

# A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding

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## Scientific summary

### Outpatient vs. inpatient polyp treatment for AUB

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# Scientific summary

## Background

Abnormal uterine bleeding (AUB) affects women of all ages and is the commonest reason for referral to secondary care. Uterine polyps are focal outgrowths of the endometrium and are frequently found in association with AUB. The available evidence supports the current practice of surgically removing uterine polyps to help alleviate bleeding symptoms. Conventional practice is to undertake this simple procedure under general anaesthesia in hospital. However, with advances in endoscopic technology, it is now possible to perform uterine polypectomy in an outpatient setting without the need for hospital admission and anaesthesia. Furthermore, treatment can be carried out at the same time as diagnosis; the 'see and treat' approach. The convenience and immediacy of outpatient treatment may appear advantageous over traditional practice. However, the limitations of operating in the genital tract using miniature equipment in a conscious patient may offset any apparent benefits. Thus, there is an urgent need for a robust health technology assessment of outpatient polyp treatment (OPT) to evaluate its effectiveness, cost-effectiveness and acceptability compared with traditional inpatient surgical treatment.

## Objectives

In undertaking the Outpatient versus inpatient Polyp Treatment (OPT) Trial, we aimed to:

1. test the hypothesis that in women with AUB associated with benign uterine polyp(s), OPT achieved as good, or no more than 25% worse (in relative terms), alleviation of bleeding symptoms at 6 months compared with standard inpatient treatment (principal objective)
2. test the hypothesis that response to uterine polyp treatment differed according to the pattern of AUB and menopausal status by three secondary analyses:
  - i. premenopausal women compared with postmenopausal women
  - ii. intermenstrual bleeding compared with excessive menstruation
  - iii. postmenopausal women on hormone replacement therapy (HRT) compared with those not on HRT
3. explore the variation in the effectiveness of OPT compared with standard inpatient polyp treatment at different periods of follow-up (12 and 24 months)
4. assess patient acceptability and impact on health-related quality of life (HRQL)
5. explore the relative cost-effectiveness of inpatient polypectomy compared with outpatient polypectomy.

## Methods

### *Randomised controlled trial and patient preference study*

A multicentre randomised controlled trial (RCT) was undertaken, supplemented by a parallel patient preference study. Five-hundred and seven women with AUB and hysteroscopically diagnosed uterine polyps were randomised to outpatient or inpatient polypectomy. A further 399 women willing to participate in the OPT study, but expressing a strong treatment preference, were recruited into the patient preference study. The primary outcome was a successful treatment at 6 months, determined by the woman's assessment of her bleeding. The prespecified non-inferiority margin for the primary outcome was 25%. Secondary outcomes included generic [European Quality of Life-5 Dimensions (EQ-5D)] and disease-specific (Menorrhagia Multi-Attribute Scale) quality-of-life measures, bleeding response on a Likert scale, visual analogue scale (VAS) bleeding scores, procedure acceptability and surgical re-intervention/

failure rates. Longer-term clinical outcomes were assessed at 12 and 24 months in the randomised trial. Primary analyses were by intention-to-treat (ITT) but per-protocol (PP) sensitivity analyses were also conducted for the primary outcome; further sensitivity analyses were also carried out to test the robustness of the results with respect to missing responses and re-interventions. Analyses were performed on predefined subgroups (type of bleeding, location and type of polyp) to examine if there was any evidence of a differential treatment effect. Point estimates [relative risks (RRs), mean differences] and 95% confidence intervals (CIs) were produced for all main outcomes.

