32 (6.3%)	3/29 (10.3%)
Overall	15/302 (4.9%)	13/301 (4.3%)	8/136 (5.9%)	13/139 (9.4%)

TABLE 126 *Other reasons*

	Baseline	6 weeks	4 months	1 year
AH	8/64 (12.5%)	30/61 (49.2%)	11/25 (44%)	9/26 (34.6%)
ALH	24/146 (16.4%)	73/139 (52.5%)	14/62 (22.6%)	15/67 (22.4%)
VH	10/29 (34.5%)	24/40 (60%)	3/17 (17.6%)	6/17 (35.3%)
VLH	11/63 (17.5%)	31/61 (50.8%)	10/32 (31.3%)	6/29 (20.7%)
Overall	53/302 (17.5%)	158/301 (52.5%)	38/136 (27.9%)	36/139 (25.9%)

is given as 'other'; in fact more than half the patients have another reason for inactivity. The most common examples of 'other reasons for inactivity' at baseline are bleeding and pain/discomfort, and at 6 weeks half the patients felt it was too soon after their operation. However, 25% 'have no partner', 'are not interested' or 'are too tired'. Still only 5% have partner-related problems as their reason for inactivity. At 4 months and 1 year the proportion of inactive patients is reduced; however, the major reasons for inactivity remain the same, but with a larger proportion reporting partner-related problems for their activity.

There does not appear to be a trend or any difference between the types of procedure. At 1 year follow-up 54% of AH patients who were not sexually active reported that they have 'no interest in sex', compared with 37% of ALH patients. However, the number of patients is relatively small and this may be purely random.

Section 3 is completed only by those patients who are sexually active. Each item can be analysed independently. *Figures 55–74* (Appendix 9) show plots of the individual items. There appears to be a trend over time, with patients enjoying, desiring and increasing the frequency of sexual activity from baseline to 4 months and 1 year; there is, as expected, a decrease in sexual activity at 6 weeks. The pattern is very similar for all types of procedure. These individual items were not formally tested. Sexual functioning can be explained by three factors: pleasure from sexual intercourse, discomfort during sexual intercourse and habit. Scoring of these three factors is by adding the raw scores of the appropriate questions.

The factor 'pleasure from sexual intercourse (desire, enjoyment and satisfaction)' is made up of the following questions: 'Was having sex an important part of your life this month?', 'Did you enjoy sexual activity this month?', 'Did you desire to have sex with your partner(s) this month?', 'In general, did you feel satisfied after sexual activity this month?', 'How often did you engage in sexual activity this month?' and 'Were you satisfied with the frequency of sexual activity this month?'. By adding the raw scores for each question, the possible range of the score for this factor is 0–18. A high score represents high pleasure.

The factor 'discomfort during sexual intercourse (dryness and pain)' is made up of two questions: 'During sexual relations, how frequently did you notice dryness of your vagina this month?' and 'Did you feel pain or discomfort during penetration this month?' The possible range of the score for this factor is 0–6, with a low score representing low discomfort.

The factor 'habit' consists of one question: 'How did this frequency of sexual activity compare with what is usual for you?'. The possible scores here are 0–3, with a high score representing a higher frequency than usual.

Results of SAQ

Tables 127–132 show the median, range, mean, SD, difference between the means, 95% CI of the difference and the *p*-value for each factor, pleasure, discomfort and habit, within the abdominal and vaginal trials.

TABLE 127 *Pleasure, abdominal trial: median (range), mean (SD) and mean difference (95% CI) at each time point*

	Baseline		6 weeks		4 months		1 year	
	AH ***n*** **= 184**	**ALH** ***n*** **= 355**	**AH** ***n*** **= 91**	**ALH** ***n*** **= 178**	**AH** ***n*** **= 119**	**ALH** ***n*** **= 252**	**AH** ***n*** **= 127**	**ALH** ***n*** **= 285**
Median (range)	11 (0–18)	10 (0–18)	11 (2–18)	11 (0–18)	14 (2–18)	15 (0–18)	14 (1–18)	14 (1–18)
Mean (SD)	10.3 (4.8)	10.6 (4.8)	11.1 (4.4)	11.4 (4.7)	13.2 (4.1)	13.2 (4.6)	12.8 (4.4)	13.3 (4.2)
Mean difference (95% CI)	–0.34 (–1.2 to 0.5)		–0.2 (–1.4 to 0.9)		–0.02 (–0.9 to 0.9)		–0.6 (–1.5 to 0.3)	
p			0.7		0.9		0.2	

TABLE 128 *Pleasure, vaginal trial: median (range), mean (SD) and mean difference (95% CI) at each time point*

	Baseline		6 weeks		4 months		1 year	
	VH ***n*** **= 110**	**VLH** ***n*** **= 221**	**VH** ***n*** **= 48**	**VLH** ***n*** **= 92**	**VH** ***n*** **= 73**	**VLH** ***n*** **= 132**	**VH** ***n*** **= 85**	**VLH** ***n*** **= 153**
Median (range)	11 (1–18)	12 (1–18)	11.5 (1–18)	13 (0–18)	15 (3–18)	16 (4–18)	15 (1–18)	16 (3–18)
Mean (SD)	10.8 (4.7)	11.4 (4.8)	11.9 (4.4)	12.5 (4.4)	14.2 (3.9)	14.5 (3.5)	14.2 (3.8)	14.7 (3.8)
Mean difference (95% CI)	–0.6 (–1.7 to 0.5)		–0.5 (–2.1 to 1.1)		–0.4 (–1.4 to 0.7)		–0.5 (–1.5 to 0.5)	
p			0.5		0.5		0.4	

TABLE 129 *Discomfort, abdominal trial: median (range), mean (SD) and mean difference (95% CI) at each time point*

	Baseline		6 weeks		4 months		1 year	
	AH ***n*** **= 189**	**ALH** ***n*** **= 367**	**AH** ***n*** **= 93**	**ALH** ***n*** **= 183**	**AH** ***n*** **= 122**	**ALH** ***n*** **= 259**	**AH** ***n*** **= 128**	**ALH** ***n*** **= 290**
Median (range)	2 (0–6)	2 (0–6)	1 (0–6)	1 (0–6)	1 (0–6)	1 0–6)	1 (0–6)	1 (0–6)
Mean (SD)	2.4 (2.0)	2.2 (1.8)	1.5 (1.5)	1.3 (1.5)	1.5 (1.6)	1.2 (1.5)	1.1 (1.5)	1.3 (1.6)
Mean difference (95% CI)	0.2 (–0.09 to 0.6)		0.2 (–0.2 to 0.6)		0.3 (–0.08 to 0.6)		–0.1 (–0.5 to 0.2)	
p			0.7		0.14		0.4	

TABLE 130 *Discomfort, vaginal trial: median (range), mean (SD) and mean difference (95% CI) at each time point*

	Baseline		6 weeks		4 months		1 year	
	VH ***n*** **= 112**	**VLH** ***n*** **= 226**	**VH** ***n*** **= 48**	**VLH** ***n*** **= 91**	**VH** ***n*** **= 75**	**VLH** ***n*** **= 132**	**VH** ***n*** **= 85**	**VLH** ***n*** **= 156**
Median (range)	1 (0–6)	2 (0–6)	1 (0–5)	1 (0–6)	1 (0–6)	1 (0–5)	0 (0–6)	1 (0–6)
Mean (SD)	1.9 (1.9)	1.9 (1.8)	1.2 (1.3)	1.3 (1.2)	1.4 (1.6)	1.3 (1.4)	1.1 (1.6)	1.1 (1.4)
Mean difference (95% CI)	0.02 (–0.4 to 0.4)		–0.1 (–0.6 to 0.3)		0.07 (–0.4 to 0.5)		0.09 (–0.3 to 0.5)	
p			0.6		0.8		0.7	

TABLE 131 *Habit, abdominal trial: median (range), mean (SD) and mean difference (95% CI) at each time point*

	Baseline		6 weeks		4 months		1 year	
	AH ***n* = 190**	**ALH** ***n* = 378**	**AH** ***n* = 102**	**ALH** ***n* = 196**	**AH** ***n* = 123**	**ALH** ***n* = 261**	**AH** ***n* = 130**	**ALH** ***n* = 295**
Median (range)	1 (0–3)	1 (0–3)	0 (0–3)	0.5 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
Mean (SD)	0.7 (0.7)	0.8 (0.7)	0.5 (0.7)	0.8 (0.9)	1.0 (0.9)	1.1 (0.9)	1.0 (0.7)	1.1 (0.8)
Mean difference (95% CI)	–0.1 (–0.3 to 0.0)		–0.3 (–0.6 to –0.1)		–0.09 (–0.3 to 0.1)		–0.02 (–0.2 to 0.1)	
p			**0.003**		0.4		0.8	

TABLE 132 *Habit, vaginal trial: median (range), mean (SD) and mean difference (95% CI) at each time point*

	Baseline		6 weeks		4 months		1 year	
	VH ***n* = 112**	**VLH** ***n* = 225**	**VH** ***n* = 53**	**VLH** ***n* = 98**	**VH** ***n* = 75**	**VLH** ***n* = 133**	**VH** ***n* = 84**	**VLH** ***n* = 160**
Median (range)	1 (0–3)	1 (0–3)	0 (0–3)	0 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
Mean (SD)	0.7 (0.6)	0.8 (0.7)	0.6 (0.8)	0.7 (0.9)	1.2 (0.8)	1.2 (0.8)	1.1 (0.7)	1.1 (0.8)
Mean difference (95% CI)	–0.04 (–0.2 to 0.1)		–0.1 (–0.4 to 0.2)		–0.007 (–0.2 to 0.2)		–0.03 (–0.2 to 0.2)	
p			0.38		0.95		0.82	

From *Table 131*, it can be seen that the *t*-test shows a significant difference in the habit factor at 6 weeks between AH and ALH, indicating that the frequency of sexual activity for ALH patients increases at 6 weeks.

EuroQol instrument (EQ-5D)

Missing data items

One hundred patients had one of the two EQ-5D assessments missing between baseline and the 6-week follow-up visit (between 5.6 and 9.9% in the trial groups), and a number of the returned EQ-5D questionnaires displayed missing response items.

EQ-5D and QALY results

Table 133 shows, separately for the two comparisons, the mean and median EQ-5D scores at baseline and the three points of follow-up. These 'utilities' are on a scale anchored by 0 (equivalent to dead) to 1 (equivalent to good health). In terms of both mean and median values, and for both comparisons, patients showed progressive improvements between baseline and 6 weeks and between 6 weeks and 4 months; very little changed between 4 months and 1 year.

The utilities are used to calculate QALYs for each woman, and *Table 133* shows mean QALYs per arm of the trial over a period of 1 year. Comparison of the arms of the trial shows very small differences, none of which reaches conventional levels of statistical significance. *Table 133* shows higher mean QALYs per patient in the VLH group compared with VH (difference of 0.0015; 95% CI –0.015 to 0.018). It also shows small additional mean QALYs per patient in the ALH group compared with AH (0.007; 95% CI –0.008 to 0.023).

Summary

SF-12

There is a highly statistically significant difference on the physical component summary score at 6 weeks in the abdominal trial between AH and LAVH. No statistically significant difference was found at the other time points or within the vaginal trial.

Owing to the number of forms that were not returned within the correct time frame and the number of forms that had at least one missing response, these results are based on a relatively

TABLE 133 *Health outcomes measured in the trial: responses to the EQ-5D and QALYs*

	Vaginal trial				Abdominal trial			
	VLH (*n* = 324)		VH (*n* = 163)		ALH (*n* = 573)		AH (*n* = 286)	
	Mean	Median (IQR)	Mean	Median (IQR)	Mean	Median (IQR)	Mean	Median (IQR)
EQ-5D utilities								
Baseline	0.746	0.760 (0.725–1)	0.758	0.796 (0.691–1)	0.716	0.760 (0.691–0.848)	0.690	0.725 (0.689–0.812)
6 weeks	0.875	0.907 (0.812–1)	0.852	0.863 (0.76 – 1)	0.832	0.869 (0.76–1)	0.833	0.883 (0.76–1)
4 months	0.911	0.971 (0.848–1)	0.918	0.959 (0.848–1)	0.886	0.959 (0.812–1)	0.866	0.888 (0.796–1)
1 year	0.920	1 (0.881–1)	0.917	1 (0.861–1)	0.897	0.929 (0.848–1)	0.892	0.959 (0.822–1)
QALYs over 1 year[a]	0.899		0.897		0.870		0.862	
Differential QALYs over 1 year[b]	0.0015				0.007			
95% CI[c]	–0.015 to 0.018				–0.008 to 0.023			

[a] Adjusting for baseline EQ-5D utility.
[b] Laparoscopic-assisted minus standard.
[c] 95% non-parametric CI based on 1000 bootstrap replications.

small subset of patients and hence are difficult to interpret.

The mean scores adjusted for baseline scores indicate that QoL measured on the physical component summary score of the SF-12 is significantly better for LH patients at 6 weeks postoperation.

BIS

There is a highly statistically significant difference on the BIS at 6 weeks within the abdominal trial between AH and ALH. There is some evidence of a difference at 4 months within the abdominal trial between AH and ALH, but this is not statistically significant. No statistically significant differences were found at the other time points or within the vaginal trial.

The mean scores adjusted for baseline scores indicate that QoL measured on the BIS is significantly better for ALH than for AH patients at 6 weeks and 4 months postoperation.

SAQ

There is a highly statistically significant difference at 6 weeks in the habit score in the abdominal trial between AH and ALH. This indicates that the frequency of sexual activity for ALH patients increases significantly more from baseline than for AH patients. No statistically significant difference was found at the other time points or for any of the other factors or within the vaginal trial.

The main reason reported for sexual inactivity is 'no partner' at baseline, 4 months and 1 year; a large proportion of patients at 6 weeks report 'too soon after their operation' as their reason for inactivity. Approximately 90% of patients are in a relationship at all time points. Of the patients who are sexually active there is a trend for enjoyment, desire and frequency to increase over time.

EQ-5D

On average, women's health-related QoL, based on their responses to the EQ-5D questionnaire, showed consistent improvements between baseline and most periods of follow-up. However, the **differences** between the groups in health outcomes were small. Over a period of 1 year postoperation, the mean differences in QALYs per patient were 0.0015 in favour of VLH in the first comparison and 0.007 in favour of ALH in the second comparison with AH.

There is an issue of whether QALYs, as measured through the EQ-5D, adequately reflect important differences in outcome between the procedures.

The value of the QALY is that it is comparable across disease areas and specialties, and this 'generic' quality is essential for resource allocation decisions across the health service. As a result, the QALY has been recommended in economic evaluation methods guidance in the UK[57] and the USA.[58] However, it can be argued that the five dimensions of health-related QoL contained in the EQ-5D, with three response levels per dimension, may fail to register important differences between the trial groups over time. This argument may be supported by the fact that the excess rate of complications in the laparoscopic-assisted groups was not reflected in terms of QALYs. However, the data from EVALUATE may support different interpretation, namely that the excess rate of complications did not impact on health-related QoL for the average woman in the trial; indeed, there appeared to be a small benefit from laparoscopic compared with the standard procedures. The results with the EQ-5D reported here are consistent with those with the SF-12.

Chapter 6

Results of the economic evaluation

Available data

Data on some resource use and outcome variables were missing for a proportion of patients. For example, owing to either admission or discharge date being missing, hospital inpatient length of stay could not be calculated for between 1.23 and 3.7% of patients in the four trial groups. Among women who had surgery, missing data relating to the duration of the procedure meant time in theatre could not be calculated for between 3.5 and 4.2% of women.

Resource use

Table 134 provides a summary of the main areas of resource use measured in the trial; results are presented separately for the two comparisons in the study. For the comparison of VLH and VH, the main differences in resource use related to time in theatre (mean 98.14 minutes for VLH versus 65.03 minutes for VH) and the use of consumables as part of the VLH. For example, in the VLH arm, a disposable linear stapler was used to achieve haemostasis in 36% of ovarian pedicles and 19% of uterine pedicles and disposable scissors were used in 37% of VLH procedures. No marked differences emerged between the procedures in length of stay or resource use subsequent to the initial hospitalisation.

The second comparison, between ALH and AH, shows more differences in terms of resource use (*Table 134*). Again, time in theatre was longer with ALH (mean 108.07 versus 74.08 minutes). As for the other comparison, there was still a high proportion of laparoscopic procedures undertaken using disposable equipment. In comparison with AH, however, ALH had a lower mean length of stay (3.95 versus 5.11 days). During follow-up, there appear to be no differences in resource use that would be expected to impact markedly on differential cost.

Costs

Mean and median costs per patient are shown in *Table 135* based on resource use measured in the trial (*Table 134*) and the UK unit costs summarised in *Table 136*. Again, results are presented separately for the two comparisons in the study. The differences in cost between the two types of procedure mirror those in resource use described above.

For the comparison of VLH with VH, the only marked difference relates to theatre cost, which reflects differences in theatre times and the use of disposable equipment in a large proportion of VLH procedures. None of the other cost components detailed in *Table 135* show marked differences between the groups. Indeed, the median costs are the same in the two groups for hotel costs, other postoperative costs and the follow-up costs at each time point. The fact that mean costs for these components are different (but never to an extent to affect overall costs in a major way) reflects the skewed nature of the data where high costs are incurred in a small number of patients as a result of complications or resource use probably unrelated to their hysterectomy. Overall, VLH has a higher mean cost per patient of £401 (95% CI £271 to £542).

The comparison of the ALH procedure with AH indicates that laparoscopic costs are closer to, but still higher than, those in the conventional arm. A mean difference of £335 in theatre costs again reflects longer time in theatre and the use of disposable equipment with ALH. However, the shorter length of stay in hospital in the laparoscopic arm offsets some of that additional cost, with a mean saving in hotel costs of £144. Overall, ALH has a higher mean cost per patient of £186 (95% CI £–26 to £375).

Health outcomes

The EQ-5D is reported in Chapter 5 with the other QoL measures. To allow interpretation of cost-effectiveness data, see *Table 133*.

Cost-effectiveness

Tables 133 and *135* show the estimates of mean differences in costs and QALYs between

TABLE 134 *Key resource use measured in the two parts of the trial*

Item of resource use	Vaginal trial				Abdominal trial			
	Laparoscopic-assisted hysterectomy (*n* = 324)		VH (*n* = 163)		Laparoscopic-assisted hysterectomy (*n* = 573)		AH (*n* = 286)	
Theatre								
Time in theatre (minutes)[a]								
Mean (SD)	98.14	(35.45)	65.03	(27.87)	108.07	(33.33)	74.08	(23.86)
Median	95	(45–180)	58	(34–147)	105	(51–182)	70	(38–141)
(2.5 centile–97.5 centile)								
Missing[b] *n* (%)	11	(4.15)	6	(4.20)	18	(3.48)	10	(3.85)
Time in recovery room								
Mean (SD)	80.61	(38.76)	80.44	(48.91)	73.63	(33.64)	73.84	(34.69)
Median	79	(25–180)	77	(25–222)	73	(21–155)	73	(15–157)
(2.5 centile–97.5 centile)								
Missing *n* (%)	16	(6.04)	9	(6.29)	34	(6.58)	16	(6.15)
Selected disposable items used during laparoscopic surgery								
Linear Stapler[c]:								
Ovarian *n* (%)	96	(36.23)	1	(0.70)	124	(23.98)	1	(0.38)
Uterine *n* (%)	51	(19.25)	1	(0.70)	84	(16.25)	1	(0.38)
Missing *n* (%)	8	(3.02)	–	(–)	12	(2.32)	–	(–)
Trocars (5 mm) *n* (%):								
0	240	(90.57)	143	(100)	498	(96.32)	260	(100)
1	8	(3.02)	–	(–)	7	(1.35)	–	(–)
>1	17	(6.42)	–	(–)	12	(2.32)	–	(–)
Trocars (10 mm) *n* (%):								
0	221	(83.40)	142	(99.30)	445	(86.07)	259	(99.65)
1	31	(11.70)	1	(0.70)	61	(11.80)	1	(0.35)
>1	13	(4.91)	–	(–)	11	(2.13)	–	(–)
Trocars (12 mm) *n* (%):								
0	179	(67.55)	141	(98.77)	397	(76.79)	258	(99.30)
1	31	(11.70)	2	(1.23)	27	(5.22)	–	(–)
>1	55	(20.75)	–	(–)	93	(17.99)	2	(0.70)
Scissors *n* (%):								
0	168	(63.40)	141	(98.77)	423	(81.82)	260	(100)
1	96	(36.23)	2	(1.23)	93	(17.99)	–	(–)
2	1	(0.38)	–	(–)	1	(0.19)	–	(–)
Main hospitalisation								
Total length of stay in hospital (days)[d]								
Mean (SD)	4.28	(2.02)	4.32	(1.99)	3.95	(2.36)	5.11	(2.70)
Median	4	(2–9)	4	(2–9)	4	(2–8)	5	(2–11)
(2.5 centile–97.5 centile)								
Missing *n* (%)	12	(3.70)	2	(1.23)	8	(1.40)	5	(1.75)
ICU *n* (%)	–	(–)	–	(–)	1	(0.18)	–	(–)
Mean length of stay in ICU (min.–max.)					2	(–)	–	(–)
HDW *n* (%)	2	(0.62)	1	(0.61)	2	(0.35)	–	(–)
Mean length of stay in HDW (min.–max.)	2.5	(1–4)	1	(–)	1.5	(1–2)	–	(–)
Missing questionnaires *n* (%)	58	(17.96)	18	(11.18)	50	(8.82)	20	(7.14)

continued

TABLE 134 *Key resource use measured in the two parts of the trial (cont'd)*

Item of resource use	Vaginal trial				Abdominal trial			
	Laparoscopic-assisted hysterectomy (*n* = 324)		VH (*n* = 163)		Laparoscopic-assisted hysterectomy (*n* = 573)		AH (*n* = 286)	
6-weeks follow-up								
Out-patient visits *n* (%)								
0	173	(76.55)	83	(69.75)	329	(71.99)	143	(66.51)
1	42	(18.58)	34	(28.57)	104	(22.76)	62	(28.84)
>1	11	(4.87)	2	(1.68)	24	(5.25)	10	(4.65)
Day-case visits *n* (%)								
0	226	(100)	119	(100)	451	(98.69)	210	(97.67)
>0	–	(–)	–	(–)	6	(1.31)	5	(2.33)
GP visits *n* (%)								
0	53	(23.45)	33	(27.73)	103	(22.54)	47	(21.86)
1–5	169	(74.78)	84	(70.59)	349	(76.37)	161	(74.88)
>5	4	(1.77)	2	(1.68)	5	(1.09)	7	(3.26)
Inpatient visits *n* (%)								
0	217	(96.02)	114	(95.80)	426	(93.22)	205	(95.35)
1	6	(2.65)	5	(4.20)	28	(6.13)	10	(4.65)
2	3	(1.33)	–	(–)	3	(0.66)	–	(–)
Length of stay of inpatient visits								
Mean (max.–min.)	8.44	(4–21)	2.2	(1–4)	6.2	(1–26)	3.8	(1–10)
Missing questionnaires *n* (%)	92	(28.93)	42	(26.09)	108	(19.05)	63	(22.66)
4-months follow-up								
Outpatient visits *n* (%)								
0	143	(74.48)	83	(81.37)	289	(75.06)	119	(70.41)
1	36	(18.75)	14	(13.73)	76	(19.74)	35	(20.71)
>1	13	(6.77)	5	(4.90)	20	(5.19)	15	(8.88)
Day-case visits *n* (%)								
0	187	(97.40)	–	(–)	382	(99.22)	166	(98.22)
1	4	(2.08)	–	(–)	3	(0.78)	3	(1.78)
2	1	(0.52)	–	(–)	–	(–)	–	(–)
GP visits *n* (%)								
0	71	(36.98)	39	(38.24)	116	(30.13)	52	(30.77)
1–5	115	(59.90)	60	(58.82)	255	(66.23)	113	(66.86)
>5	6	(3.13)	3	(2.94)	14	(3.64)	4	(2.37)
Inpatient visits *n* (%)								
0	189	(98.44)	100	(98.04)	381	(98.96)	162	(95.86)
1	3	(1.56)	2	(1.96)	3	(0.78)	7	(4.14)
>1	–	(–)	–	(–)	1	(0.26)	–	(–)
Length of stay of inpatient visits								
Mean (max.–min.)	4.33	(4–5)	6	(3–9)	5.25	(3–7)	7.14	(3–21)
Missing questionnaires *n* (%)	57	(22.89)	28	(21.54)	84	(17.91)	58	(25.55)

continued

TABLE 134 *Key resource use measured in the two parts of the trial (cont'd)*

Item of resource use	Vaginal trial				Abdominal trial			
	Laparoscopic-assisted hysterectomy (*n* = 324)		VH (*n* = 163)		Laparoscopic-assisted hysterectomy (*n* = 573)		AH (*n* = 286)	
1-year follow-up								
Outpatient visits *n* (%)								
0	177	(81.19)	87	(76.99)	392	(93.78)	162	(86.17)
1	26	(11.93)	18	(15.93)	18	(4.31)	18	(9.57)
>1	15	(6.88)	8	(7.08)	8	(1.91)	8	(4.26)
Day-case visits *n* (%)								
0	215	(98.62)	110	(97.35)	405	(96.89)	183	(97.34)
>0	3	(1.38)	3	(2.65)	13	(3.11)	5	(2.66)
GP visits *n* (%)								
0	55	(25.23)	26	(23.01)	95	(22.73)	47	(25.00)
1–5	131	(60.09)	72	(63.72)	259	(61.96)	117	(62.23)
>5	32	(14.68)	15	(13.27)	64	(15.31)	24	(12.77)
Inpatient visits *n* (%)								
0	213	(97.71)	104	(92.04)	402	(96.17)	177	(94.15)
>0	5	(2.29)	9	(7.96)	16	(3.83)	11	(5.85)
Length of stay of inpatient visits								
Mean (max.–min.)	4	(2–5)	3.5	(1–8)	6.06	(1–24)	6.17	(1–46)
Missing questionnaires *n* (%)	100	(31.45)	46	(28.93)	140	(25.09)	87	(31.64)

[a] Calculated as theatre patient's preparation time + time from first incision to last suture.
[b] The term 'missing' includes data unavailable because of loss to follow-up and particular data items being missing.
[c] As first method of haemostasis.
[d] Calculated as discharge date – admission date.

laparoscopic-assisted hysterectomy and the standard forms of surgery. For the comparison of the VLH approach and VH, mean per patient costs (£401) and QALYs (0.0015) are both higher with VLH. In this circumstance, the issue is whether decision-makers are willing to pay the implied incremental cost-effectiveness ratio (ICER). The ICER is the mean difference in costs divided by the mean difference in QALYs, here £267,333 (£401/0.0015). However, mean differential costs and QALYs are estimated with uncertainty as shown in the CIs detailed above. *Figure 5* represents this uncertainty in the form of a cost-effectiveness acceptability curve which shows the probability that VLH is more cost-effective than VH for a range of maximum values that decision-makers may place on generating an additional QALY. It can be seen that the probability that VLH is the more cost-effective is never above 50%.

Turning to the comparison of ALH and AH, *Tables 133* and *135* show that the laparoscopic procedure has higher mean cost (£186) and higher mean QALY (0.007) per patient. This generates an ICER of £26,571. *Figure 5* shows the cost-effectiveness acceptability curve for this comparison, with the ICER marked on the *x*-axis. The figure shows that the higher the value decision-makers place on an additional QALY, the higher is the probability that the laparoscopic procedure will be more cost-effective than AH. For example, at a maximum value of £30,000, the probability reaches 56%. If the health service is willing to pay up to £50,000 per additional QALY, this probability increases to 67%.

Time away from paid work

EVALUATE collected data on time away from paid work and the results are shown in *Figure 6*. The mean (SD) number of days it took women to return to work after VLH [78.68 (44.2)] was similar to that in patients undergoing the vaginal procedure [70.21 (34.4)], and this would not have altered the relative cost-effectiveness of these two procedures. However, in the other comparison, the mean (SD) number of days it took women to return to work after laparoscopic-assisted hysterectomy [77.8

TABLE 135 *Comparison of costs between laparoscopic-assisted and standard hysterectomy (1999–2000 prices, UK £)*

	Vaginal trial				Abdominal trial			
	Laparoscopic-assisted hysterectomy (VLH) (*n* = 324)		VH (*n* = 163)		Laparoscopic-assisted hysterectomy (ALH) (*n* = 573)		AH (*n* = 286)	
	Mean	Median (IQR)	Mean	Median (IQR)	Mean	Median (IQR)	Mean	Median (IQR)
Theatre cost	806.54	635.43 (512.65–919.46)	395.72	361.98 (309.08–420.07)	788.37	646.11 (523.35–890.44)	453.10	430.52 (380.7 – 489.51)
Hospital 'hotel' cost	589.26	542.00 (406.5–677.5)	591.37	542.00 (406.5–677.5)	548.43	542.00 (406.5–677.5)	692.45	677.50 (542–813)
Other postoperative cost	14.20	0.05 (0–0)	17.64	0.00 (0–0)	21.48	0.00 (0–0)	12.74	0.00 (0–0)
Follow-up cost at 6 weeks	143.65	45.75 (0–107.75)	89.32	45.75 (0–107.75)	192.65	45.75 (0–107.75)	127.51	45.75 (0–107.75)
Follow-up cost at 4 months	36.57	0.00 (0–45.75)	46.87	0.00 (0–45.75)	39.46	0.00 (0–45.75)	87.90	0.00 (0–45.75)
Follow-up cost at 1-year	63.78	45.75 (0–45.75)	112.29	45.75 (0–45.75)	115.33	45.75 (0–45.75)	145.88	45.75 (0–45.75)
Total cost	1654.00		1253.20		1705.72		1519.64	
Differential mean cost[a]	400.79				186.08			
(95% CI)[b]	270.54 to 541.50				–25.96 to 375.47			

[a] Laparoscopic-assisted minus standard.
[b] 95% non-parametric CI based on 1000 bootstrap replications.

TABLE 136 *Key unit costs used to value resource use measured in the trial (1999–2000 prices, UK £)*

Item of resource	Unit	Unit cost (£)	Source
Ward			
General ward	Day	135.50	Two specific hospitals recruiting to EVALUATE
HDW	Day	393.66	Reference 59
ICU	Day	866.83	Reference 59
Theatre			
Staff (variable)	Minute	2.26	References 60, 61
Staff (fixed)	Fixed	1.36	References 60, 61
Overheads	Minute	1.83	Two specific hospitals recruiting to EVALUATE
Selected consumables used during laparoscopic procedure			
Linear stapler	Item	257.72	Manufacturer
Laparoscopic scissors	Item	120.44	Manufacturer
Disposable trocars	Item	76.57	Manufacturer
Visits			
GP visits	Visit	15.75	Reference 62
Outpatient hospital visits	Visit	62.00	Reference 44
Day-case visits	Visit	62.00	Assumed the same as outpatient visit

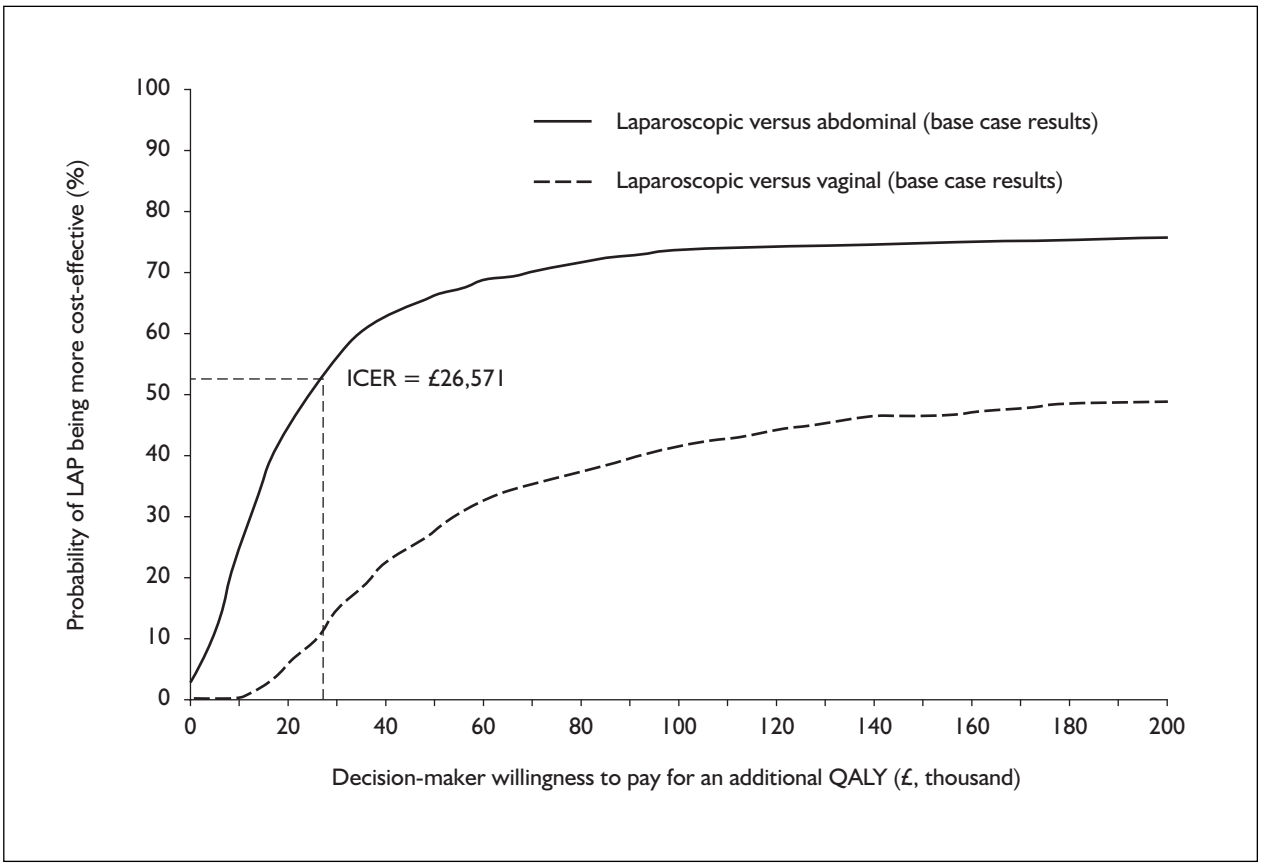

FIGURE 5 *Cost-effectiveness acceptability curve for laparoscopic-assisted hysterectomy versus standard hysterectomy (abdominal or vaginal)*

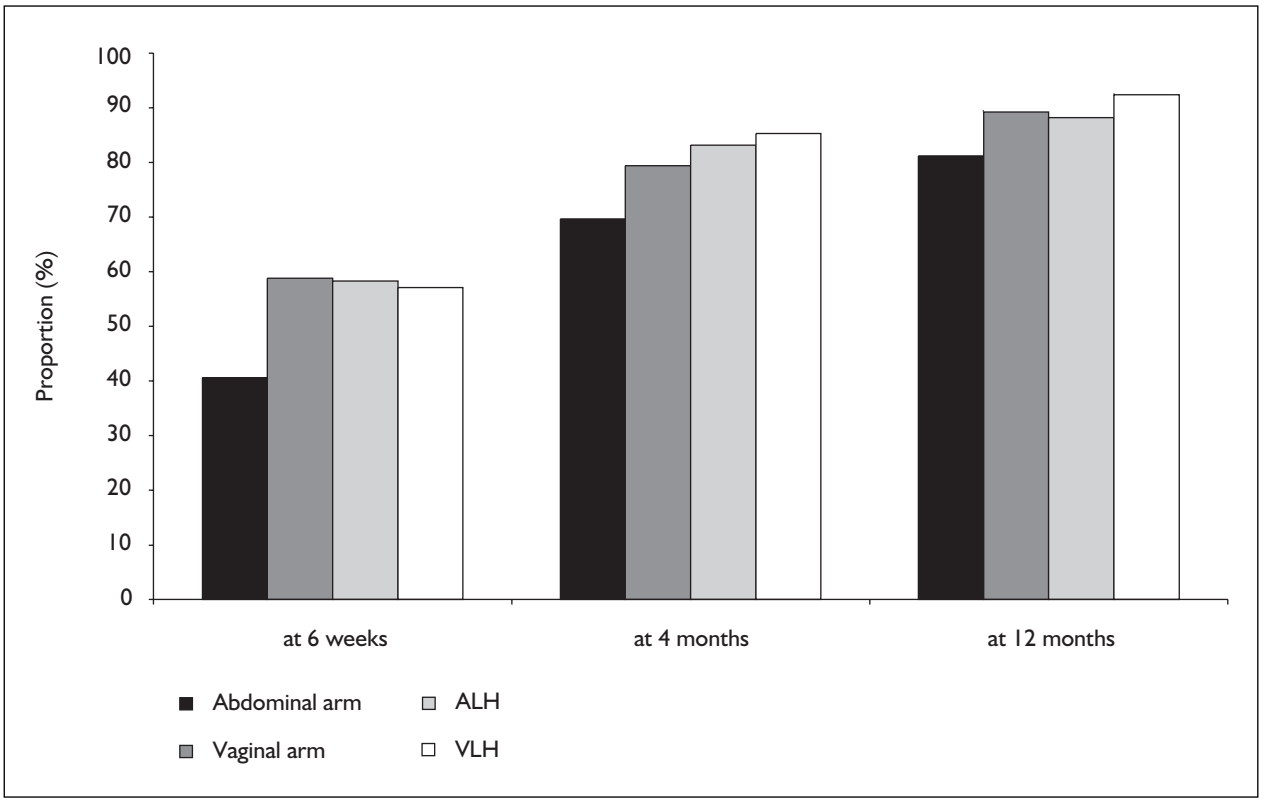

FIGURE 6 *Proportion returning to work after surgery*

(39.5)] was lower than that in patients undergoing the abdominal procedure [94.87 (60.0)]. If all or part of this difference can reasonably be reflected in terms of productivity savings in monetary terms, this would increase the likelihood that ALH would be considered more cost-effective than AH.

Sensitivity analysis

The acceptability curves in *Figure 5* show the sampling uncertainty in the cost-effectiveness results. However, there are two sources of variation in clinical practice between centres which should be explored using sensitivity analysis. These sources of variation are important because they have a potentially large effect on differences in cost between the laparoscopic-assisted and standard forms of hysterectomy.

The first source of variation is in the prices and use of disposable consumables during laparoscopic procedures. To explore variation in prices, a questionnaire was sent to each centre in the trial seeking information about the prices they paid for these disposables. Of the 28 questionnaires sent out, 17 were returned and the information provided revealed modest variations in the prices paid (i.e. <10% range of variation), compared with those used in the base-case analysis; this would be expected to have little impact on total cost differences.

Surgeons in the trial varied in terms of their use of disposable consumables versus reusable equipment as part of laparoscopic procedures; in the primary analysis here, costs have been averaged across surgeons whatever their policy. However, underlying this average are two different policies: a 'largely reusable' policy where centres do not use disposables as part of their laparoscopic procedures and prefer to sterilise and reuse equipment, and a 'largely disposable' policy where consumables are typically used on a single patient only. A sensitivity analysis was conducted to assess how differential costs would have changed under these two policies. It should be emphasised that it was assumed that there would be no effect on health outcomes. Given the results reported in Chapter 3 regarding the elevated risk of a major complication in women who were sutured on the uterine pedicle, this sensitivity analysis should be interpreted with some caution.

Under the 'largely disposable' policy, the mean additional cost of laparoscopic-assisted procedures increases markedly: to £1981 in the comparison with vaginal and to £1816 in the comparison with

abdominal. In terms of cost-effectiveness, the ICER for VLH relative to VH increases to £1,320,667 and that of ALH relative to AH increases to £259,428.

The second source of variation which may impact on these results is in the ward cost per inpatient day, which will affect the hotel costs shown in *Table 135*. The base-case results are based on the average daily costs in two EVALUATE centres. Data on inpatient costs per day are published annually for English hospitals,[44] but these include a range of costs not incorporated into the 'hotel' costs per day presented in *Table 136* because they have been costed separately here (e.g. the cost of therapeutic and diagnostic procedures). Therefore, each inpatient day in the English hospital cost database has been adjusted to a hotel cost per day based on the proportion of total costs per day made up of hotel costs in the two EVALUATE centres where detailed costings were available. *Figures 7* and *8* show the implications of this sensitivity analysis in terms of the cost-effectiveness acceptability curves, where a curve is provided for the median UK costs and the lower and upper quartile. Given that there is very little difference between laparoscopic-assisted hysterectomy and VH in hospital length of stay, the curves are very similar for this comparison (*Figure 7*). In the case of the comparison of laparoscopic-assisted hysterectomy and AH, however, the shorter mean length of stay for the laparoscopic procedure results in the use of the upper quartile in national daily ward costs, increasing the probability of laparoscopic-assisted hysterectomy being more cost-effective (e.g. to 74% at a maximum willingness to pay for an additional QALY of £30,000).

Discussion

The EVALUATE study is by far the largest randomised controlled trial yet undertaken to assess the costs and effects of alternative forms of hysterectomy. Furthermore, although several smaller trials comparing laparoscopic and standard hysterectomy have supported a cost analysis,[33,34] none has generated data for a full cost-effectiveness analysis of ALH with AH, and no economic analysis has previously been undertaken comparing VLH with VH. EVALUATE is, then, a major clinical and economic evaluation, and its results are likely to have a considerable impact on healthcare policy and practice.

The decision about whether these incremental costs per QALY are worth paying by the UK NHS depends in part on the cost of implementing the technology. Implementation costs would include relevant training for surgeons. These costs have not been included here as they are inconsequential on a per-patient basis but, in planning the service, they will contribute to the total budget impact.

A number of methodological issues relating to this analysis should be considered. The first is the fact that a health service (payer) perspective was used to estimate the costs of the alternative procedures. However, any differential impact of the procedures on time away from usual activities, including paid employment, might be reflected in differential productivity costs. The issue of whether such productivity costs should be included in cost-effectiveness analysis and, if so, how, is a source of controversy in the field.[63] In the UK, the National Institute for Clinical Excellence (NICE) has, in its technical guidance to those making submissions to its appraisal process, indicated its preference for a health service perspective.[57] However, guidance in the USA[58] has argued for a role for productivity costs, albeit estimated in part through the QALY.

The second methodological issue is how decisions should be taken regarding which of the interventions is the more cost-effective. Conventional statistical inference, where a new intervention is only considered cost-effective if it achieves a p-value of <0.05 on a null hypothesis of no difference in cost-effectiveness with respect to standard therapy, has a limited role in decision-making about resource allocation.[64] The first reason for this is that the sample size calculation for EVALUATE, as in most randomised clinical trials, was based on a clinical end-point rather than cost-effectiveness. Furthermore, given the typically large variability in costs and QALYs, such a trial would usually be under-powered with respect to cost-effectiveness. The second, and more fundamental, reason is that decision rules for cost-effectiveness focus on selecting the intervention which maximises health gain from limited resources, which should be based on expected (mean) costs and outcomes, and uncertainty in these values is important only in establishing where additional research might be concentrated. The third reason is that, although in practice decision-makers may be concerned with uncertainty (e.g. because of the political and resource costs of policy change, where these costs may not have been adequately reflected in the cost-effectiveness analysis), there is no reason to think that the threshold probability of making the wrong decision should be 5% as implied by conventional statistical inference. The cost-

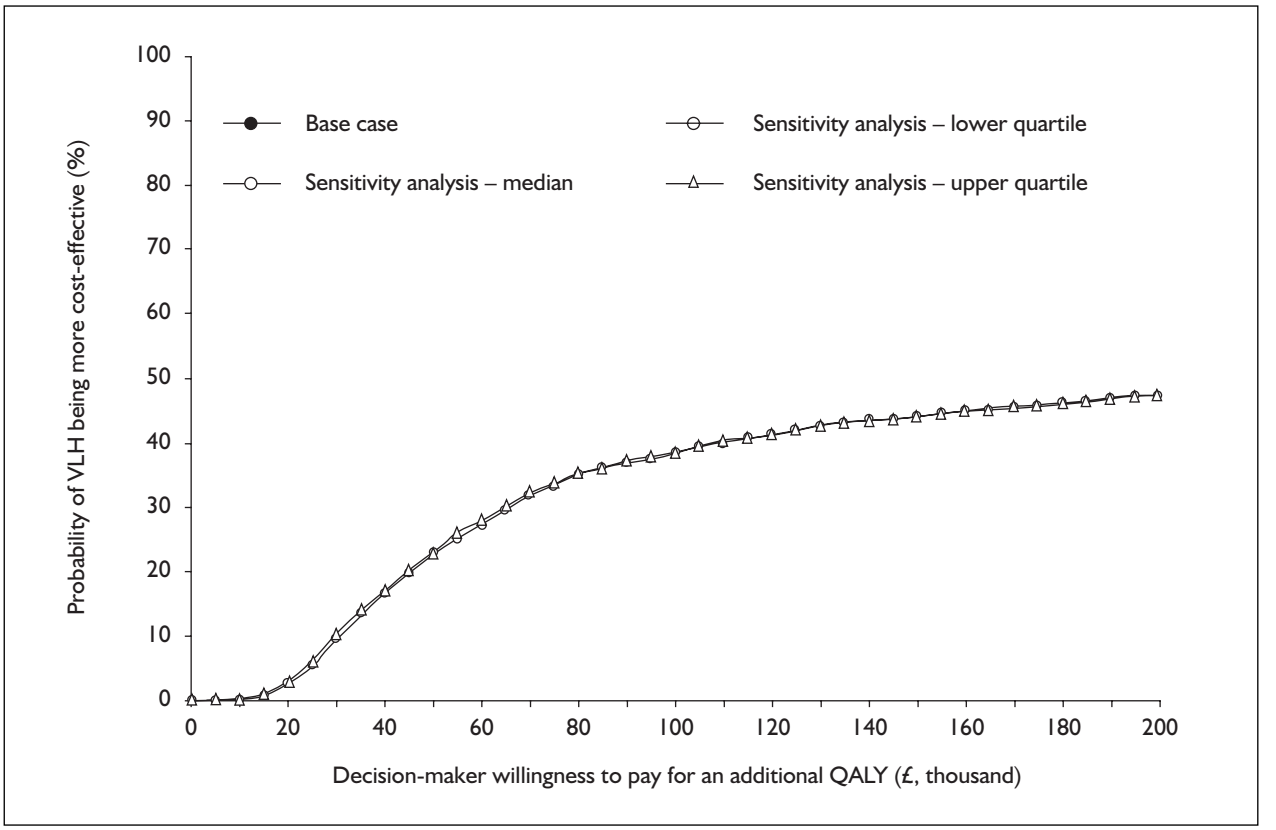

FIGURE 7 *Cost effectiveness acceptability curve, sensitivity analysis regarding the 'hotel' cost (VLH versus VH)*

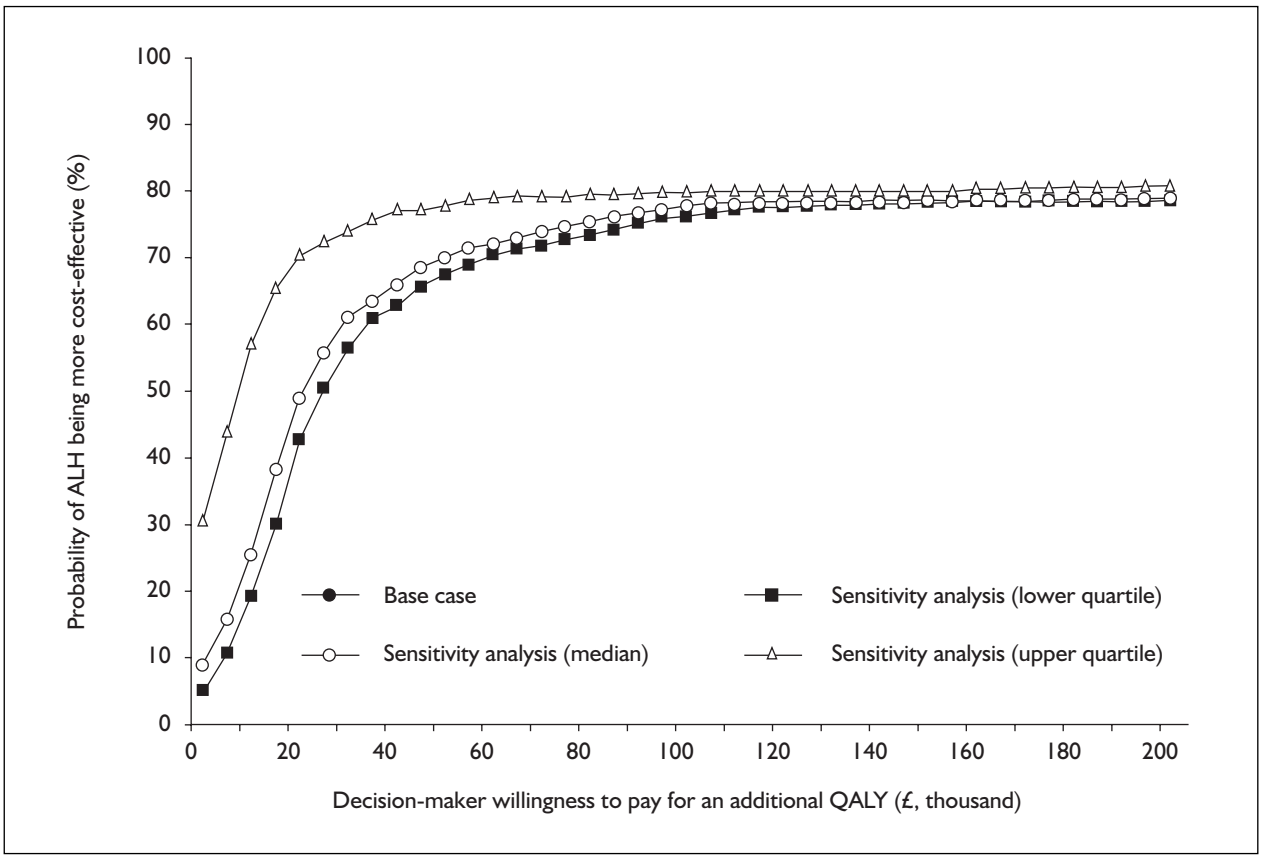

FIGURE 8 *Cost-effectiveness acceptability curve, sensitivity analysis regarding the 'hotel' cost (ALH versus AH)*

effectiveness acceptability curves presented here allow decision-makers to consider uncertainty in cost-effectiveness and to select their own threshold probabilities of making the wrong decision.

Summary

The economic evaluation detailed in this chapter provides some clear messages. There are important differences in resource use and cost between laparoscopic-assisted and standard procedures. Compared with both vaginal and abdominal procedures, laparoscopic procedures resulted in a higher mean time in theatre and more extensive use of disposable surgical consumables (*Table 134*). This had the effect of generating a higher mean theatre cost per patient in the laparoscopic arms. In the comparison with AH, however, there was a marked cost offset for laparoscopic-assisted hysterectomy in the form of a shorter mean stay in hospital (3.95 versus 5.11 days). None of the other cost components measured and costed in the trial showed any notable differences between laparoscopic and standard hysterectomy. To the extent that modest differences in mean cost per patient emerged in follow-up costs (e.g. complications, return to hospital, GP visits), this was due to a small number of women generating large costs, a fact confirmed by the similarity between the arms of the trial in median costs in these cost components. The net effect of these cost results was that laparoscopic-assisted hysterectomy had a higher overall mean cost per patient of £401 and £186 compared with VH and AH, respectively.

Cost-effectiveness analysis involves relating these differences in mean costs and outcomes. As regards the first comparison, the laparoscopic-assisted procedure had an ICER, compared with VH, of £267,333. Given the uncertainty around these mean estimates, the cost-effectiveness acceptability curve in *Figure 5* shows that the probability of laparoscopic-assisted hysterectomy being more cost-effective than VH if the health service is willing to pay £30,000 per additional QALY – a value consistent with some recent decisions by NICE[65] – is only 14.3%. Furthermore, these results are not particularly sensitive to alternative assumptions about the use of reusable or disposable equipment during the laparoscopic procedure. On this evidence, there seems to be little case to replace VH by the laparoscopic-assisted procedure.

The cost-effectiveness of ALH compared with AH is different because of the cost offset due to the shorter mean stay in hospital. In terms of differences in mean costs and QALYs, ALH is both more costly and more effective (in terms of QALYs), with an incremental cost per additional QALY of £26,571. This is within the range of the ICERs that NICE has shown itself willing to pay for other healthcare interventions.[63] Allowing for the uncertainty in these estimates of mean difference (*Figure 5*), the probability that LH is cost saving (that is, when decision-makers are not willing to pay anything for additional QALYs) is only 3%. If decision-makers are willing to pay as much as £30,000 per additional QALY, the probability of being more cost-effective than AH increases to 56%. This probability increases to 66% when decision-makers are willing to pay up to £50,000 per additional QALY. Whether ALH should be considered cost-effective based on these results alone is uncertain. This depends on what the NHS decision-makers are willing to pay for an additional QALY in this group and the error probability that they are willing to accept (indicated by the cost-effectiveness acceptability curves in *Figure 5*) for the decision.

The sensitivity analysis indicates that, if surgeons use largely reusable equipment in preference to relatively expensive disposables, then the ICER of ALH falls markedly to £10,571, which is more likely to be considered good value for money. However, this sensitivity analysis rests on the assumption that the use of a largely reusable policy would have no effect, on average, on the outcomes from the laparoscopic procedure. Given the results reported in Chapter 3 regarding the elevated risk of a major complication in women who were sutured on the uterine pedicle, this sensitivity analysis should be interpreted with some caution.