### **Economic analysis**

An economic evaluation was carried out, which included both a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). The CEA was based on the patient-reported outcomes, and reported in terms of cost per successful treatment. The CUA was carried out based on an outcome of quality of life estimated from the EQ-5D (3L) questionnaire and reported in terms of additional cost per quality-adjusted life-year (QALY) gained. The costs and outcome measures incorporated into the economic analysis were collected prospectively during the OPT Trial. Costs were estimated using published standard sources of costs for UK NHS procedures (NHS reference costs 2011–12 and Personal Social Services Resource Unit 2012). Bottom-up costing was also undertaken and used in a sensitivity analysis. The robustness of the base-case results to plausible variations during the uptake of these procedures in routine NHS use was explored using a range of one-way deterministic sensitivity analyses (DSAs). In addition, probabilistic sensitivity analysis (PSA) was carried for the base case to enable the simultaneous exploration of the uncertainties in the cost and outcome data. The results of these analyses were presented in terms of incremental cost-effectiveness ratios (ICERs) at 6 and 12 months, reflecting the additional cost per additional outcome of interest of outpatient treatment compared with inpatient treatment. The analysis took the perspective of the NHS, but a wider societal perspective was also explored, as far as possible using the patient self-reported out-of-pocket costs.

### **Acceptability study**

A patient acceptability study was undertaken using a phenomenological approach. This qualitative study was undertaken in order to aid interpretation and understanding of the questionnaire data on acceptability of the procedure, and to gain insight into women's experiences of undergoing outpatient and inpatient treatment. A series of semistructured interviews were undertaken with a purposive sample of RCT and preference patients to explore the ways in which women make sense of their experience and to elicit their motivations for participation in the RCT.

## **Results**

### **Randomised controlled trial and patient preference study**

At 6 months, 73% (166/228) of women who underwent outpatient polypectomy were found to have been successfully treated, compared with 80% (168/211) who had undergone inpatient polypectomy (ITT RR 0.91, 95% CI 0.82 to 1.02; PP RR 0.92, 95% CI 0.82 to 1.02). The lower end of the CI showed that outpatient polypectomy was at most 18% (RR 0.82) worse in relative terms than inpatient treatment (same for both ITT and PP analyses), within the 25% margin of non-inferiority set at the outset of the study. In absolute terms this translates to a risk difference of  $-0.07$  (95% CI  $-0.16$  to  $0.03$ ) and a lower bound of the CI for number needed to harm (NNTH) of six with outpatient treatment (NNTH 15, 95% CI 6 to number needed to benefit 39). By 1 and 2 years, the corresponding proportions were very similar between groups, producing RRs that were close to unity. There was no evidence that the treatment effect differed according to any of the predefined subgroups when treatment by variable interaction parameters were examined. There were no significant differences in quality of life or VAS scores.

Failure to completely remove polyps was higher in the outpatient treatment group than in the inpatient treatment group (19% vs. 8% respectively; RR 2.5, 95% CI 1.5 to 4.1). There was reduced acceptability in the outpatient group (83% vs. 92%; RR 0.90, 95% CI 0.84 to 0.97), although the number of women

responding at least 'fairly acceptable' was 98% in both groups. Four uterine perforations occurred in the inpatient treatment group.

In the patient preference study, 81% of women expressed a preference for outpatient treatment. Eighty two per cent of women reported a successful response to surgery at 6 months in both the outpatient group and inpatient polypectomy group (RR 0.99, 95% CI 0.87 to 1.12). As with the RCT, no differences in quality-of-life or VAS scores were observed. The inpatient treatment setting was associated with increased acceptability, although overall acceptability (at least 'fairly acceptable') was 98% for outpatient treatment. Lower rates of procedure failure were seen compared with the RCT groups [odds ratio (OR) 0.64, 95% CI 0.42 to 0.99] but no differences between groups were seen.

### Economic analysis

For the base-case analysis, the point estimates of the mean costs incurred at 6 months on the outpatient and inpatient treatment groups were £822 and £1482, respectively, with a cost difference of £660. The proportion of patients who reported improvement in symptoms following polypectomy were 0.74 and 0.81 at 6 months for outpatient and inpatient treatment groups, respectively. The point estimates for mean QALY levels in the inpatient and the outpatient groups at 6 months were equal at 0.41. In the ITT analysis at 6 months, it cost an extra £9421 per patient successfully treated with inpatient treatment compared with outpatient treatment. The additional cost per QALY was £1,099,167 per additional QALY gained in the inpatient group. At 12 months, the corresponding costs were an extra £22,293 per additional effectively treated inpatient and the additional cost per QALY was £668,800. Similar results were obtained using the PP analysis, although outpatient treatment dominated inpatient treatment (i.e. it was less expensive while being more effective) at 12 months.