Chapter 7
Discussion

Background

Hysterectomy is a commonly performed major intra-abdominal surgical operation with about 100,000 performed annually in the UK.[66] Traditionally the uterus may be removed from the abdomen either through a classical incision in the abdominal wall or via a vaginal approach. Their selection is usually dependent on personal experience and training and seldom relies on formal evidence-based considerations. The recent introduction of a third method of hysterectomy using laparoscopic techniques has further complicated the assessment of the most suitable surgical approach to employ when removing the uterus. Despite the absence of any randomised controlled trial, most gynaecologists have clear personal preferences for the performance of each of the traditional surgical approaches. In the recently published VALUE study of hysterectomies performed during 1994–95,[3] 67% of women in the UK received an AH, 30% a VH and 3% an LH.

The EVALUATE trial was undertaken to provide objective evidence to assist gynaecological surgeons in their selection of the most appropriate method of hysterectomy and to provide data to permit patients to make an informed decision about their preferred type of hysterectomy. The EVALUATE trial is also by far the largest randomised controlled trial yet undertaken to assess the costs and effects of alternative forms of hysterectomy. Furthermore, no previous study has generated data for a full cost-effectiveness analysis of ALH with AH and none has previously been undertaken comparing VLH with VH.

Study design

The study was designed as two separate but parallel trials to allow each surgeon to maintain equipoise and maximise recruitment. For similar reasons, we excluded some conditions such as large fibroids that the majority of surgeons would prefer to undertake as AH, and major degrees of utero-vaginal prolapse that almost all would undertake as a VH. This pragmatic approach excluded many patients and several of the most important indications for hysterectomy. These decisions will reduce the generalisability; however, the design did maximise surgeon and patient recruitment and concentrated the study where the indications as to preferred method were least clear. The results showed that the baseline characteristics of patients within the abdominal and vaginal trials varied, indicating that clinicians had preferred clinical criteria for the abdominal or vaginal approach to hysterectomy. The preferred surgical approach varied for patients with certain baseline characteristics (parity, palpable endometriosis, endometriosis, pelvic pain, number of indications for hysterectomy, intended oopherectomy, uterine mobility and descent). This justified the design of this study and verified that the two trials contained different populations of patients. The different baseline and clinical characteristics indicated that the LH procedures may be more complex in one group than another, and therefore safety and efficacy of LH may be different within each subset; hence the two groups needed to be analysed separately. In addition comparisons across the trials are not valid.

The trials were unavoidably not blinded owing to the different incision sites. We do not know whether this resulted in bias or, if this occurred, in which direction.

Most of the patients included in the study were operated on in the UK, but 68 patients operated on by two gynaecologists in South Africa were also included in the study. No significant differences between these or any other centres were detected. A patient could be included in the study if she and her gynaecologist agreed she had an indication for hysterectomy, fitted the inclusion criteria and had none of the exclusion criteria. The inclusion of any particular patient in the trial was pragmatic, however, and patients were selected at the mutual convenience of the gynaecologist and themselves. Owing to the large numbers of women undergoing a hysterectomy, it was not considered feasible to expect non-research staff to keep a non-randomisation log; therefore, we have no details of the number, type and reasons for patients who fitted the inclusion and exclusion criteria but did not participate in the trial. This is a weakness of the study but we have no reason to suspect that there was any systematic recruitment bias.

Patients were stratified according to surgeon, size (BMI) and whether ovary removal was intended. In the design of the study, it was expected that both the skill and experience of the surgeon might influence the ultimate outcome in a manner independent of the method of hysterectomy employed. To avoid bias from the learning curve, each surgeon was required to have undertaken at least 25 of each type of hysterectomy before recruiting patients to the trial. Surgeons of all grades and experience participated in the trial, and we believe that the participants reflect the current standards of UK gynaecologists with an interest in surgery.

Almost all hysterectomies are performed for non-malignant indications and the causative pathologies are seldom life threatening. All the diseases, however, produce significant ill-health and impairment of the QoL of the women affected. In order to determine the relative effectiveness of each of the types of hysterectomy, we asked patients to complete a number of well-validated QoL instruments. Measurement of patient satisfaction was not carried out as it was decided (with the agreement of the Trial Steering Committee) that global satisfaction measurement would not have sufficient value.

Recruitment

The trial was planned to recruit 1800 patients over a 2-year period. In the event, 1380 patients were recruited over $3\frac{1}{2}$ years. There are several reasons for the below-expected recruitment. There was an initial overestimate of the popularity of the new LH procedure resulting in a substantially smaller pool available for recruitment. Many of the patients who in fact had LH were referred to specialists particularly for this specific procedure and were not available for randomisation. There was also a lack of equipoise for some of the participating surgeons in certain clinical situations, making randomisation difficult. Some units had restricted funding to buy the additional disposable equipment they felt necessary to complete the surgery. Financial constraints were present periodically throughout the study, particularly near the end of the financial year, and this preferentially impacted on ability to perform laparoscopic surgery. There were delays in some units obtaining Local Research Ethics Committee approval before the trial was required to obtain Multicentre Research Ethics Committee approval and the former were slow to give approval.

As a result of slow recruitment, the trial received an 18-month extension to recruitment. This increased the overall recruitment numbers but at a decreasing rate and so the Trial Steering Committee decided to close the trial at the end of this additional period rather than continuing to prolong the trial. This decision was ratified by the Data Monitoring and Ethics Committee.

Results of the abdominal hysterectomy trial (AH versus ALH)

No previous studies[14–25] were powered to determine adequately the complication rate and hence investigate the safety of the various procedures, whereas the EVALUATE trial is the first trial of sufficient size to enable clinically important differences in the respective complication rates to be detected.

This trial confirms some previous results but challenges the existing data on complication rates. It demonstrated that this population of general gynaecologists could use the laparoscopic approach to obtain benefits for the patients.

ALH took significantly longer to perform than AH, with a median time penalty of 34 minutes. The primary end-point for this trial was the rate of major complications. These, although infrequent, occurred significantly more frequently in association with ALH than AH cases. Of particular importance were severe haemorrhage cases (which occurred in 4.6% of the ALH group and 2.4% of the AH group) and ureteric injuries. All six of the damaged ureters occurred in the LH arms of the study and there were none in the AH or VH arms.

The major complication rates within the abdominal trial were 6.25% (AH), 11.1% (ALH) with a difference of –4.9 (95% CI –9.1 to –0.9%). However, the true difference between the complication rates could lie between 0.9 and 9.1%. If the true difference is at the lower end of this range, it may not be a clinically important difference. Neither the size and body mass of the patient nor the performance of oophorectomy had any short-term influence on the main study outcomes. It is important to note that the most common minor complication was infection; however, there was no evidence to suggest that this increased length of stay in hospital.

The disadvantages of the laparoscopic approach were to a great extent offset by improvements in patient-perceived events. Patients who had an ALH experienced less operative pain and left hospital earlier. They also felt better 6 weeks after surgery than those who had AH. This was demonstrated by an improved mean physical component of the SF-12 score and better BIS. Patients also had more frequent sexual intercourse at 6 weeks after ALH than AH. The implications of these QoL findings are that patients who undergo LH have less pain and feel better more rapidly after surgery. These effects are short term and are maximal during the first 6 weeks after surgery. By 4 months similar improvements were observed in the various QoL measures irrespective of the route chosen. It is reasonable to suggest, however, that if all other features are equal, most patients will select the procedure which is least painful and associated with the shortest recovery time. These QoL studies favour LH over AH.

The economic evaluation indicated that the longer operating times and more expensive equipment costs generated a higher mean theatre cost per patient in the laparoscopic arm. These increases in costs were to a large extent offset by a shorter mean hospital stay (3.25 versus 5.11 days). The net effect of these variations was that LH had a higher overall mean cost of £186 compared with AH. There was a small difference in the women's health-related QoL as determined by the EQ-5D questionnaire, leading to higher mean QALYs in the laparoscopic approach (0.007).

ALH is, therefore, both more costly and more effective (in terms of QALYs) with an incremental cost per additional QALY of £26,571. Allowing for the uncertainty in these estimates of mean difference, the probability that ALH is cost saving is only 3%. However, if decision-makers are willing to pay as much as £30,000 per additional QALY, the probability of being more cost-effective than AH increases to 56%. On the basis of this evidence, the question of whether ALH would be considered better value for money than AH is likely to be finely balanced. The likelihood that ALH would be considered more cost-effective than AH would increase if surgeons were to employ largely reusable equipment (ICER = £10,571), although this sensitivity analysis assumes that such a policy would leave mean outcomes unchanged from that seen in the trial. This may be a strong assumption, given the finding reported in Chapter 3, that the risk of major complications was higher in women whose uterine pedicle was sutured as part of ALH. A number of methodological issues are raised by this analysis, including the role of productivity costs, the extent to which the uncertainty in the results should influence decision-makers in allocating resources in hysterectomy and the sensitivity of the EQ-5D. As considered in Chapter 6, the conclusions of the analysis are likely to be robust to these methodological uncertainties.

Results of the vaginal hysterectomy trial (VH versus LH)

In the previously published studies in which the outcomes of VH and LH have been compared,[5,26–30] the only significant difference demonstrated was that LH took longer to perform. Our study confirmed that LH took almost twice as long as VH to perform. The only other significant difference between the groups was the probability of detecting unexpected pathology. Even when the indication for the hysterectomy was dysfunctional uterine bleeding, additional pathology was found in 5% of patients in the VH group and 15% in the LH group. We have no data as to whether these findings led to additional treatment or affected subsequent clinical outcomes. The surgeon must make a value judgement as to whether improved diagnostic accuracy justifies the considerable extra operating time required for an LH.

The vaginal trial was not planned to have sufficient power to detect a statistically significant difference in major complications between VH and LH. The major complication rates within the vaginal trial were 9.5% (VH) and 9.8% (ALH) with a difference of 0.3 (95% CI –5.8 to 5.2%). The difference between the complication rates for VH and VLH is very close to zero and the 95% CI is in the range ±5%, that is, the true difference may in fact be +5%, which may be a clinically important difference. There was an overall major complication rate of 9.6%. The rate for VH complications is somewhat higher in this study than is generally stated in the literature. We are not certain of the reasons for this. It may be that many studies in the literature quote data from individual surgeons in VH 'centres of excellence' that may achieve results not reproduced by more general gynaecological surgeons. This study does not include patients with major prolapse, which is the most common indication for VH for many gynaecologists, and this is certainly technically the easiest and hence the indication that may be associated with the lowest rate of major complications.

In the economic evaluation, VLH had both a higher mean cost per patient than VH and (modestly) higher mean QALYs. Together this generates a relatively high incremental cost-effectiveness ratio compared with VH (£267,333). Given the uncertainty around these mean estimates, the probability of VLH being more cost-effective than VH, if the health service is willing to pay up to £30,000 per additional QALY, is only 14.3%. Furthermore, the likely conclusion that VLH is not cost-effective relative to VH is not sensitive to alternative assumptions about the use of reusable or disposable equipment during LH.

Interpretation of findings

The major complications were defined in the protocol; although this was a complex issue, all major complications were potentially life threatening and therefore equally weighted in the analysis. The severity of such complications was problematic, as surgeons had reported a 'major haemorrhage' or an 'anaesthetic problem' with a wide range in definition: anaesthetic problems ranged from "anaphalactic reaction, 10 hours postoperatively due to morphine" to "postoperative patient drowsy, given Narcan". A major haemorrhage or haematoma was considered to be a major complication when a blood transfusion and surgical drainage, respectively, were required.

The importance of unintended laparotomy as a major complication was the subject of much debate within the Trial Steering Committee. It represented the second most common complication, affecting 45 patients. Thirteen of these had associated complications and were unequivocally correctly classified as having suffered major complications. The remaining 32, however, were those whom the surgeon converted from one method to another without other complication. These procedures could have been considered as being prudent surgery rather than classified as a complication. Excluding such cases would have substantially reduced the overall complication rates associated with LH. On the other hand, intraoperative conversions represent failure of the planned procedure. It was decided that as this was a failure to undertake and successfully complete the planned procedure, it should be regarded as a major complication.

There are a number of different forms of LH, ranging from a diagnostic laparoscopy with minimal laparoscopic surgical intervention through to total LH during which all steps of the operation are completed entirely with laparoscopic techniques. In this trial, most of the procedures were of the LAVH type in which only part of the procedure (down to but not including division of the uterine artery) was performed laparoscopically. There were insufficient numbers of other LH types to make valid comparisons between different laparoscopic approaches. The method used to secure the blood vessel pedicles did appear to influence the rate of complications, with the lowest risk apparently associated with securing vascular pedicles with diathermy or staples rather than sutures. The clinical details obtained of this aspect are unfortunately incomplete and, for example, we do not know what proportion of the vascular pedicles were sutured laparoscopically from above and what proportion vaginally from below. Without such additional data it is difficult to assess the importance of this observation. The nature of the laparoscopic equipment employed did not appear to influence clinical outcomes but it did influence the cost effectiveness of LH. The use of reusable rather than single-use trocars and other devices significantly improved the relative cost-effectiveness of LH.

One of the secondary end-points was degree of post-operative pain. This is notoriously difficult information to collect, it is subjective and it is affected by the use of opiates and many other analgesic agents. Pain is, however, a very important end-point for patients and although there are issues around its subjectivity and use of opiates, patients were randomised to operation and should be balanced across operations in terms of individual exaggerating/underestimating their own pain. Clearly the use of opiates in the immediate postoperative period must be considered when assessing a patient's description of pain. A patient's subjective report of pain 6 hours after surgery but 1 hour after a large dose of opiate may not actually reflect the pain-reducing effect of the procedure. We therefore attempted to correct for opiate use in our assessments of early postoperative pain.

A further end-point was blood loss, which is also information that is surprisingly difficult to collect accurately after laparoscopic surgery. Much blood loss in laparoscopic surgery cannot be measured accurately in the conventional manner as it is difficult to remove major quantities of blood from the abdominal cavity by suction and considerable quantities of irrigation fluid are introduced into the abdomen, diluting the removed fluids. Surgeons' subjective assessment of blood loss is unreliable. Changes in haemoglobin levels and

haematocrit values are reasonably objective if somewhat imprecise measures of operative blood loss in the absence of blood transfusion.

The outcomes seemed better in the group of procedures performed by trainees. This is probably because only the technically most simple procedures would be selected as training cases.

In terms of external validity, a strength of the EVALUATE study was that so many centres and surgeons participated. Concerning the surgeon effect, some of the 43 surgeons recruited patients into only one of the trials; also, there was a wide range in the number of patients recruited by surgeons (1–115). Therefore, it is probable that the statistical test lacked sufficient power to detect a surgeon effect if one existed. Also, the likelihood ratio test for such random effects is not strictly correct, owing to the variance parameter being tested at a boundary point of the permissible parameter space, zero. Hence the test results should only be used as a rough guide for decision-making. It is also possible that by insisting that recruiting surgeons had previously undertaken 25 procedures the trial design itself may have removed enough of the variation between surgeons for there not to be a surgeon effect. The analysis did not find a surgeon effect but it is difficult to conclude that there was not a difference between surgeons in the trial. The variance estimates are small, suggesting that there may not be much variation to detect; however, the larger SEs of these estimates indicate that their precision may be questionable.

We are not able to explain adequately the intriguing observation that in the vaginal trial non-smokers are three times more likely to suffer complications than smokers, and this of course may be a chance finding. There appeared to be some evidence of interaction between type of operation and smoking history, with smokers being less likely to have major complications with VLH and non-smokers less likely to have complications with VH.

Overall, the compliance with QoL questionnaires was excellent, but only 60% of patients returned questionnaires at all three time points. These results should therefore be confirmed by others.

It is difficult to gauge the implication of the printing error in the SF-12 questionnaire. It applied to all arms of the trial, however. The use of the SF-12 in further research for women having hysterectomy would be helpful to clarify our results.

The BIS was originally developed for use in cancer patients. There is a lack of validated body image tools for use in non-malignant conditions. This dataset was used to evaluate the psychometric properties of the BIS in women with benign gynaecological conditions.[56] The validation demonstrated that the BIS had acceptable internal reliability for the whole sample and for each subsample. Due to the often significant length of time between randomisation and surgery, patients completed questionnaires both at randomisation and immediately preoperatively. This allowed test/retesting reliability. Clinical validity of the BIS was assessed using discriminant validity, sensitivity to change and response prevalence. The BIS was shown to be able to discriminate between groups expected to have differences and to be responsive to changes in body image over time, irrespective of type of operation. One question referred to a patient's satisfaction with their scar, which was not applicable before surgery and was difficult for patients after VH. A 'not applicable' category would be recommended for future use of this scale in non-cancer patients. Despite this difficulty, women reported little dissatisfaction with their scars. Many women, however, felt less physically attractive as a result of their condition or treatment and this was particularly marked in women undergoing AH. Although not every question in the questionnaires generated high response rates, the total volume of data generated in these areas was substantial and informative.

A principal result of this study is that ALH is associated with a higher risk of major complications than AH. The economic analysis includes the health service costs of these complications within its calculations but does not include any additional costs associated with subsequent litigation. The report does not quantify patient costs, such as out-of-pocket costs (e.g. travel) because the data quality was poor (i.e. lots of missing data). However, productivity costs (associated with time away from usual activities) were analysed and reported.

Attention to the minutiae of surgical detail may influence the risk of such complications and it is possible that the method of securing the vascular pedicles could be important in determining the risk of subsequent complications. Gynaecologists undertaking laparoscopic hysterectomy should be fully appraised of the increased potential for harm associated with this approach and should develop sound techniques to minimise such risks.

Summary of findings

Abdominal hysterectomy trial (LH versus AH)

- LH is associated with a higher rate of major complications than AH.
- LH takes longer to perform than AH.
- LH is associated with less operative pain than AH.
- LH is associated with a shorter hospital stay than AH.
- LH is associated with a better QoL 6 weeks after surgery than AH.
- LH is associated with a better BIS at 6 weeks and 4 months after surgery than AH.
- LH is associated with a more rapid return of satisfactory sexual activity than AH.
- LH has higher mean costs than AH.
- LH is slightly more effective (in terms of mean QALYs) than AH.
- LH has an incremental cost per additional QALY of £26,571 relative to AH.
- If the NHS is willing to pay £30,000 for additional QALYs, the probability that LH is cost-effective is 56%.

Vaginal hysterectomy trial (LH versus VH)

Results are inconclusive as trial was under-powered, but may suggest:

- LH takes longer to perform than VH.
- LH is associated with the detection of more unsuspected pathology than VH.
- LH has higher mean costs than VH.
- LH is slightly more effective (in terms of mean QALYs) than VH.
- LH has an incremental cost per additional QALY of £267,333 relative to VH.
- The probability that LH is cost-effective was <50% for a large range of willingness to pay values for an additional QALY.

Recommendations for future research

1. **QoL** following hysterectomy: Application and relevance of QoL measures and long-term follow-up. This study contains a large, well-defined cohort of women with good preoperative, intraoperative and short-term postoperative data. The long-term effects of hysterectomy on such a closely defined group would be of considerable value to the understanding of the effects of this common and economically important procedure.
2. **Patient preferences**: Research is needed to determine patients' views of balance between risks and benefits of the various forms of hysterectomy.
3. **Reducing complication rates**: As the major complication rate after any form of hysterectomy is of the order of 1 in 20, further work is needed to determine ways of reducing such complications. In laparoscopic surgery there have been many refinements in both instrumentation and technique and it would be useful to assess the impact of these.
4. **Improving gynaecological surgical training**: This study raises general issues about the adequacy of gynaecological surgical training. Studies into the development of virtual reality, animals and other laboratory-based training models both to complement conventional apprenticeship training and to provide validated systems to monitor surgical competence are urgently required.
5. **Surgeon effect in surgery trials**: Investigation of the effect of surgeon on patient outcome.
6. **Care pathways for hysterectomy**: Given the variation in types of hysterectomies and uncertainties in pathways.
7. **Additional pathology identification in laparoscopic hysterectomy**: Identification of reasons for this.
8. **Meta-analysis/further trials**: Comparing VH and LH.

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In addition, we thankfully acknowledge the statistical contribution at the grant application stage of David Braunholtz.

This trial would not have been possible without the valued contributions of the women who were willing to give their time and share their experiences to extend our knowledge in this area.

Trial Steering Committee

See Appendix 2.

Data Monitoring and Ethics Committee

See Appendix 3.

Participating clinicians

The following were members of the EVALUATE Study Group and contributed patients to the trial: Mr Jason Abbott, South Cleveland Hospital, Middlesborough; Mr Al'samarrai, Princess Alexandra Hospital, Essex; Mr Bob Balfour, Princess of Wales Hospital, Mid-Glamorgan; Mr Colin Bone, Queen Elizabeth Hospital, Norfolk; Mr R Callender, Wordsley Hospital, West Midlands; Mr James Campbell, St James's University Hospital, Leeds; Mr C Chandler, Billinge Hospital, Wigan; Mr Rick Clayton, Bradford Royal Infirmary; Dr K Cooper, Aberdeen Royal Infirmary; Dr Daponte, Johannesburg Hospital, South Africa; Mr John Day, St Helier Hospital, Jersey; Dr P De Jong, University of Cape Town, South Africa; Mr Ellis Downes, Leeds General Infirmary; Mr Sean Duffy, St James's University Hospital, Leeds; Dr Peter Fisher, Aberdeen Royal Infirmary; Mr J Frappell, Derriford Hospital, Plymouth; Mr Mike Gannon, Leeds General Infirmary; Mr Ray Garry, St James's University Hospital, Leeds/South Cleveland Hospital, Middlesbrough; Mr Godfrey, Sunderland General Hospital; Mr J K Gupta, University of Birmingham; Mr Jed Hawe, South Cleveland Hospital; Mr Rob Hawthorn, Southern General Hospital, Glasgow; Mr Neil Hebblethwaite, Friarage Hospital, Northallerton; Mr Chris Kremer, St James's University Hospital, Leeds; Mr Geoff Lane, St James's University Hospital, Leeds; Mr Gavin MacNab, Sunderland General Hospital; Mr Sandeep Mane, University Hospital, Cardiff; Mr Okolo, North Middlesex Hospital; Mr R Penketh, University Hospital, Cardiff; Mr Graham Phillips, South Cleveland Hospital; Mr K Phillips, Castle Hill Hospital, Cottingham; Mr B Ramsay, Peterborough District Hospital; Mr Randle, Castle Hill Hospital, Cottingham; Mr Mark Roberts, Sunderland District General Hospital; Mr Naren Samtaney, Airedale Hospital, Keighley; Mr David Sanderson, Colchester General Hospital; Mr E Shaxted, Northampton General Hospital; Mr RW Stones, Princess Anne Hospital, Southampton; Mr Chris Sutton, Royal Surrey County Hospital; Mr CC Welch, Basildon Hospital, Essex; Mr Mark Whittaker, St James's University Hospital, Leeds; Mr M S Zaklama, Birch Hill Hospital, Rochdale.

Clinical Trials Research Unit staff contributing to the EVALUATE trial

Julia Brown, Head of Unit; Will Crocombe, Head of Information Systems; Dawood Dassu, Senior Medical Statistician; Jayne Fountain, Medical Statistician; Alice Hamar, Senior Secretary; Kim Hawkins, Senior Medical Statistician; Louise Hope, Trial Coordinator; Julie Kitcheman, Assistant Trial Coordinator; Ranjit Lall, Medical Statistician; Su Mason, Principal Research Fellow; Vicky Napp, Head of Trial Coordination; Sally Stubbs, Trial Coordinator.

Contributions of authors

Ray Garry (Professor of Clinical Gynaecology) conceived and designed the study, contributed to the acquisition of data, the conduct of the trial, the analysis, the interpretation of the data and the drafting of the report. Jayne Fountain (Medical Statistician) contributed to the analysis of the data and the drafting of the report. Julia Brown (Head of Clinical Trials Research Unit) contributed to the design of the study, the analysis of the data and the drafting of the report. Andrea Manca (Research Fellow) contributed to

the analysis of the data and the drafting of the report. Su Mason (Principal Research Fellow) contributed to the trial management, the conduct of the trial, analysis of the data and the drafting of the report. Mark Sculpher (Professor of Health Economics) contributed to the design of the study, the analysis, the interpretation of the data and the drafting of the report. Vicky Napp (Head of Trial Co-ordination) contributed to the trial management and the revising of the report. Stephen Bridgman (Director of Public Health) contributed to the design of the study, the conduct of the trial and the revising of the report. Janine Gray (Deputy Director of Clinical Trials Unit, University of Newcastle) contributed to the analysis of the data. Richard Lilford (Professor of Health Services Research) contributed to the design of the study, the conduct of the trial and the revising of the report.

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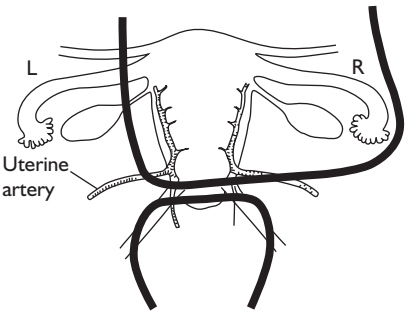
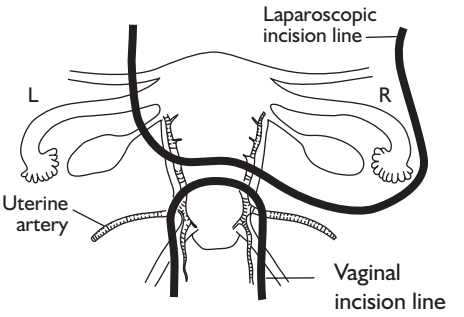
Appendix 1

Diagrams of types of laparoscopic hysterectomy

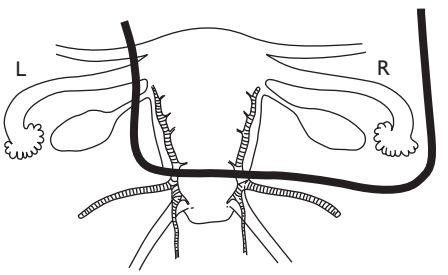
Laparoscopic hysterectomy (LH).



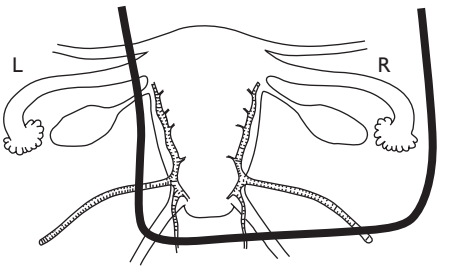
Laparoscopic assisted vaginal hysterectomy (LAVH).



Laparoscopic supracarvical hysterectomy (LSH).



Total laparoscopic hysterectomy (TLH).



Appendix 2

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Over the course of the trial, the following attended the Trial Steering Committee:

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Appendix 3

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Appendix 4

Patient information sheets

Patient information sheet for trial arm abdominal versus laparoscopic hysterectomy

Trial of laparoscopic, vaginal and abdominal hysterectomy

You and your gynaecologist have been talking about your need to have an abdominal hysterectomy (removal of the womb through a cut in the abdomen).

A new surgical method has been developed called a laparoscopic-assisted hysterectomy (or 'keyhole' hysterectomy). This uses fine, long instruments and a very small tubular camera (a laparoscope) inserted through small cuts in the abdomen to do the operation.

We would like to compare this new surgical method with the usual abdominal hysterectomy. We do not know which method will be best. This is why we are doing what is called a 'controlled clinical trial' and we would like to ask you if you would be willing to take part.

Information about the operations

In the laparoscopic-assisted hysterectomy, small cuts (about three) are made in the abdomen. Through these, the laparoscope (small camera) and fine, long instruments are inserted to carry out the operation. The surgeon uses the laparoscope to watch on TV screens exactly what he/she is doing inside the abdomen during the operation. Being able to see your womb clearly makes it easier for the gynaecologist to do the operation. Since the cuts needed are much smaller than with the abdominal hysterectomy, recovery may be quicker and less painful. You would also have less scarring. This approach may be associated with complications due to the insertion of sharp instruments into the abdominal cavity since the bowel or blood vessels can be damaged in this way, but great care will be taken to avoid this. We need evidence to show whether this method results in fewer complications.

There are complications which can sometimes happen in any surgical operation. These include anaesthetic problems, bleeding, wound infection and, very rarely, pulmonary embolism (a blood clot on the lungs). With any type of hysterectomy there is always a possible complication of damage to your bladder, ureters (tubes to the bladder) or to the bowel.

What will the trial involve for me?

If you agree to take part in this trial you will either have a traditional abdominal hysterectomy or the newer, laparoscopic-assisted hysterectomy. This will be chosen randomly as if 'by the toss of a coin'. It is a fair way of deciding between the operations in the trial, and means that they can be compared in an unbiased way.

As part of this trial we will be monitoring your progress very closely. You will be asked to fill in some questionnaires before your operation. In addition, we would like you to fill in a daily diary in hospital and for 6 weeks after you go home. More questionnaires for you to complete will be posted to you at 6 weeks, 4 months and 12 months after your operation.

Your decision

If you agree to take part in this trial, you may at any time, without giving any explanation, withdraw from the trial. Should this happen, you will continue to have the best possible treatment.

We do not know whether laparoscopic-assisted hysterectomy is really better than the traditional abdominal hysterectomy. This is why we are asking you to think about joining this trial. This trial is being carried out in a number of centres across the United Kingdom. All of the gynaecologists taking part in this trial are experienced in performing hysterectomies both laparoscopically and through the normal abdominal procedure.

If you decide not to take part in this trial, you do not have to give a reason and please be assured that your medical care will not be affected in any way.

Do ask your gynaecologist if you have any questions or would like to know more about the trial.

Patient information sheet for trial arm vaginal versus laparoscopic hysterectomy

Trial of laparoscopic, vaginal and abdominal hysterectomy

You and your gynaecologist have been talking about your need to have a vaginal hysterectomy (removal of the womb through a cut in the top of the vagina).

A new surgical method has been developed called a laparoscopic-assisted hysterectomy (or 'keyhole' hysterectomy). This uses fine, long instruments and a very small tubular camera (a laparoscope) inserted through small cuts in the abdomen to do the operation.

We would like to compare this new surgical method with the usual vaginal hysterectomy. We do not know which method will be best. This is why we are doing what is called a 'controlled clinical trial' and we would like to ask you if you would be willing to take part.

Information about the operations

In the laparoscopic-assisted vaginal hysterectomy, small cuts (about three) are made in the abdomen. Through these, the laparoscope (small camera) and fine, long instruments are inserted to carry out the operation. The surgeon uses the laparoscope to watch on TV screens exactly what he/she is doing inside the abdomen during the operation. Being able to see your womb clearly makes it easier for the gynaecologist to do the operation. This approach may be associated with complications due to the insertion of sharp instruments into the abdominal cavity. The bowel or blood vessels can be damaged in this way but great care will be taken to avoid this. We need evidence to show whether this method results in fewer complications.

There are complications which can sometimes happen in any surgical operation. These include anaesthetic problems, bleeding, wound infection and, very rarely, pulmonary embolism (a blood clot on the lungs). With any type of hysterectomy there is always a possible complication of damage to your bladder, ureters (tubes to the bladder) or to the bowel.

What will the trial involve for me?

If you agree to take part in this trial you will either have a traditional vaginal hysterectomy or the newer, laparoscopic-assisted vaginal hysterectomy. This will be chosen randomly as if 'by the toss of a coin'. It is a fair way of deciding between the operations in the trial, and means that they can be compared in an unbiased way.

As part of this trial we will be monitoring your progress very closely. You will be asked to fill in some questionnaires before your operation. In addition we would like you to fill in a daily diary in hospital and for 6 weeks after you go home. More questionnaires for you to complete will be posted to you at 6 weeks, 4 months and 12 months after your operation.

Your decision

If you agree to take part in this trial, you may at any time, without giving any explanation, withdraw from the trial. Should this happen, you will continue to have the best possible treatment.

We do not know whether laparoscopic-assisted vaginal hysterectomy is really better than the traditional vaginal hysterectomy. This is why we are asking you to think about joining this trial. This trial is being carried out in a number of centres across the United Kingdom. All of the gynaecologists taking part in this trial are experienced in performing hysterectomies both laparoscopically and through the normal vaginal procedure.

If you decide not to take part in this trial, you do not have to give a reason and please be assured that your medical care will not be affected in any way.

Do ask your gynaecologist if you have any questions or would like to know more about the trial.

Appendix 5

Standard postoperative instructions regarding resuming normal activities

This sheet gives you some advice about what you can do after your operation. The main thing to keep in mind is that everyone is different and reacts differently after a hysterectomy. There are no hard and fast rules about when you should be doing particular activities – your body will tell you if you have overdone things!

This advice applies to any type of hysterectomy – we want to see what YOU feel comfortable doing after your operation.

General advice

Eat a well-balanced diet with plenty of fibre and drink plenty of fluids – this will help to stop you becoming constipated.

Exercise and rest

Allow yourself time to rest each day. You will find the time you need to rest will slowly become shorter. Make sure you spend some time each day exercising – the best way is to go for a walk, just a short distance at first but slowly increasing to as much as you feel happy with. It is quite safe to go up and down stairs.

Housework

Light housework is fine from the time you get home, such as making a cup of tea. Try to avoid lifting heavy weights for at least 6 weeks, but build up to things like dusting and ironing.

What about my wound?

You may have one cut on your abdomen or three cuts or none at all. The area around the cut(s) will probably feel a little strange and numb. Bathe or shower regularly and dry the area thoroughly afterwards. If the wound becomes swollen or starts to leak fluid then see your GP for advice. Whatever operation you have had, you will have some stitches in the top of the vagina. This may cause a red or brown discharge which will slowly get less over a few weeks. If this loss becomes heavy or smelly you may need some treatment from your GP.

When can I drive?

You can start again when you can perform an emergency stop, i.e. when you can stamp on the brake pedal without causing discomfort. It may be best to check with your insurance company as some companies have set time limits before you are insured to drive again.

What about sex?

Allow time for the stitches in the vagina to heal – perhaps 3–4 weeks. Most women find that sexual response is not much different after a hysterectomy. Your partner should be gentle at first and you may need to use some lubrication such as KY Jelly because the vagina may not produce enough natural lubrication if you are tense or anxious about starting intercourse again.

Returning to work

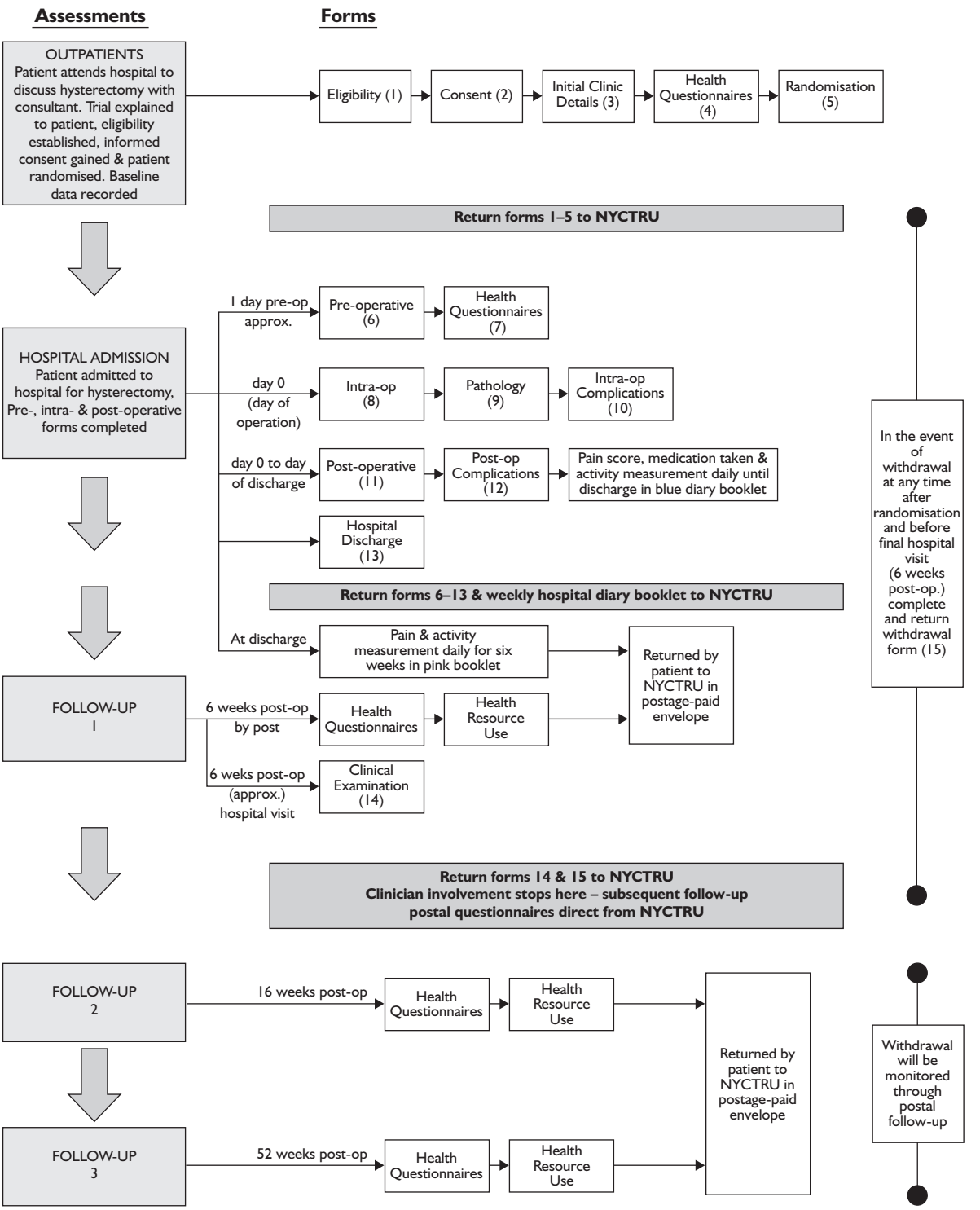
This will depend on your job and the degree of physical exertion involved. You will have an idea yourself about when you feel able to cope but this will probably be at least 4 weeks after the operation.

Follow-up visits

You will be seen in the outpatients' clinic 6 weeks after your operation. Please remember to fill in the booklet that we send home with you. We will also send you questionnaires through the post, at 6 weeks, 4 months and 12 months after your operation. We would be grateful if you could fill these in and return them.

Appendix 6

EVALUATE data collection structure



Appendix 7

Patient hospital diary

*

[Questions repeated for daily data collection are not shown here to save space, but are indicated where appropriate]

*

EVALUATE Hysterectomy Trial

Patient Diary Booklet

for use in hospital

Patient Initials .....

Date of Birth .....

Trial Number .....

Instructions for the use of this booklet

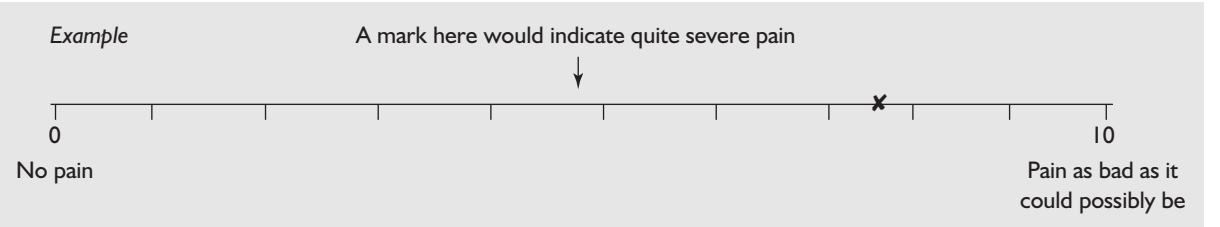
Thank you for agreeing to take part in this trial.

This blue booklet should be filled in whilst you are **in hospital**. It contains the following:

A double page each day for keeping a daily record of any pain you may have

There are two scales numbered 0–10 which should be used to record any pain you may have. Please complete one scale in the morning (approx. 9.00 am) and one in the evening (approx. 9.00 pm). Each scale is a measure of the intensity of your pain (i.e. how bad it is) at the time when you fill it in. You simply have to mark along the line the position which represents the level of any pain at that moment.

0 = No pain, 10 = pain as bad as it could possibly be.



This means that the further you mark along the line, the worse your pain is at that moment. Please note that we only want you to score your pain **related to your operation**, although we realise that you may well have other troublesome pains. If you are uncertain which pain this refers to please discuss it further with your doctor.

Questions related to your activities

We would also like you to answer a few questions which are related to activities that you *might* do during a typical day. These questions should be answered at the end of the day at the same time as filling in the pain scale (approx. 9.00 pm).

Medication taken

If you have taken any medication (e.g. pain killers etc.) for your pain, which is related to your operation, then we would like you list these medicines. Please ask the nurse to help you complete this.

Discharge from hospital

Before you leave hospital, we would like you to fill in the pain scale for that morning, and any medications you might have taken. You will be issued with a new **pink** diary booklet to take home, and we would like you to carry on filling in this from the evening of the day you were discharged.

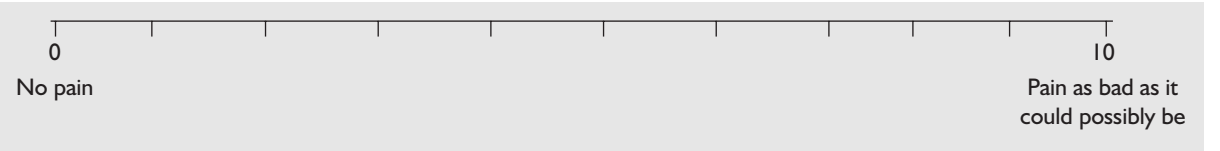
The information we are gaining from this trial will help us to improve the care of patients in the future and we are very grateful for your help and cooperation.

	Day	Month	Year
Day 0 (**day of operation**)			

EVENING – 9 pm

Pain

Please complete this pain score in the **evening**. Please mark on the line the position that best reflects your pain level at the moment.



Medication taken

Please list below details of any medication taken for pain relief **before 9pm today**.

Please ask a nurse to help you fill in this section.

Drug	Tick box if PCAS	Dose	Time (approx.)

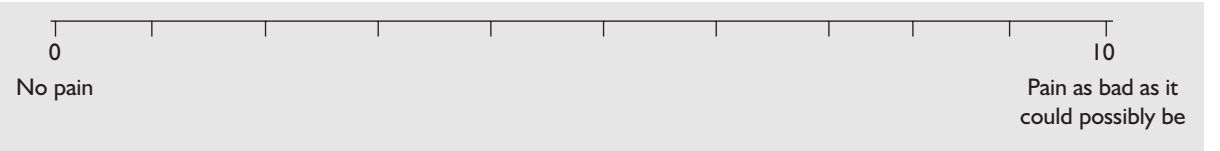
Are you going home today? (please tick) ☐

	Day	Month	Year
Day 1 (**day after operation**)	☐☐	☐☐	☐☐

MORNING – 9 am

Pain

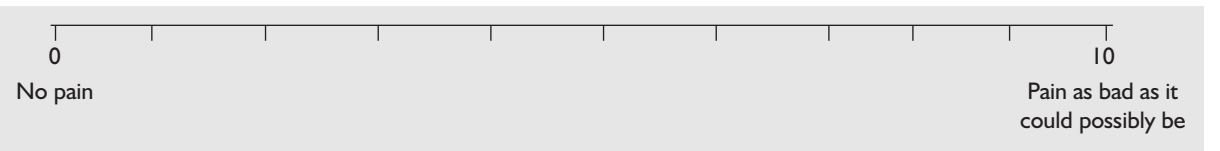
Please complete this pain score in the **morning**. Please mark on the line the position that best reflects your pain level at the moment.



EVENING – 9 pm

Pain

Please complete this pain score in the **evening**. Please mark on the line the position that best reflects your pain level at the moment.



Activities

Please complete this section in the **evening**. The following questions are about activities you might have done **today**. Would your health have limited you in these activities **today**? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Walking to the toilet	☐	☐	☐
Dressing yourself	☐	☐	☐
Carrying a light shopping bag	☐	☐	☐
Climbing a flight of stairs	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

Medication taken

Please list below details of any medication taken for pain relief to cover the period from **9pm yesterday to 9pm today**.

Please ask a nurse to help you fill in this section.

Drug	Tick box if PCAS	Dose	Time (approx.)

Are you going home today? (please tick) ☐

[The information requested for 'Day 1' was repeated so that the hospital diary contained data for 7 days. At the end of the booklet was the following paragraph:]

If you are to remain in hospital after today, please ask the nurse for a further blue diary. Thank you for your help in completing this booklet.

Appendix 8

Patient home diary

*

[Questions repeated for daily data collection are not shown here to save space, but are indicated where appropriate]

*

EVALUATE Hysterectomy Trial

Patient Diary Booklet

for use at home

Patient Initials .....

Date of Birth .....

Trial Number .....

Instructions for the use of this booklet

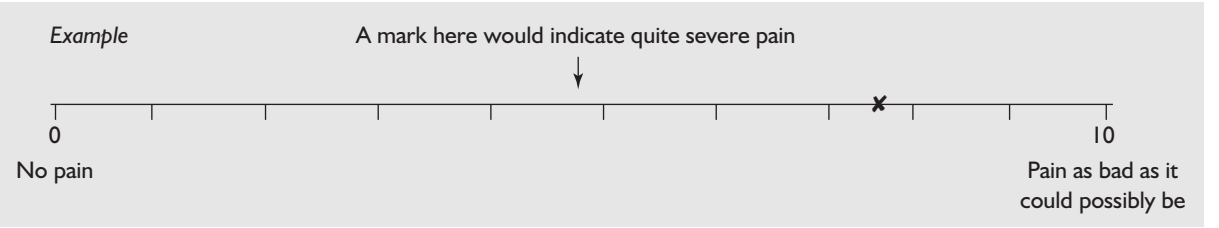
Thank you again for agreeing to enter this trial.

This **pink** booklet should be filled in after you have been discharged home from the hospital, and then everyday for 6 weeks. It contains the following:

A page each day for keeping a daily record of any pain you may have

There are two scales numbered 0–10 which should be used to record your pain. Please complete one scale in the morning (approx. 9.00 am) and one in the evening (approx. 9.00 pm), as you did when you were in hospital. Each scale is a measure of the intensity of your pain (i.e. how bad it is) at the time when you fill it in. As before, you simply have to mark along the line the position which represents the level of any pain at that moment.

0 = No pain, 10 = pain as bad as it could possibly be.



This means that the further you mark along the line, the worse your pain is at that moment. Please note that we only want you to score your pain **related to your operation**, although we realise that you may well have other troublesome pains.

Questions related to your activities

As before, we would also like you to answer a few questions which are related to activities that you *might* do during a typical day. These questions should be answered at the end of the day and can be answered at the same time as filling in the pain scale (approx. 9.00 pm).

Patient satisfaction question

The first page of this booklet contains a question asking you to comment on your stay in hospital. Any information given here will be treated in the strictest confidence.

What do I do when the diary is complete?

When you have completely filled in the diary for the full 6 weeks, please return it in the pre-paid envelope provided to:

Yorkshire Clinical Trials and Research Unit
Arthington House
Hospital Lane
Leeds
LS16 6QB

Again, we would like to thank you for taking part in this trial.

CONFIDENTIAL

Patient Satisfaction Question

Did you feel that the length of your stay in hospital during your hysterectomy was:

☐ Too short

☐ About right

☐ Too long

If you were unhappy with your length of stay or have any other comments you would like to give, please do so in the space below:

.....

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.....

.....

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.....

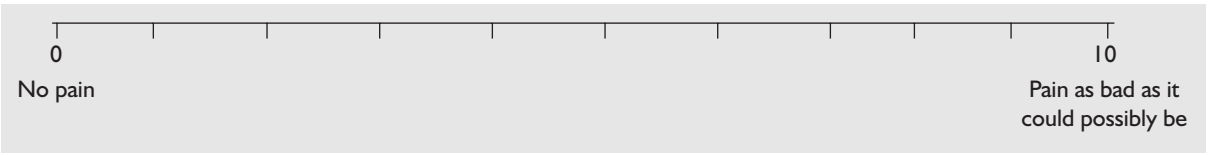
.....

Day 1 Day ☐☐ Month ☐☐ Year ☐☐

MORNING – 9 am

Pain

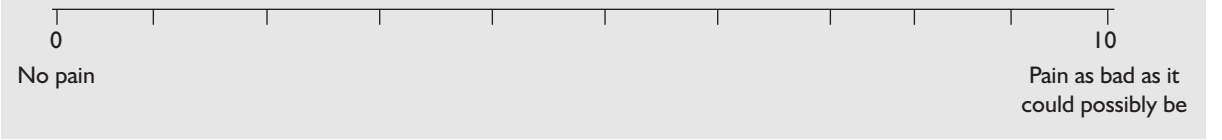
Please complete this pain score in the **morning**. Please mark on the line the position that best reflects your pain level at the moment.



EVENING – 9 pm

Pain

Please complete this pain score in the **evening**. Please mark on the line the position that best reflects your pain level at the moment.



Activities

Please complete this section in the **evening**. The following questions are about activities you might have done **today**. Has your health limited you in these activities **today**? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Walking to the toilet	☐	☐	☐
Dressing yourself	☐	☐	☐
Carrying a light shopping bag	☐	☐	☐
Climbing a flight of stairs	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

[The information requested for 'Day 1' was repeated so that the home diary contained data for 42 days. At the end of the booklet was the following paragraph:]

Thank you very much for completing this booklet.

By now you should have received through the post your 6 week follow-up questionnaires. Please complete these and return them and this diary booklet using the pre-paid envelope provided to the address below.

If you have not received your follow-up questionnaires by the time you have finished this diary booklet, please telephone the YCTRU on Leeds (0113) 292 4449.

Yorkshire Clinical Trials & Research Unit
Arthington House
Hospital Lane
Leeds
LS16 6QB

[This is the old title, address and telephone number of the Clinical Trials Research Unit, University of Leeds]

Appendix 9

Quality of life charts

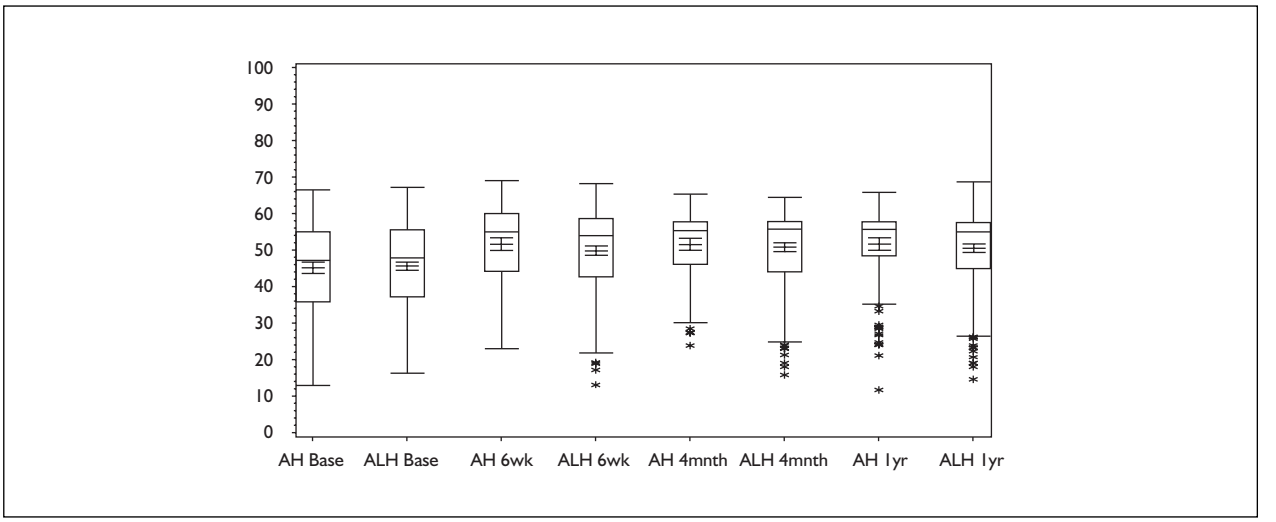


FIGURE 9 *SF-12 mental component summary score: abdominal trial*

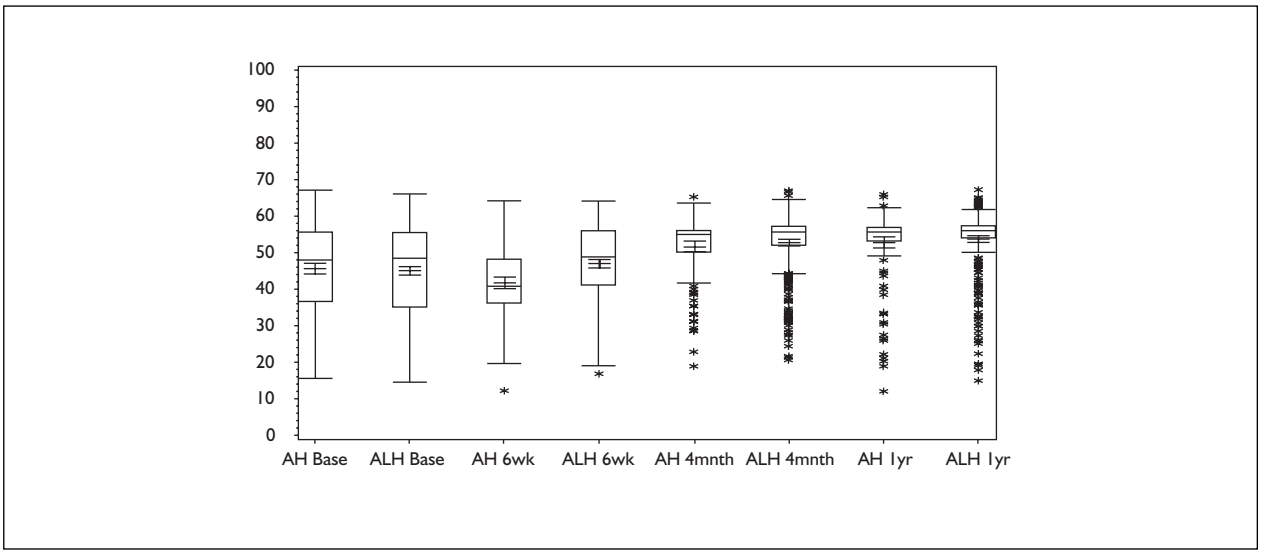


FIGURE 10 *SF-12 physical component summary score: abdominal trial*

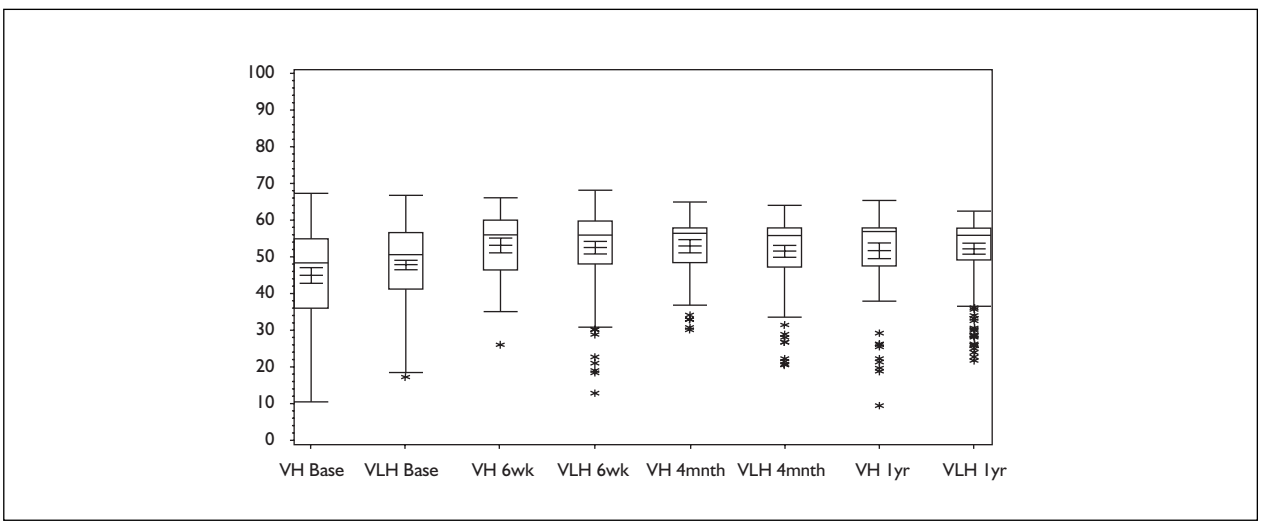


FIGURE 11 *SF-12 mental component summary score: vaginal trial*

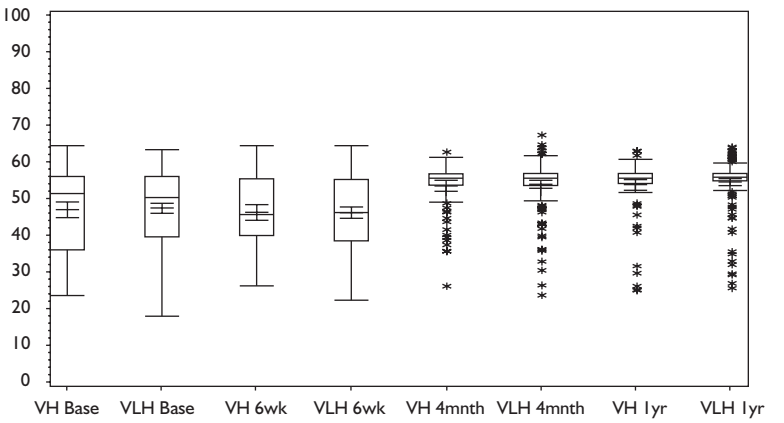


FIGURE 12 *SF-12 physical component summary score: vaginal trial*

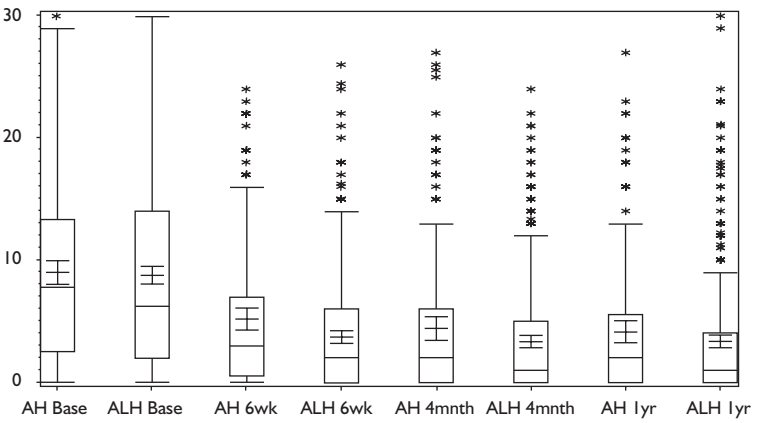


FIGURE 13 *BIS score: abdominal trial*

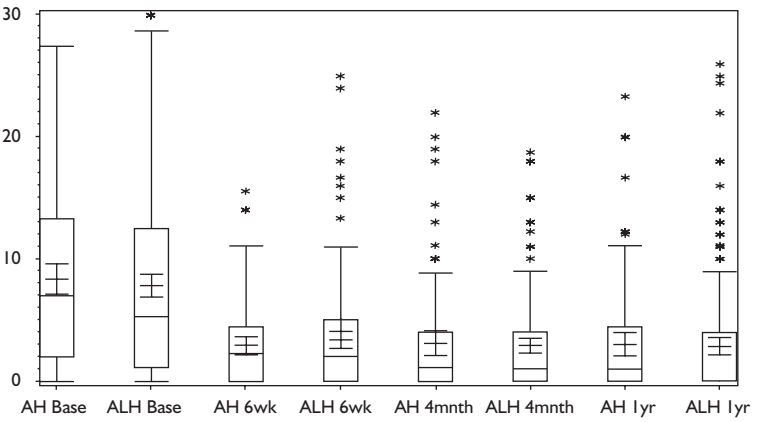


FIGURE 14 *BIS score: vaginal trial*

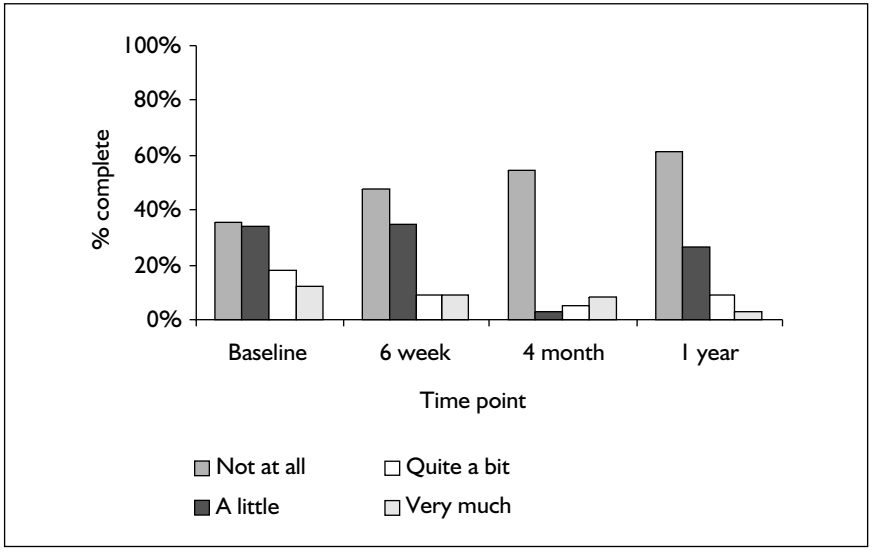


FIGURE 15 *Have you been feeling self-conscious about your appearance? (AH)*

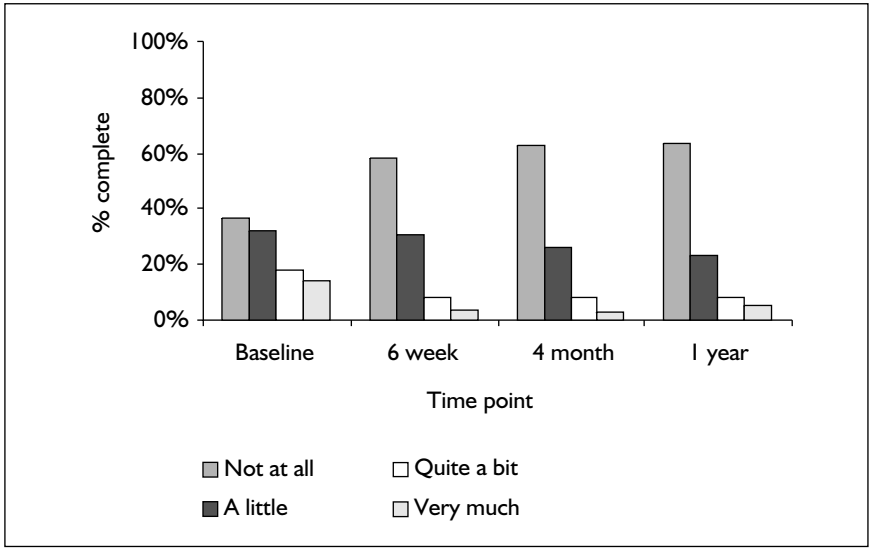


FIGURE 16 *Have you been feeling self-conscious about your appearance? (ALH)*

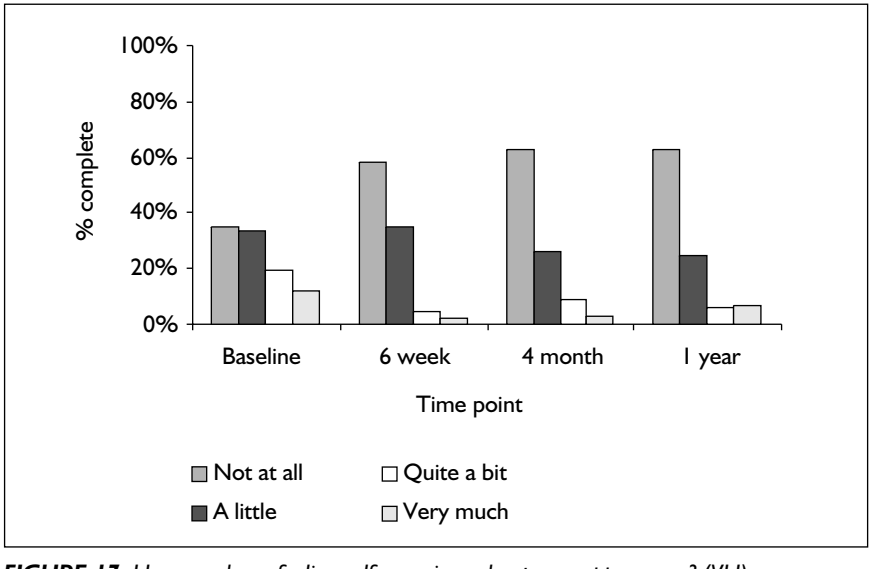


FIGURE 17 *Have you been feeling self-conscious about your appearance? (VH)*

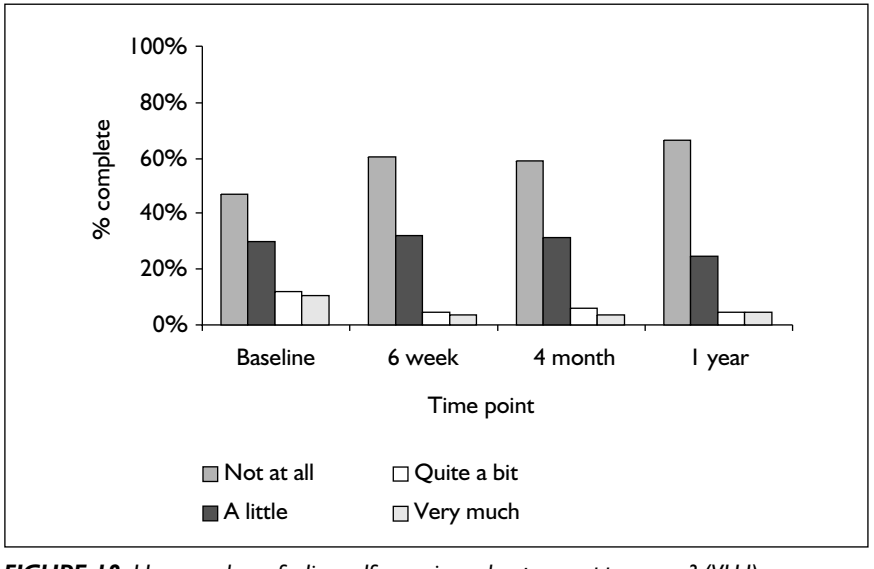


FIGURE 18 *Have you been feeling self-conscious about your appearance? (VLH)*

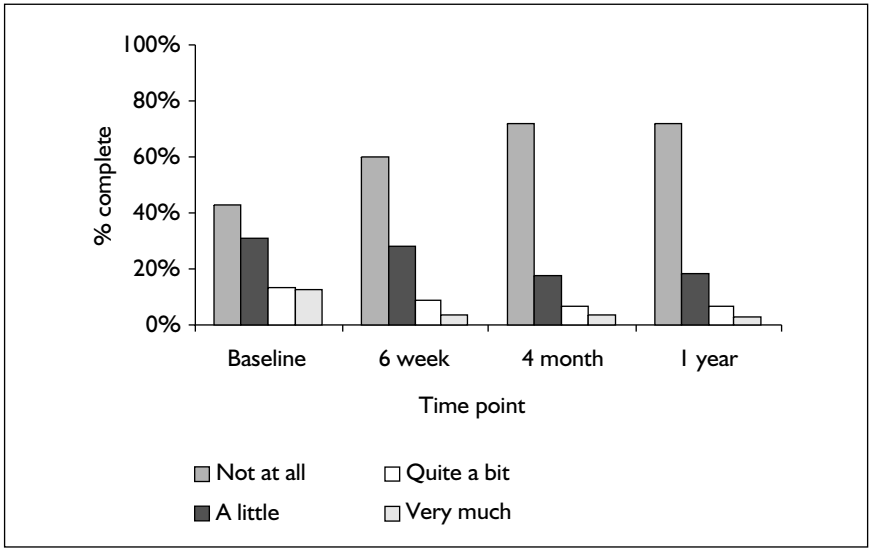


FIGURE 19 *Have you felt less physically attractive as a result of your disease or treatment? (AH)*

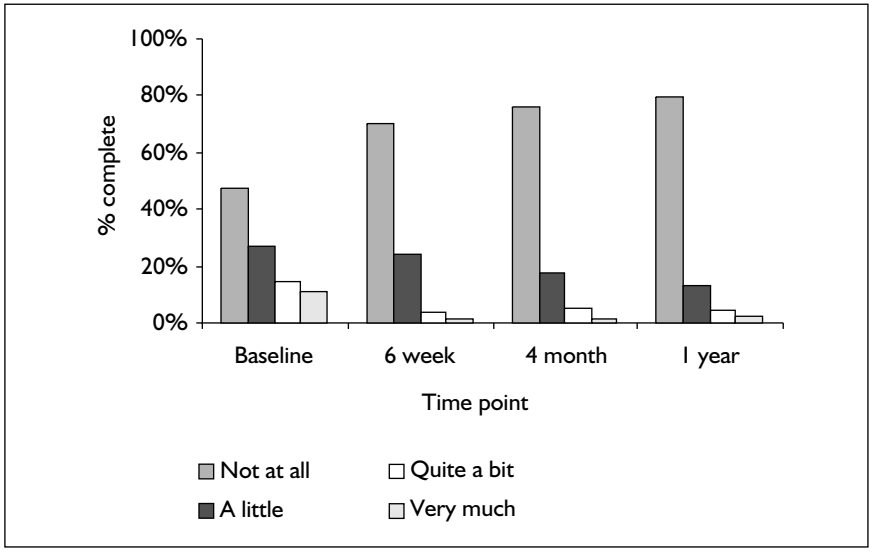


FIGURE 20 *Have you felt less physically attractive as a result of your disease or treatment? (ALH)*

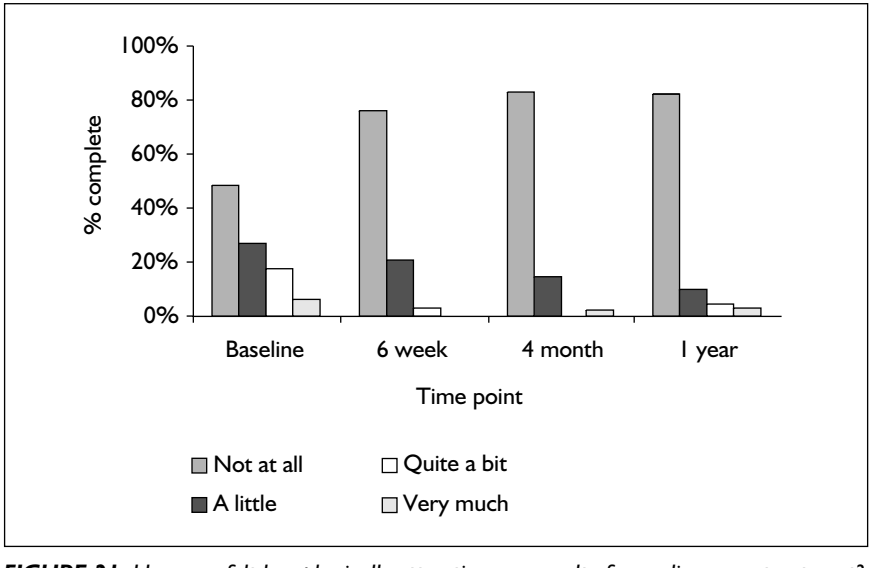


FIGURE 21 *Have you felt less physically attractive as a result of your disease or treatment? (VH)*

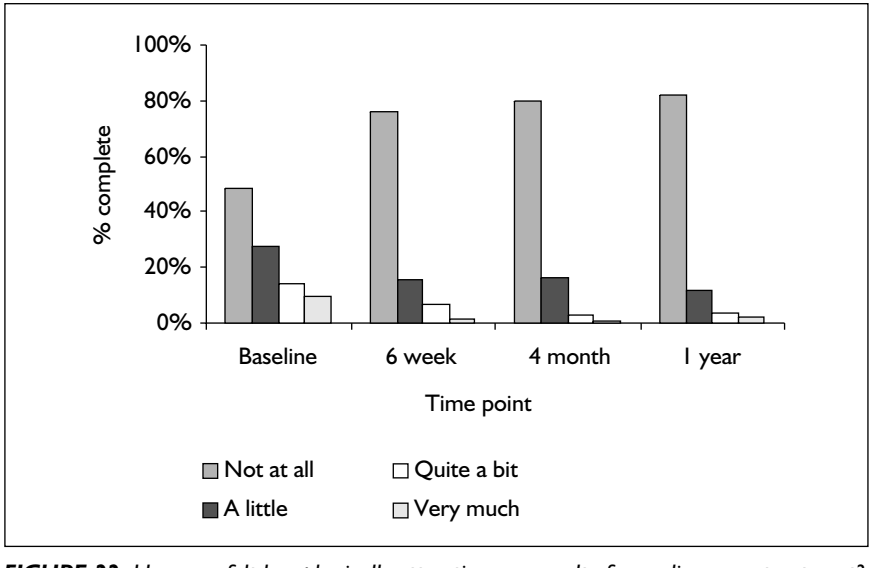


FIGURE 22 *Have you felt less physically attractive as a result of your disease or treatment? (VLH)*

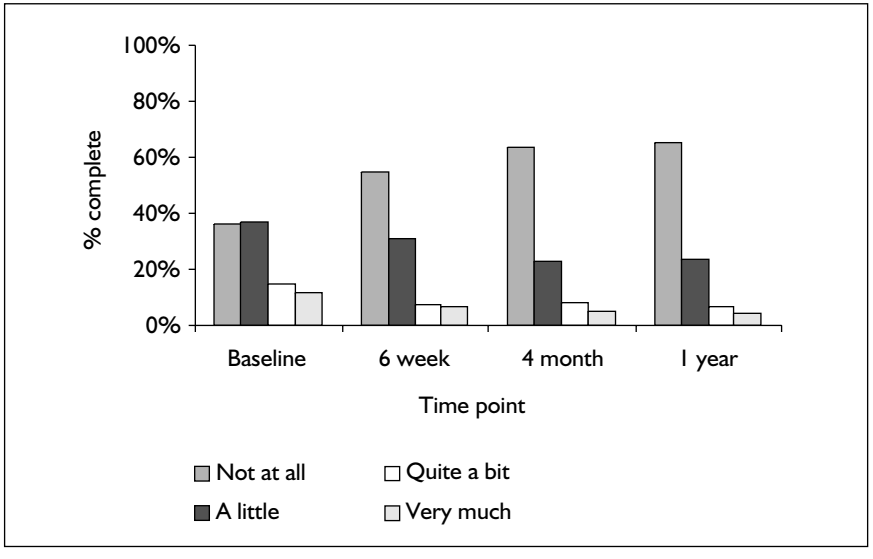


FIGURE 23 *Have you been dissatisfied with your appearance when dressed? (AH)*

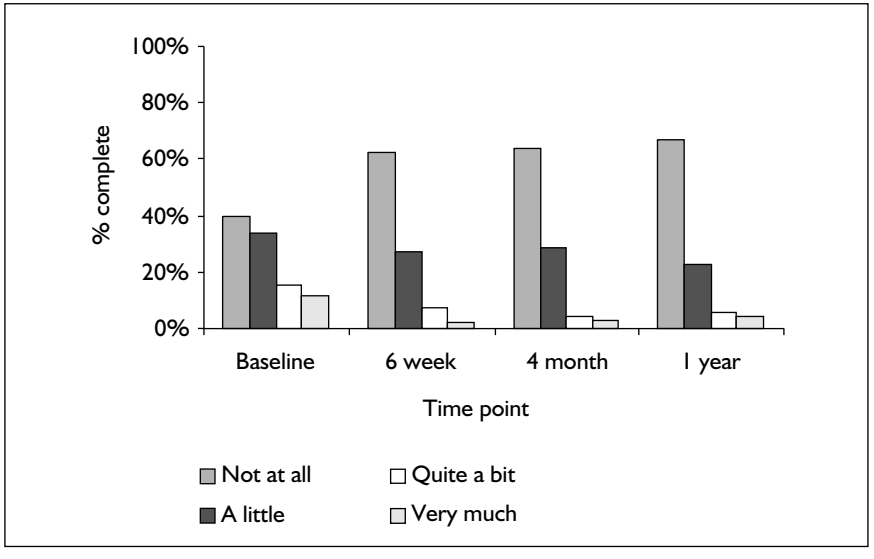


FIGURE 24 *Have you been dissatisfied with your appearance when dressed? (ALH)*

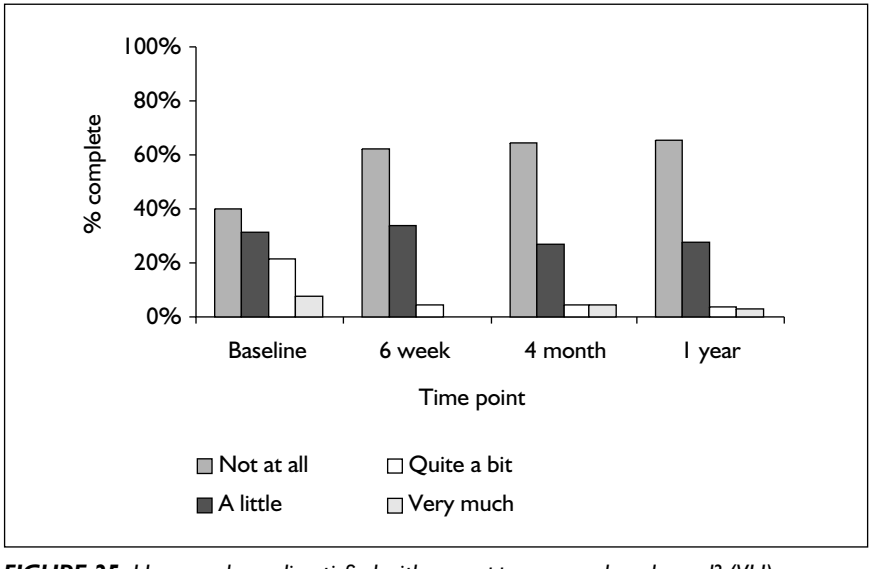


FIGURE 25 *Have you been dissatisfied with your appearance when dressed? (VH)*

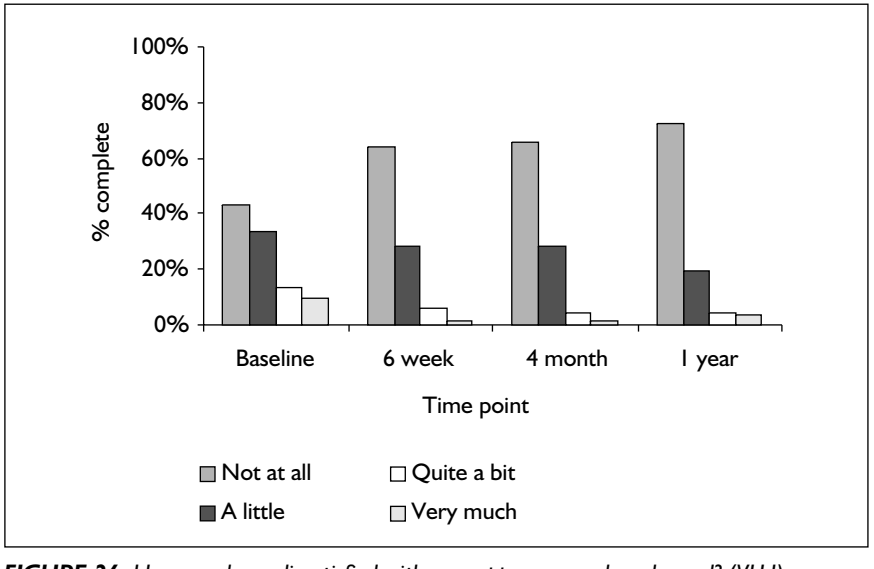


FIGURE 26 *Have you been dissatisfied with your appearance when dressed? (VLH)*

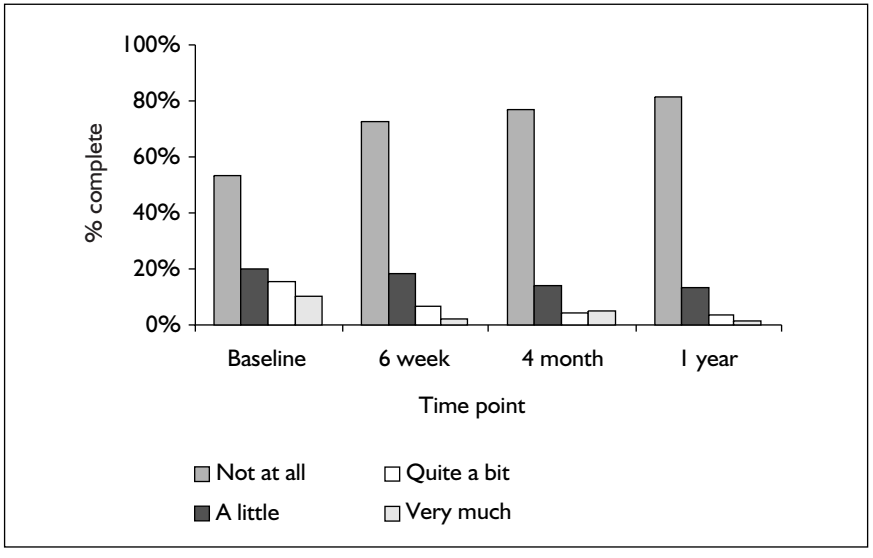


FIGURE 27 *Have you been feeling less feminine as a result of your disease or treatment? (AH)*

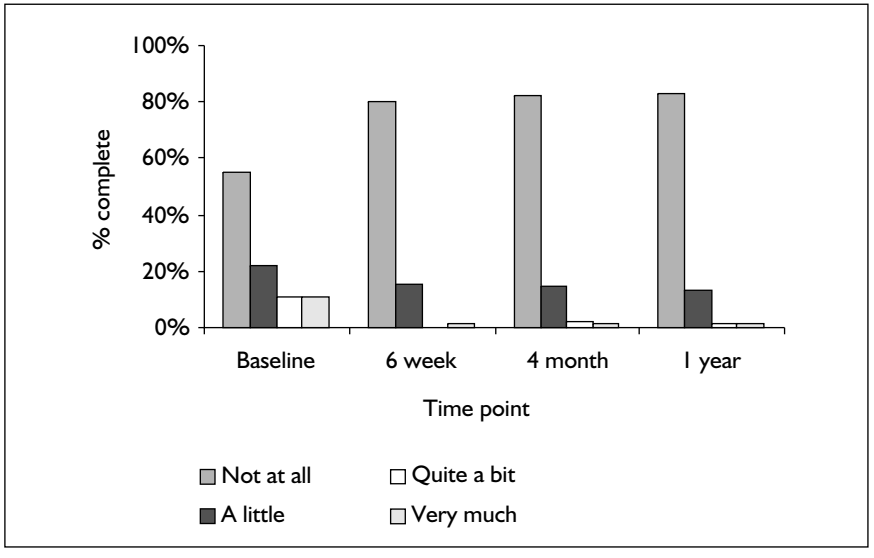


FIGURE 28 *Have you been feeling less feminine as a result of your disease or treatment? (ALH)*

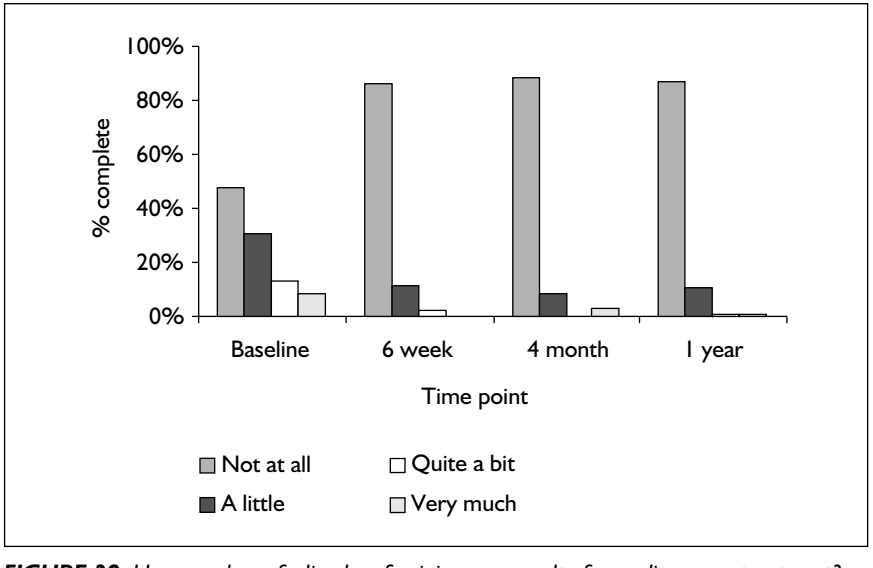


FIGURE 29 *Have you been feeling less feminine as a result of your disease or treatment? (VH)*

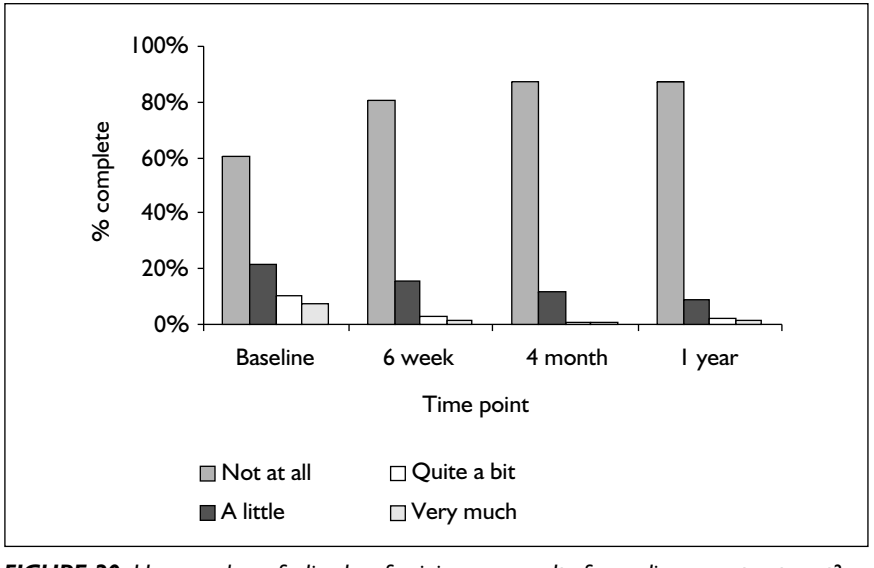


FIGURE 30 *Have you been feeling less feminine as a result of your disease or treatment? (VLH)*

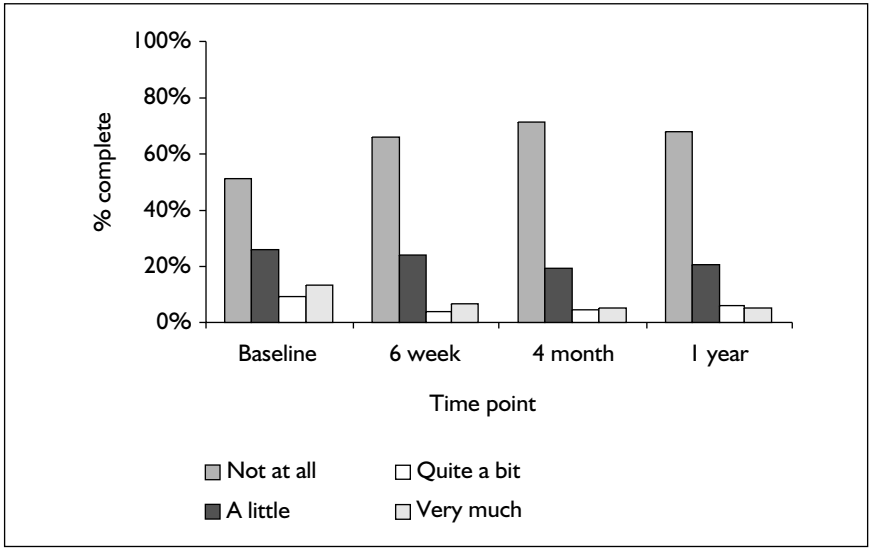


FIGURE 31 *Did you find it difficult to look at yourself naked? (AH)*

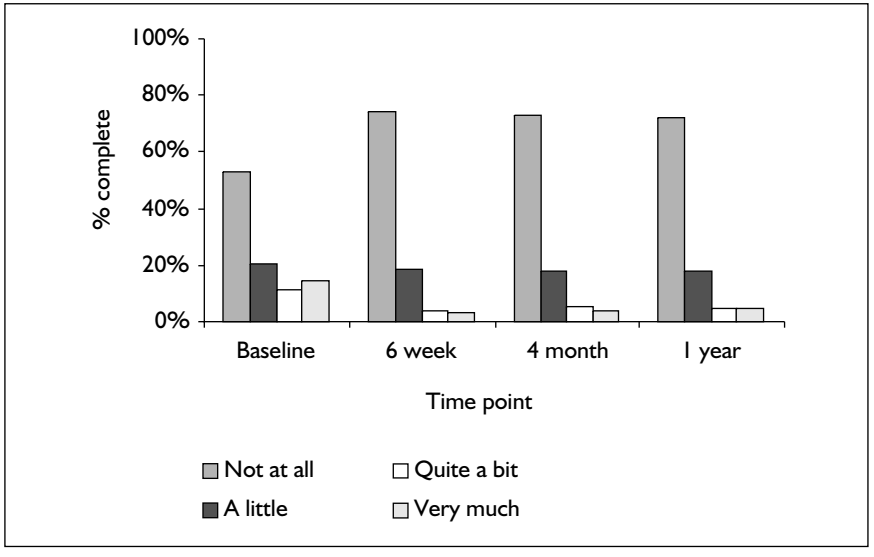


FIGURE 32 *Did you find it difficult to look at yourself naked? (ALH)*

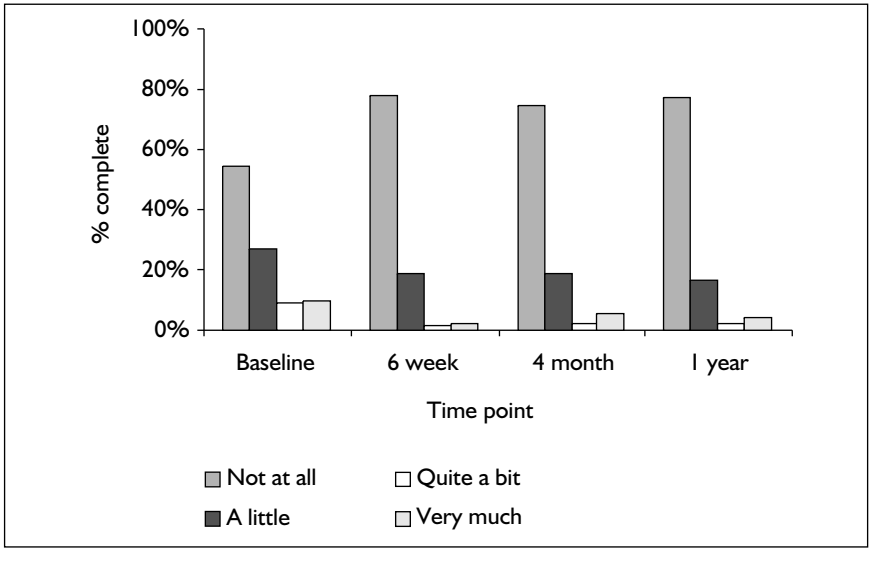


FIGURE 33 *Did you find it difficult to look at yourself naked? (VH)*

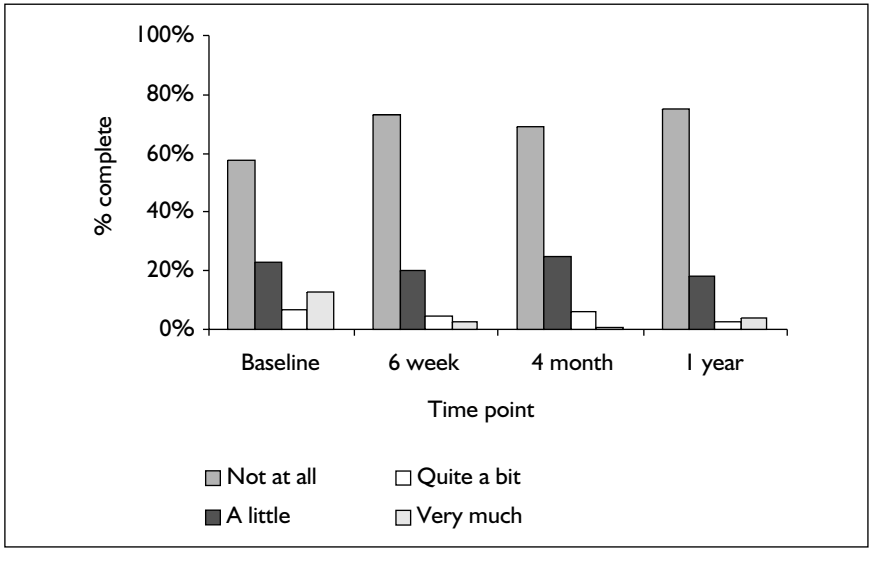


FIGURE 34 *Did you find it difficult to look at yourself naked? (VLH)*

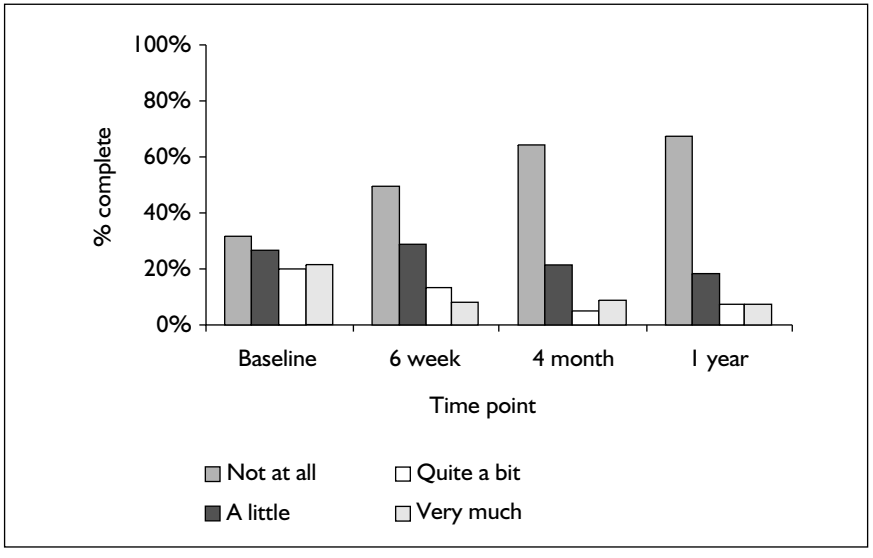


FIGURE 35 *Have you been feeling less sexually attractive as a result of your disease or treatment? (AH)*

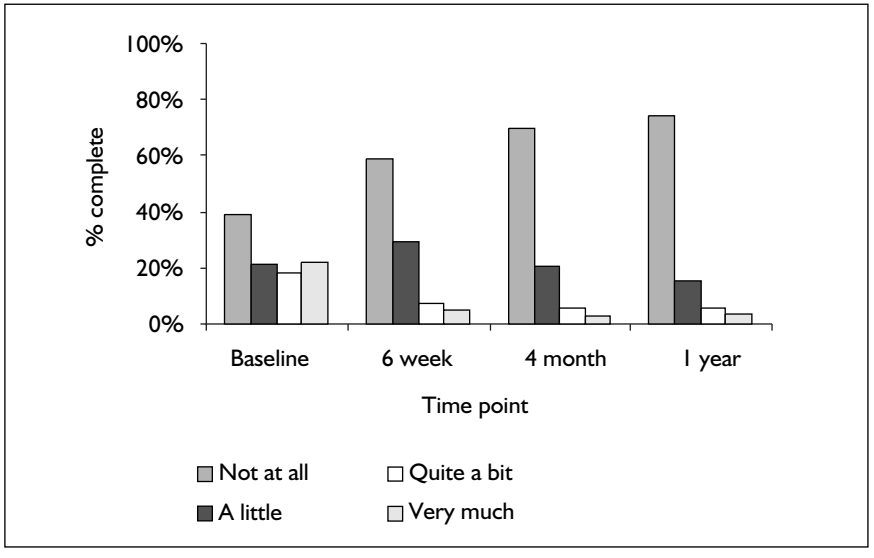


FIGURE 36 *Have you been feeling less sexually attractive as a result of your disease or treatment? (ALH)*

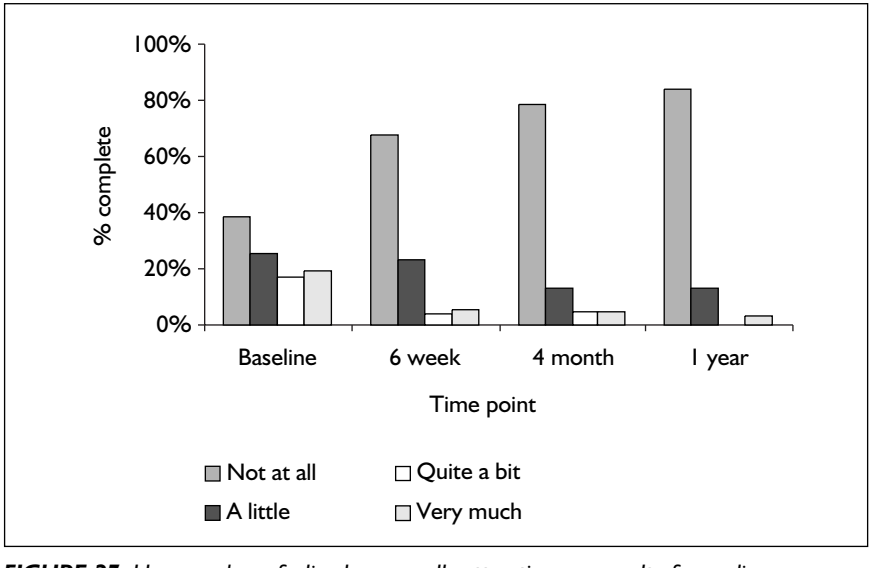


FIGURE 37 *Have you been feeling less sexually attractive as a result of your disease or treatment? (VH)*

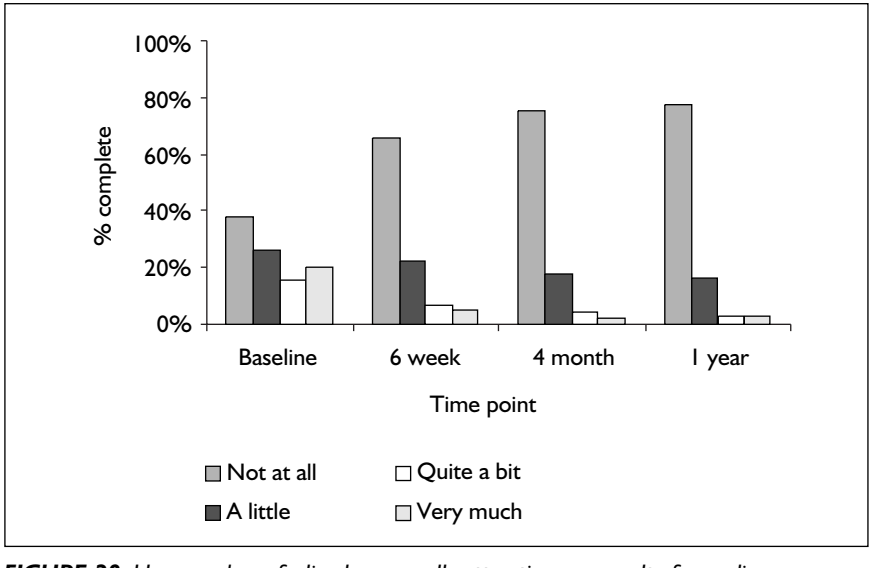


FIGURE 38 *Have you been feeling less sexually attractive as a result of your disease or treatment? (VLH)*

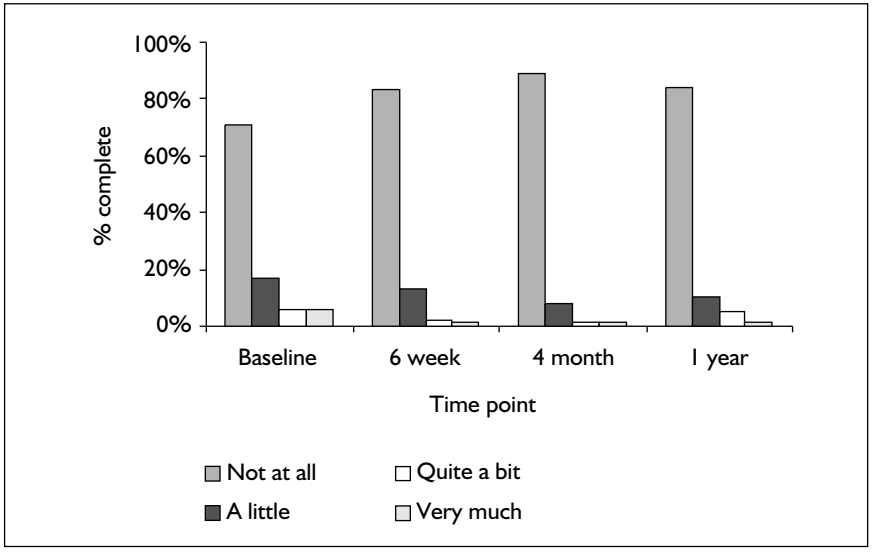


FIGURE 39 *Did you avoid people because of the way you felt about your appearance? (AH)*

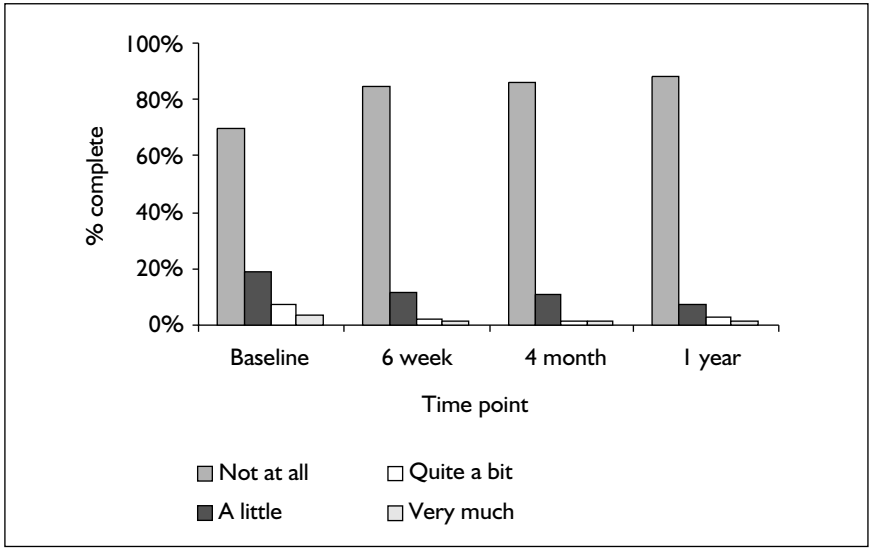


FIGURE 40 *Did you avoid people because of the way you felt about your appearance? (ALH)*

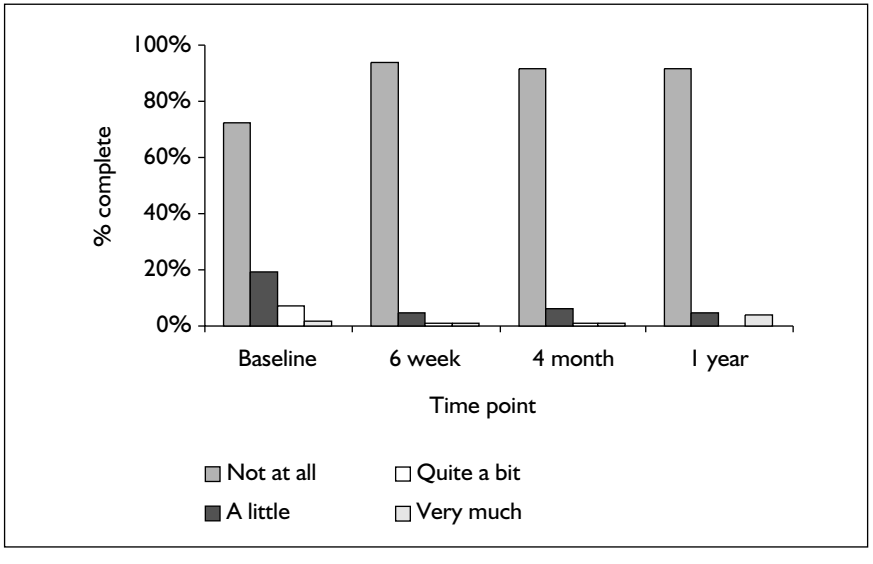


FIGURE 41 *Did you avoid people because of the way you felt about your appearance? (VH)*

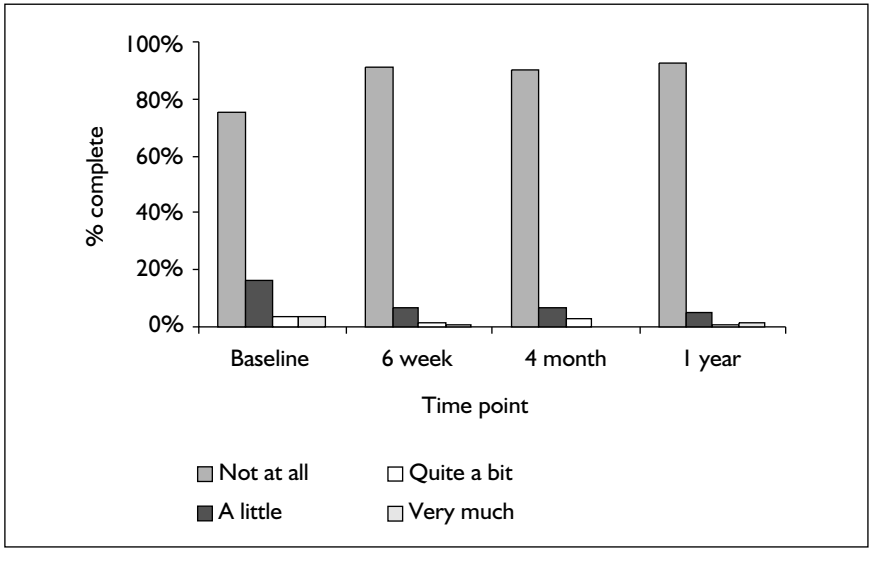


FIGURE 42 *Did you avoid people because of the way you felt about your appearance? (VLH)*

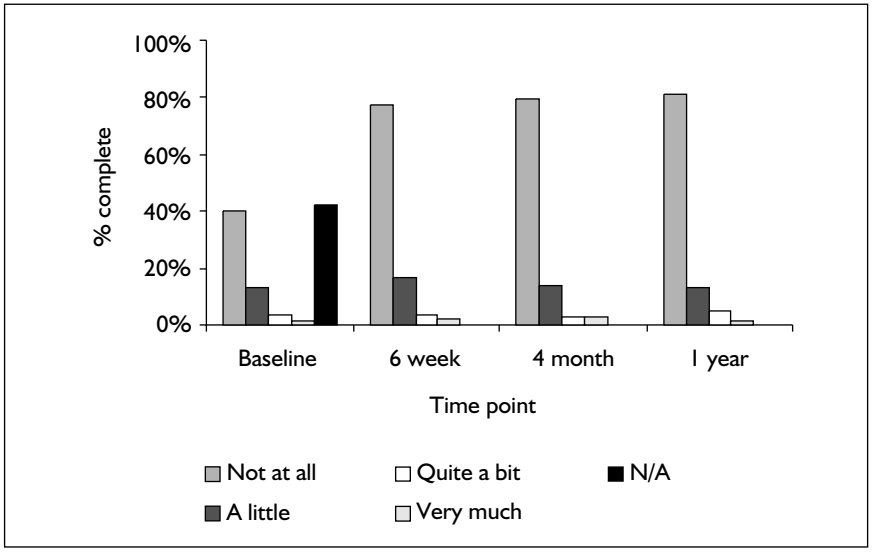


FIGURE 43 *Have you been feeling the treatment has left your body less whole? (AH)*

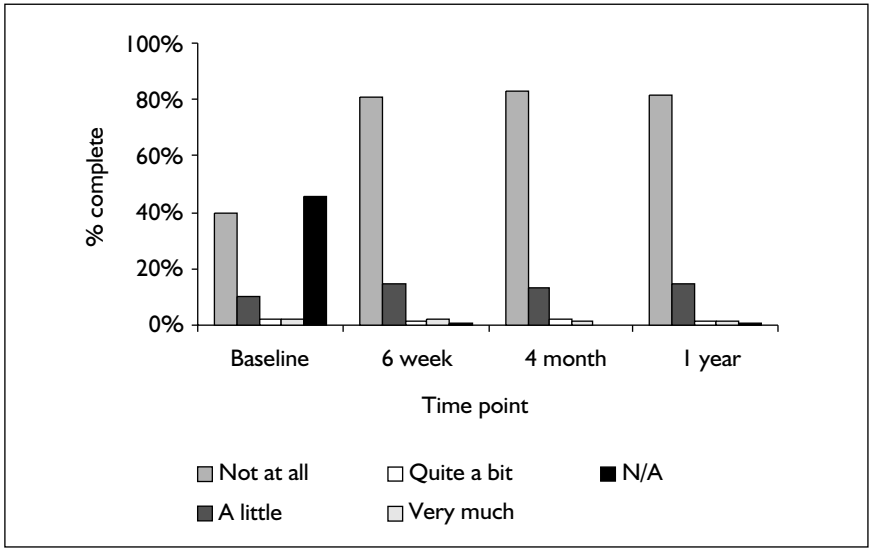


FIGURE 44 *Have you been feeling the treatment has left your body less whole? (ALH)*

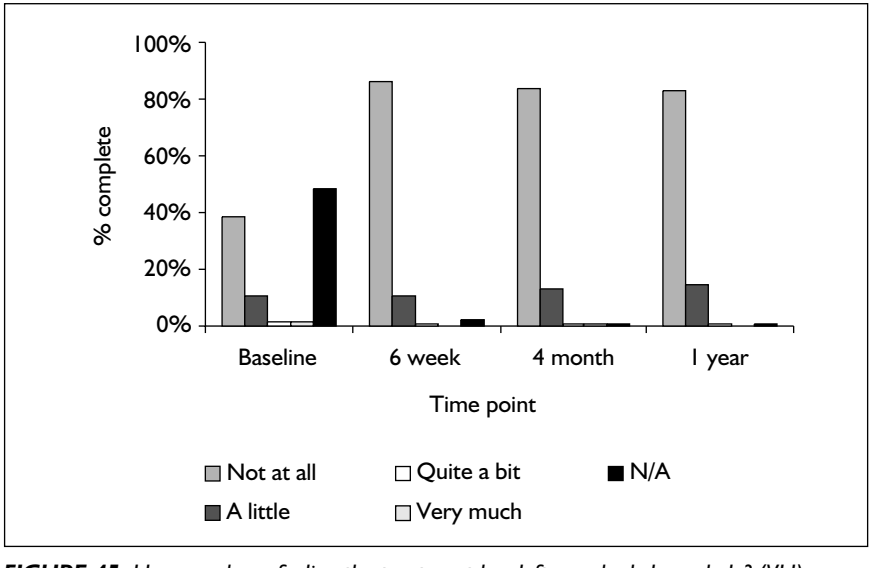


FIGURE 45 *Have you been feeling the treatment has left your body less whole? (VH)*

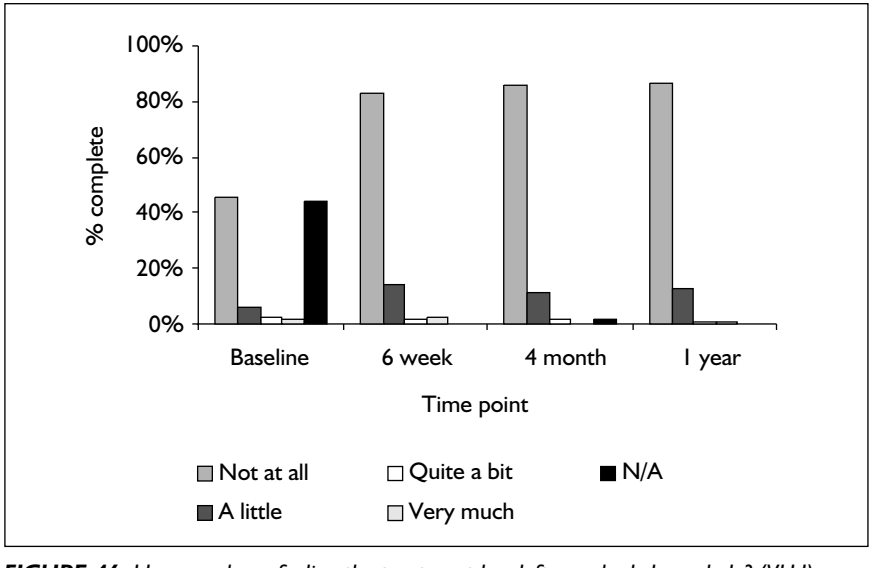


FIGURE 46 *Have you been feeling the treatment has left your body less whole? (VLH)*

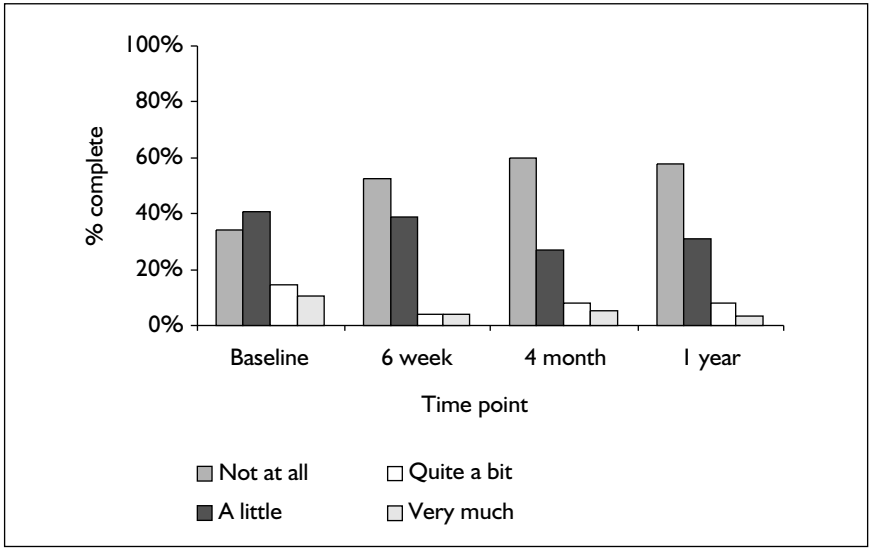


FIGURE 47 *Have you been dissatisfied with your body? (AH)*

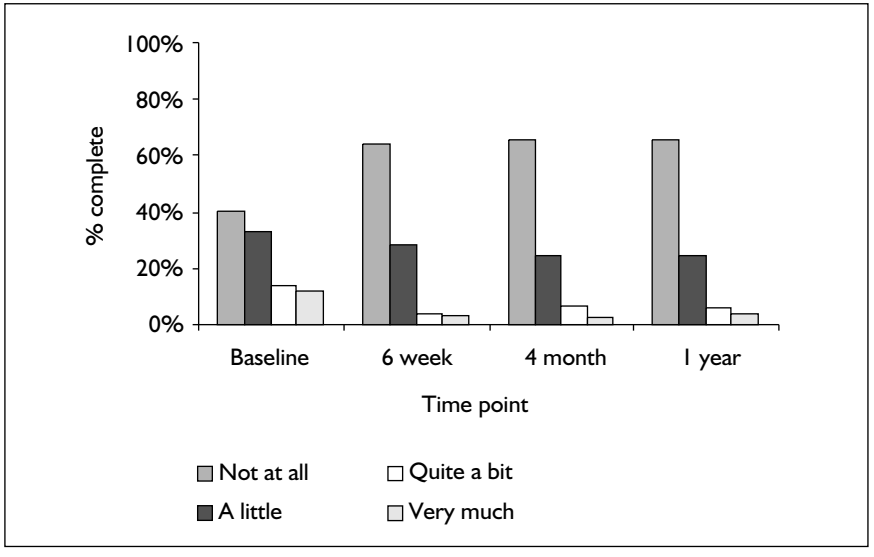


FIGURE 48 *Have you been dissatisfied with your body? (ALH)*

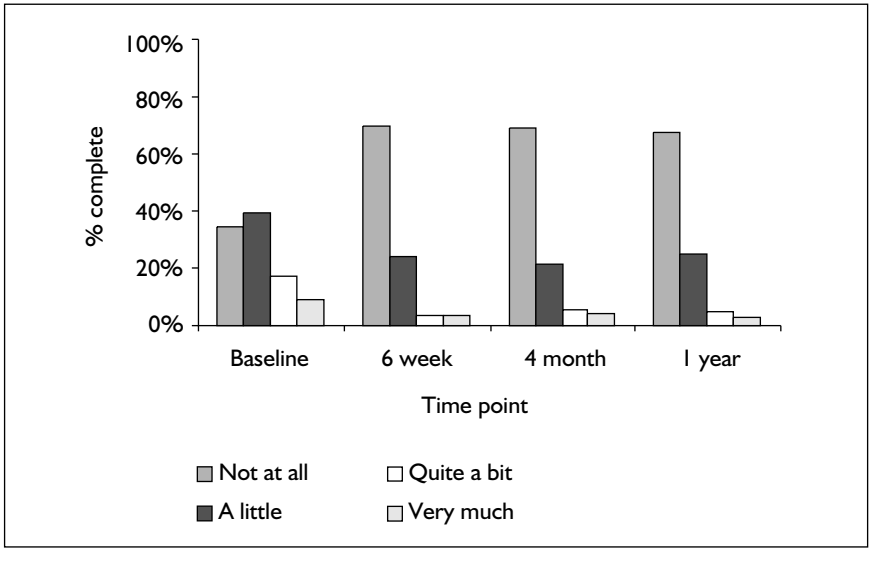


FIGURE 49 *Have you been dissatisfield with your body? (VH)*

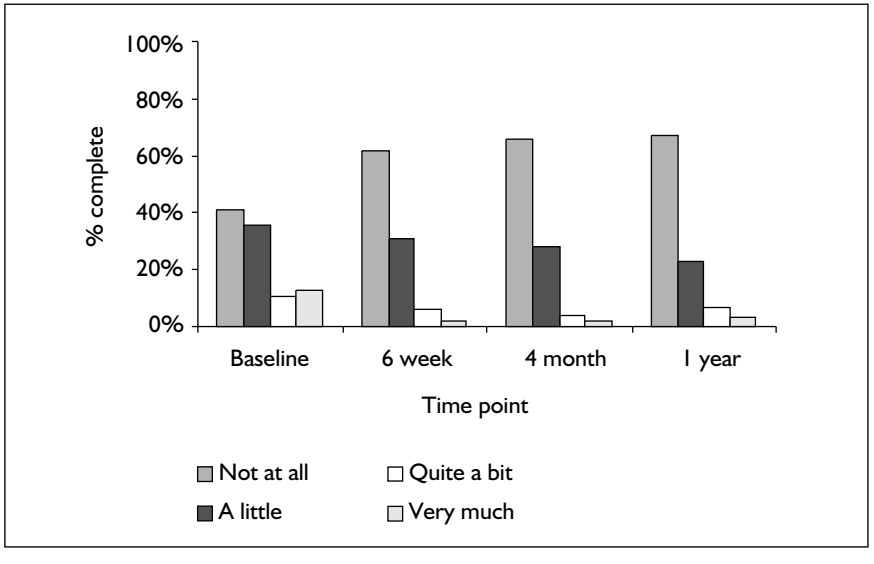


FIGURE 50 *Have you been dissatisfied with your body? (VLH)*

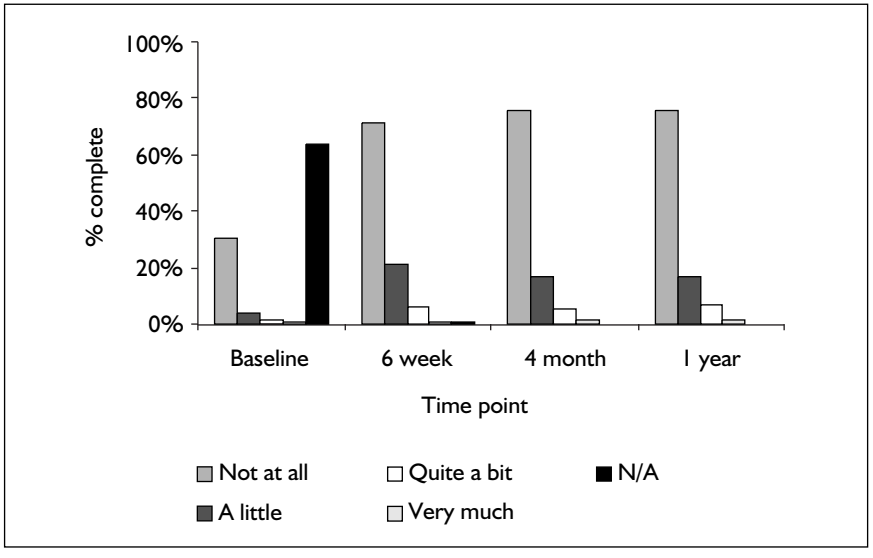


FIGURE 51 *Have you been dissatisfied with the appearance of your scar? (AH)*

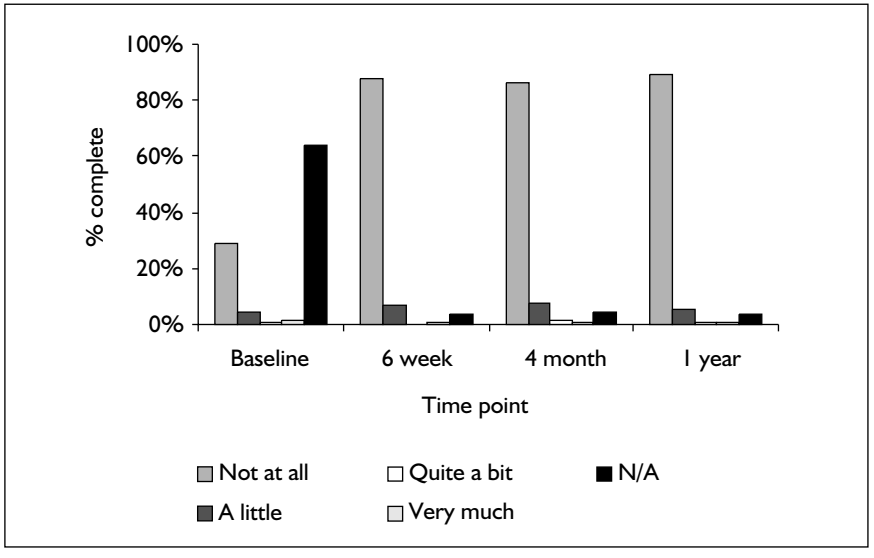


FIGURE 52 *Have you been dissatisfied with the appearance of your scar? (ALH)*

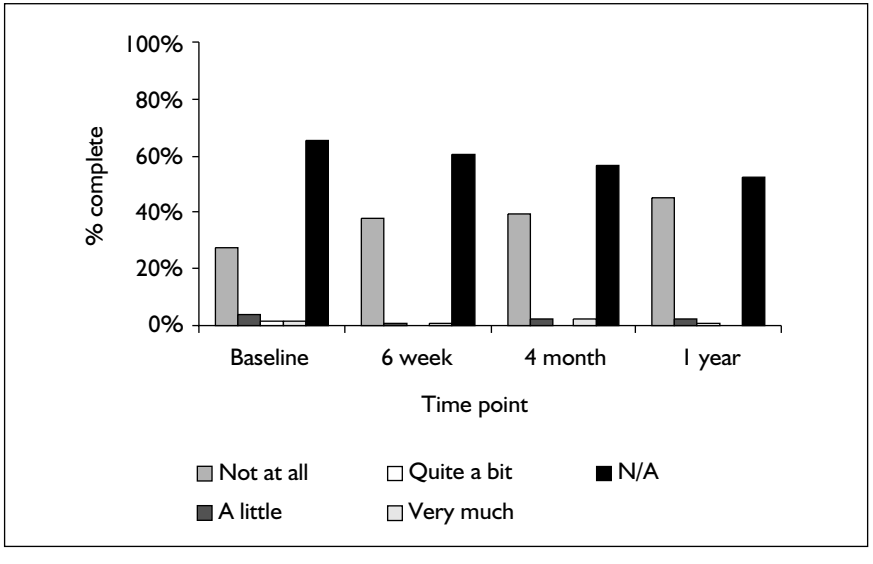


FIGURE 53 *Have you been dissatisfied with the appearance of your scar? (VH)*

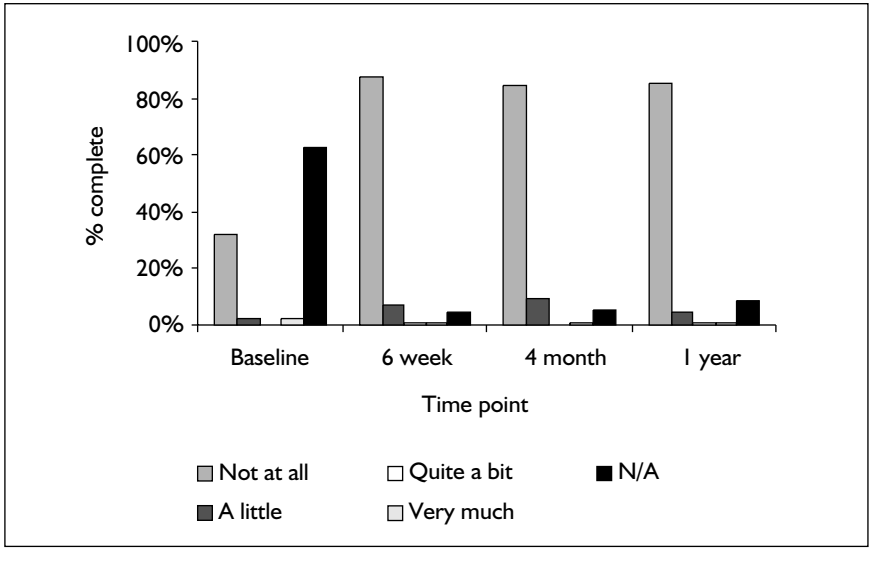


FIGURE 54 *Have you been dissatisfied with the appearance of your scar? (VLH)*

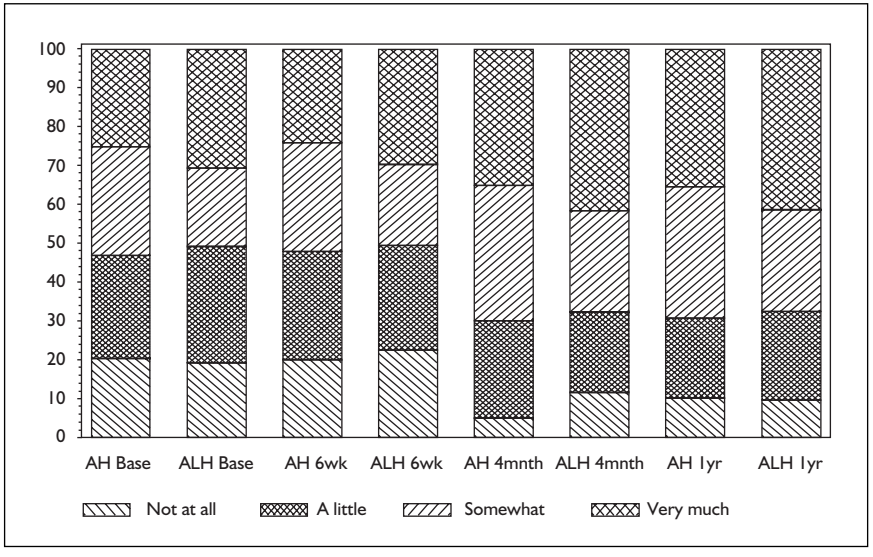


FIGURE 55 *Was having sex an important part of your life this month? Abdominal trial*

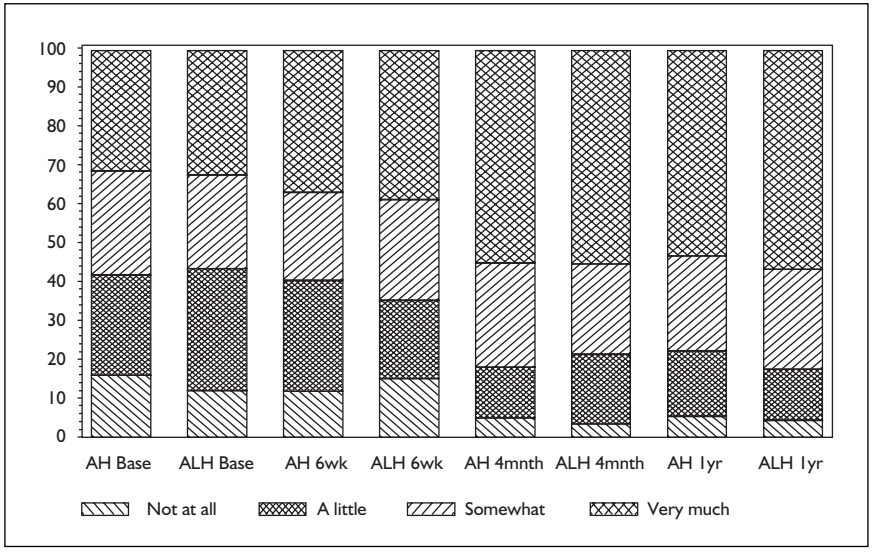


FIGURE 56 *Did you enjoy sexual activity this month? Abdominal trial*

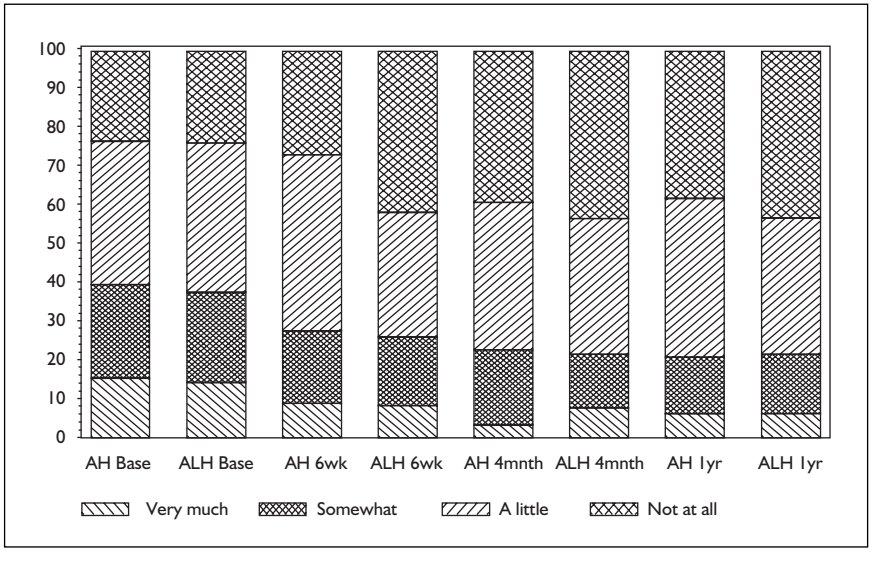


FIGURE 57 *Were you too tired to have sex? Abdominal trial*

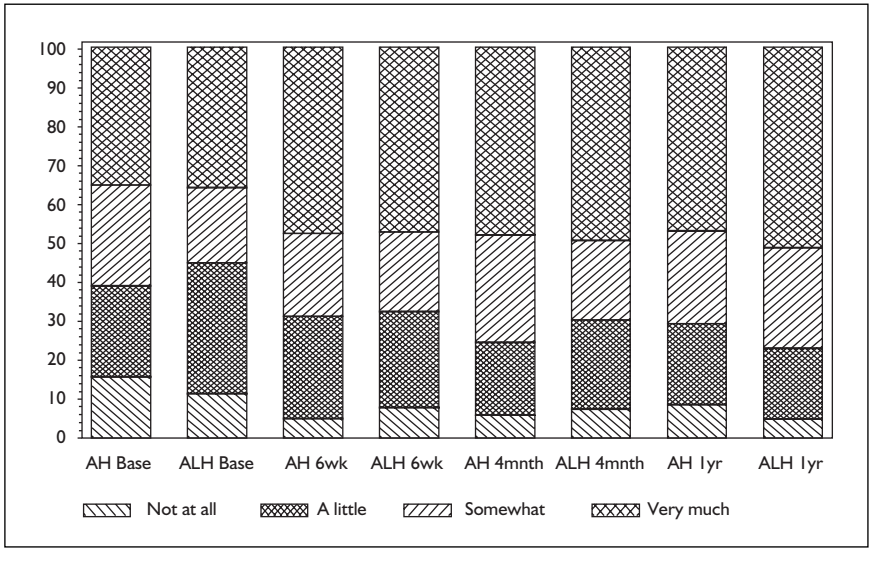


FIGURE 58 *Did you desire to have sex with your partner this month? Abdominal trial*

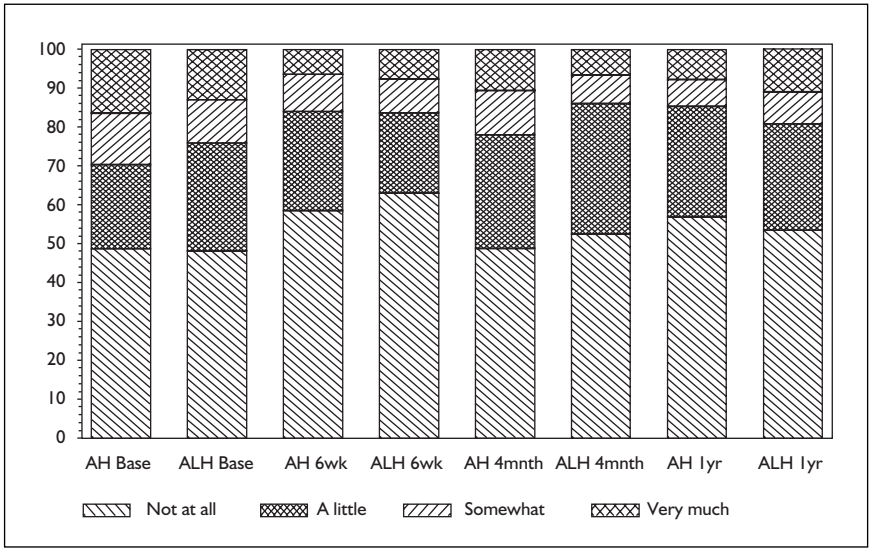


FIGURE 59 *How frequently did you notice dryness of your vagina this month? Abdominal trial*

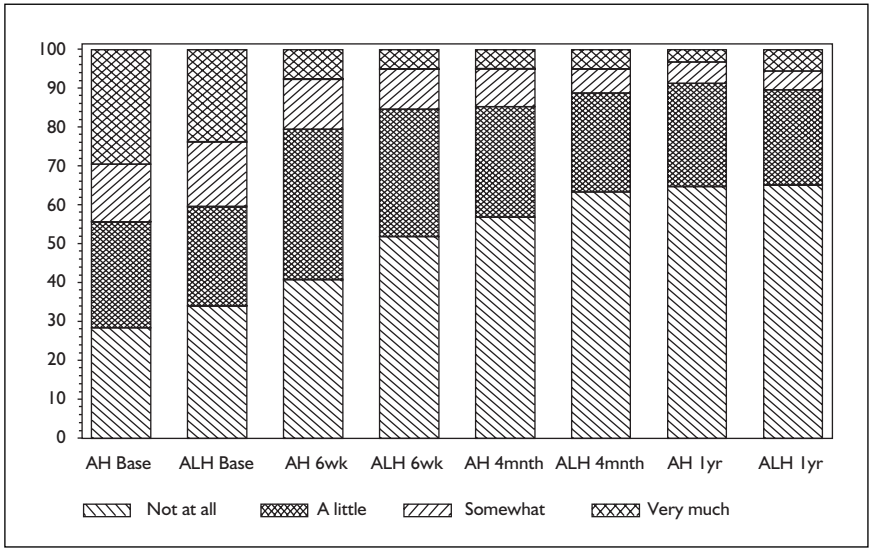


FIGURE 60 *Did you feel pain or discomfort during penetration this month? Abdominal trial*

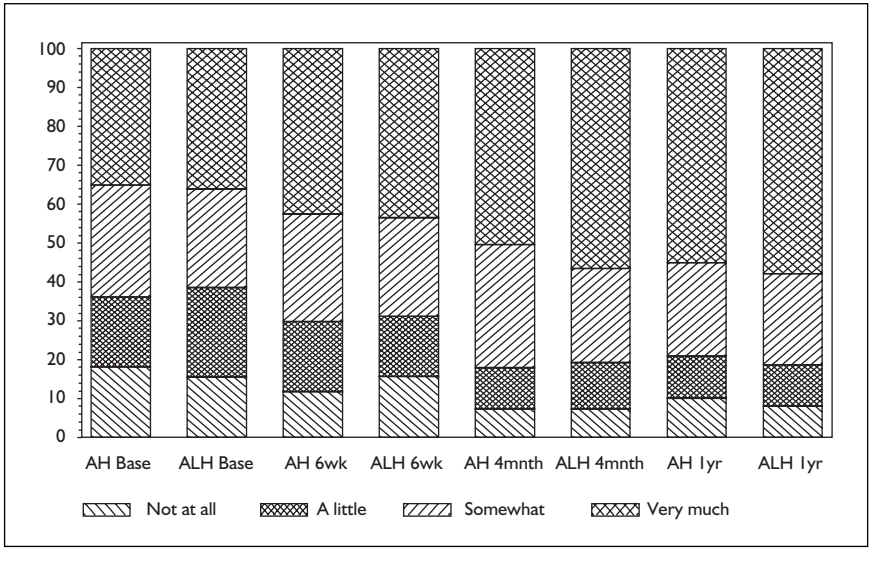


FIGURE 61 *Did you feel satisfied after sexual activity this month? Abdominal trial*

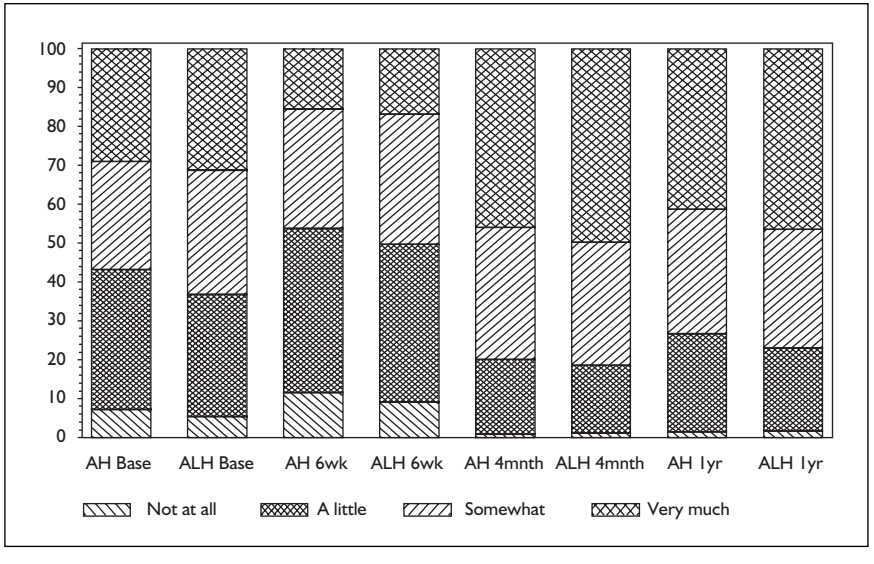


FIGURE 62 *How often did you engage in sexual activity this month? Abdominal trial*

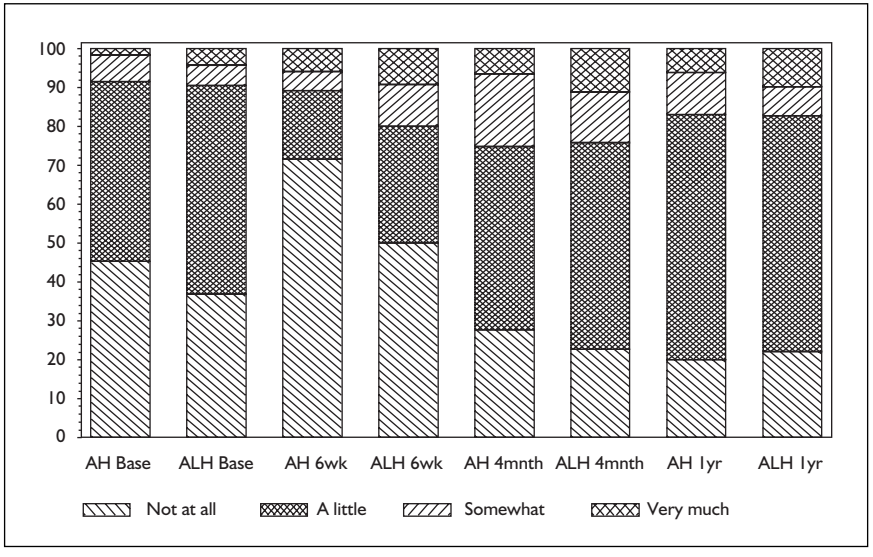


FIGURE 63 *How did frequency of sexual activity compare with what is usual for you? Abdominal trial*

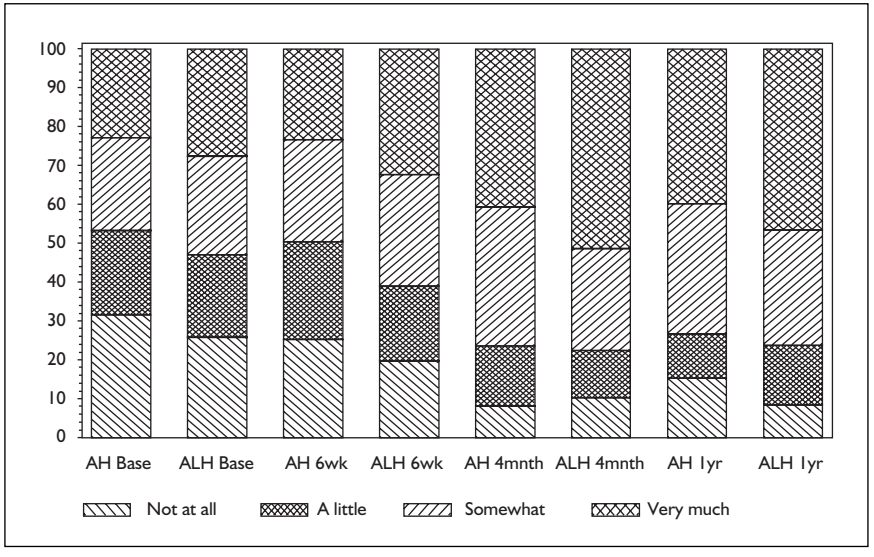


FIGURE 64 *Were you satisfied with the frequency of sexual activity this month? Abdominal trial*

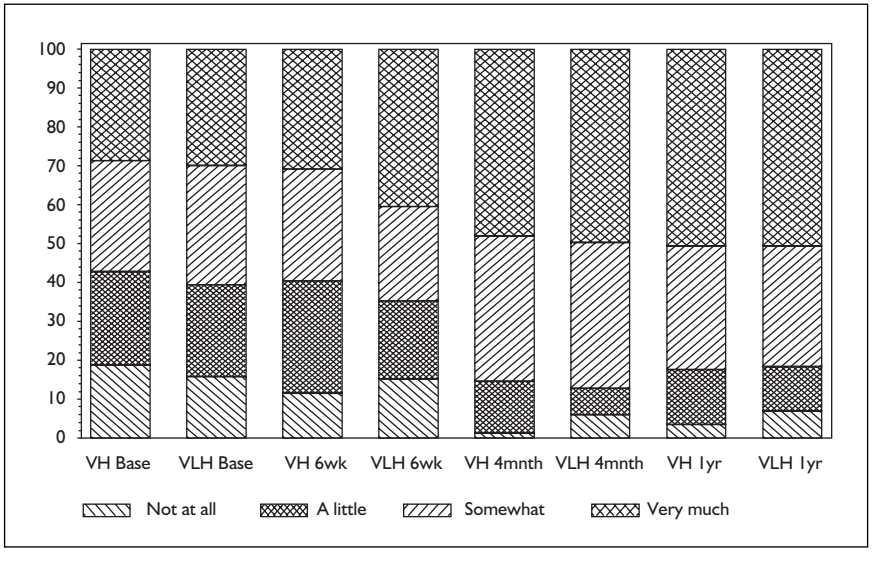


FIGURE 65 *Was having sex an important part of your life this month? Vaginal trial*

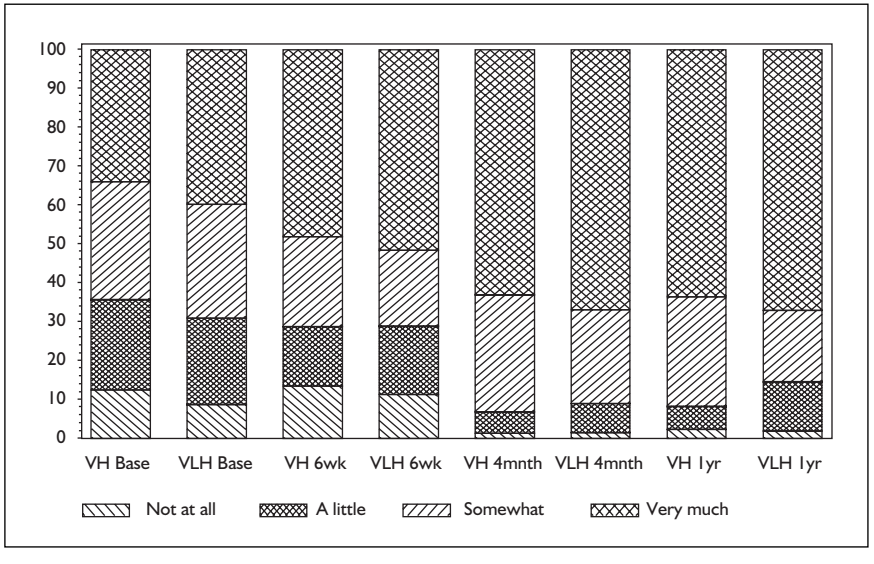


FIGURE 66 *Did you enjoy sexual activity this month? Vaginal trial*

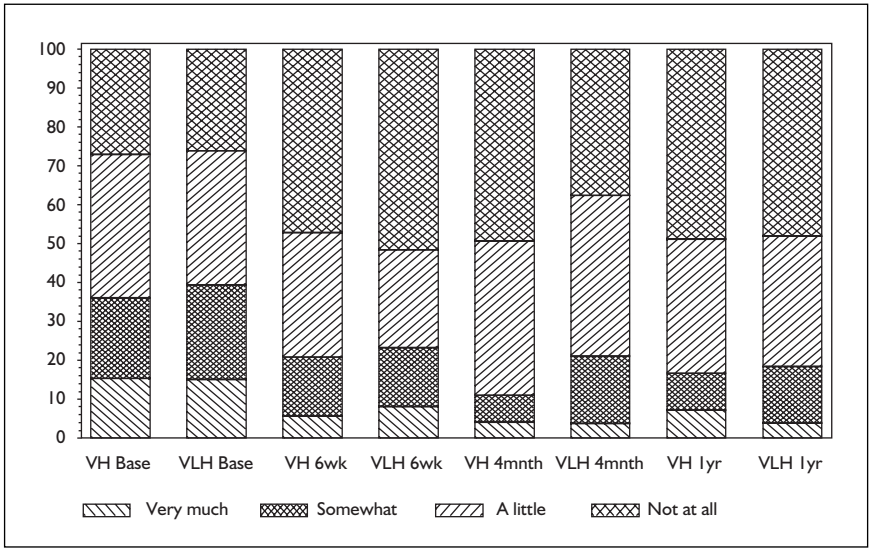


FIGURE 67 *Were you too tired to have sex? Vaginal trial*

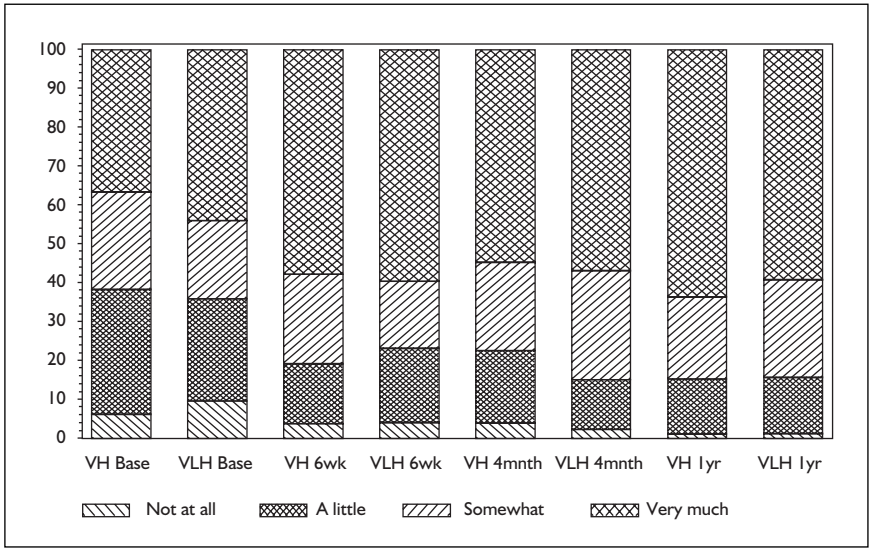


FIGURE 68 *Did you desire to have sex with your partner this month? Vaginal trial*

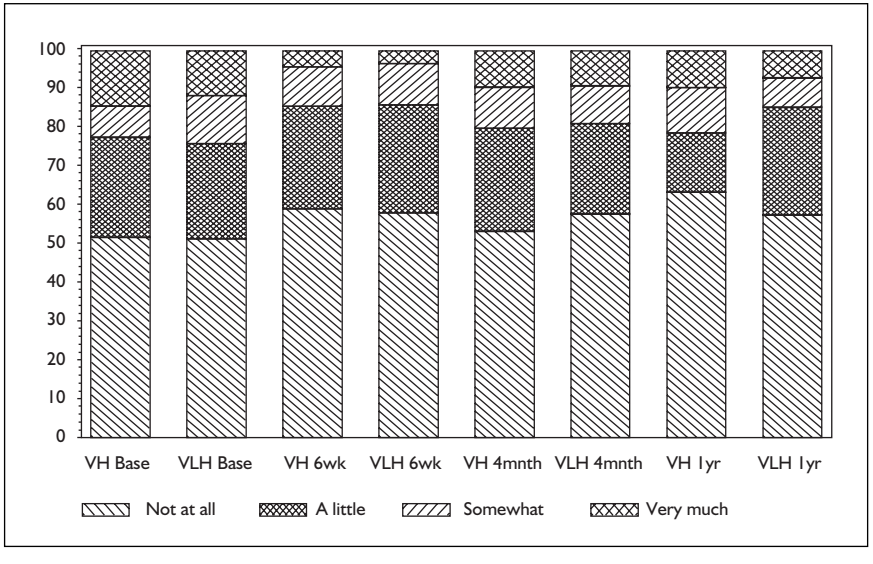


FIGURE 69 *How frequently did you notice dryness of your vagina this month? Vaginal trial*

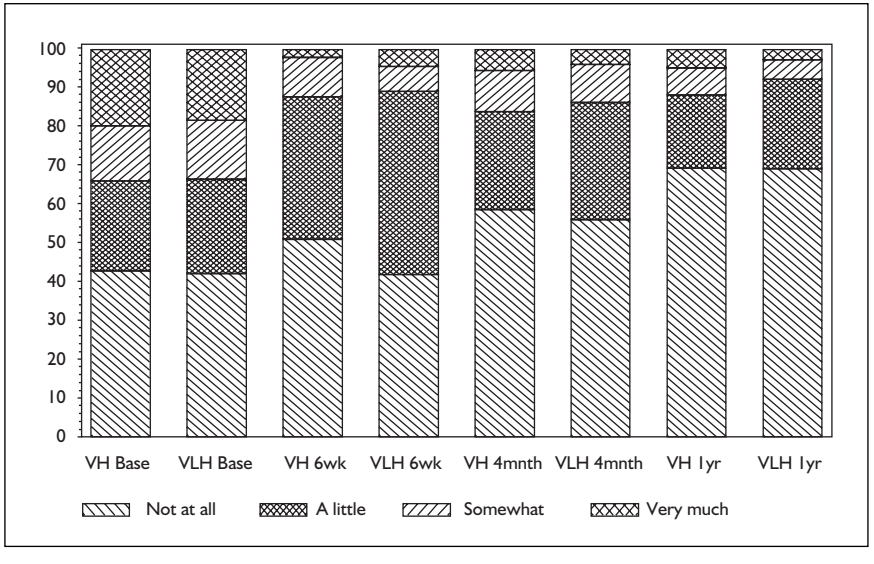


FIGURE 70 *Did you feel pain or discomfort during penetration this month? Vaginal trial*

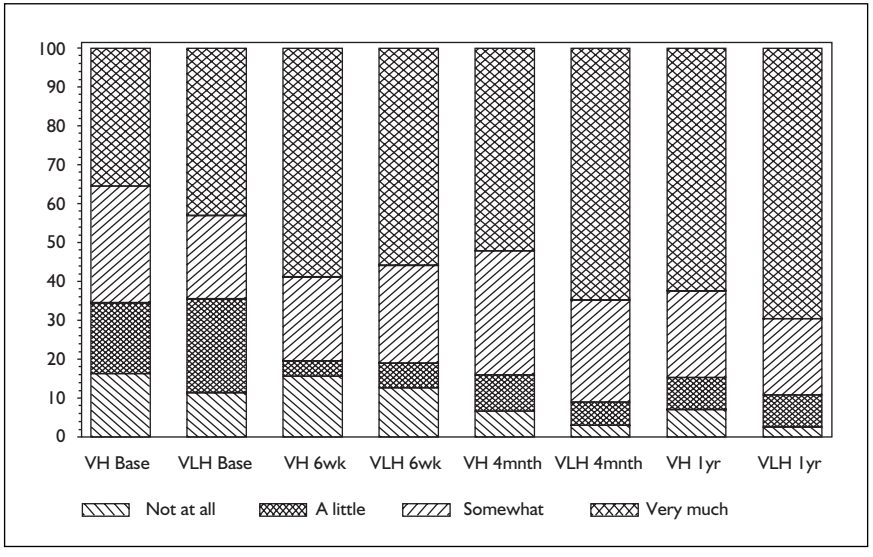


FIGURE 71 *Did you feel satisfied after sexual activity this month? Vaginal trial*

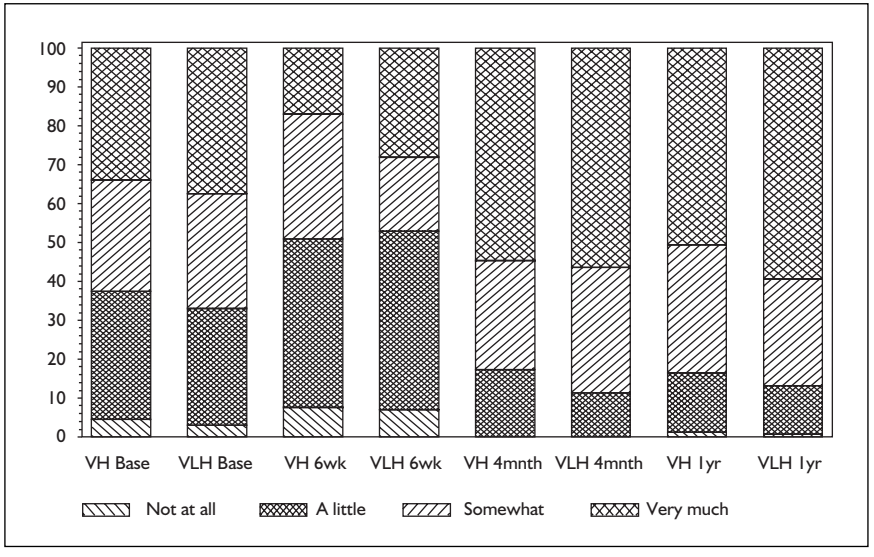


FIGURE 72 *How often did you engage in sexual activity this month? Vaginal trial*

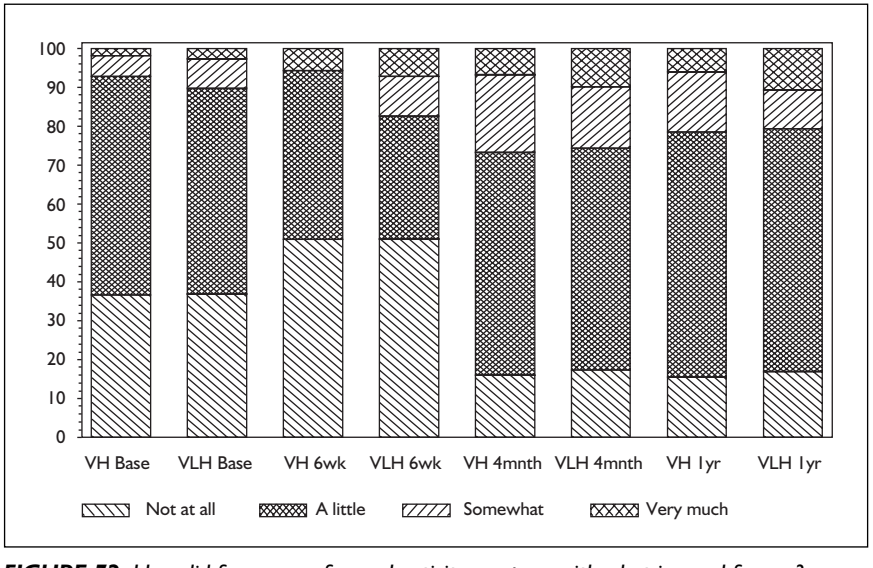


FIGURE 73 *How did frequency of sexual activity compare with what is usual for you? Vaginal trial*

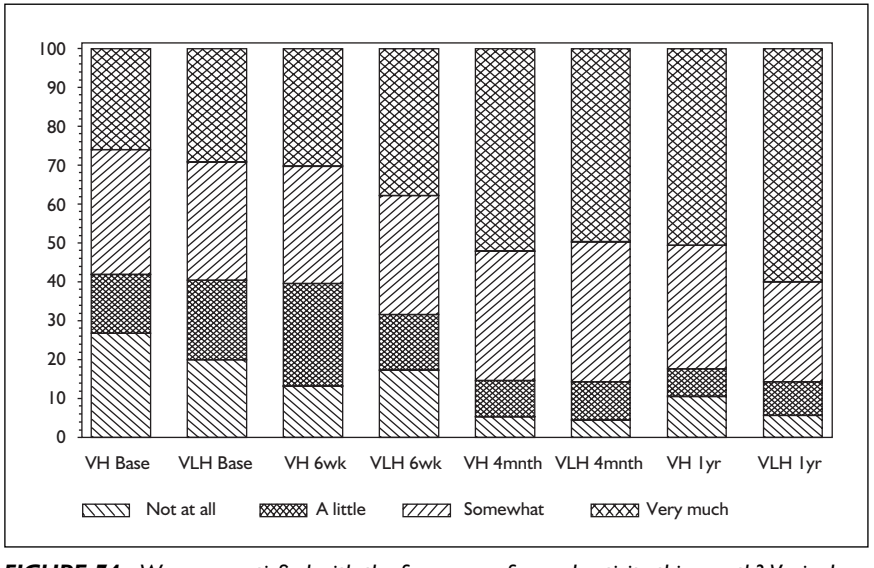


FIGURE 74 *Were you satisfied with the frequency of sexual activity this month? Vaginal trial*

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We look forward to hearing from you.

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