Inpatient polypectomy remained more expensive than outpatient treatment in all of the scenarios considered, and the ICERs were similar in DSA to those obtained by the base-case analysis. PSA showed that although inpatient treatment is more expensive than the outpatient treatment, there was uncertainty around the difference in effectiveness, implying that the effectiveness of the two treatments was broadly similar. Outpatient treatment was the preferred procedure at lower willingness-to-pay (WTP) thresholds; only at WTP thresholds of  $\geq$  £90,000 did the two alternatives have equal chance of being considered cost-effective.

### Acceptability study

Various factors were found to be influential to women when deciding whether to take part in the OPT study. Altruistic reasons around helping other women were common in the RCT, whereas preference patients had more individual reasons for choosing one treatment option over the other; most women choosing outpatient treatment wanted it over and done with in one hospital visit. Women expressed satisfaction with their treatment, whatever their preference for treatment. The main difference in procedural experience was that outpatients reported some pain and embarrassment during the procedure, whereas inpatients reported some level of fatigue from the general anaesthetic.

## Conclusions

When treating women with AUB associated with uterine polyps, outpatient polypectomy was non-inferior to inpatient polypectomy at 6 and 12 months and more cost-effective. However, patients need to be aware that failure to remove a polyp is more likely with outpatient treatment and procedure acceptability slightly lower.

We found outpatient surgical treatment of uterine polyps to be non-inferior to traditional inpatient treatment under general anaesthesia for the successful alleviation of AUB when compared with our prespecified margin of non-inferiority of 25%. The removal of these focal pathologies was associated with symptomatic control in three-quarters of women at 6 months, and treatment outcomes were maintained

at 12 and 24 months. There was no evidence that the treatment effect differed depending on whether the presenting complaint was heavy, intermenstrual or postmenopausal bleeding, neither was it affected by the location or type of polyp. A significant improvement in generic and disease-specific HRQL was seen following polypectomy in both treatment groups at 6, 12 and 24 months, with no differences observed according to treatment setting. Although outpatient polypectomy was successfully completed in four out of five women, the odds of failure to complete polyp removal were two and a half times more likely in the conscious patient than with traditional inpatient treatment.

Outpatient polyp treatment was less expensive than traditional inpatient treatment and similarly effective, resulting in slightly lower self-reported effectiveness and QALY values at 6 and 12 months. The differences in costs and outcomes between these procedures were fairly constant at these time points, suggesting that the treatment has very few longer-term implications on health and resource use. The ICERs obtained by cost-effectiveness and CUAs were very high, reflecting the equivalence in effectiveness between these procedures. Sensitivity analyses clearly demonstrated that although outpatient therapy was definitely cheaper than inpatient treatment, there was uncertainty around the effectiveness estimates implying the effectiveness of the two alternatives was broadly similar. Thus, outpatient polypectomy appears to be more cost-effective than current inpatient approaches to polypectomy at current acceptable WTP thresholds for the NHS.

Rates of acceptability were high for both treatment groups, although acceptability with inpatient therapy as measured on a Likert scale on the day of treatment was higher. When women were willing to take part in the study but had a preference for treatment setting, > 80% chose to have the treatment awake as an outpatient. Exploring acceptability and patient experience by semistructured interviews within 2 weeks of treatment revealed that women expressed satisfaction with their treatment, whatever their preference for inpatient or outpatient treatment. Women valued expeditious treatment and saw the immediacy and convenience of 'see and treat' outpatient treatment as a proportionate response to resolving their problem. Women considered the rapid discharge and return to normal activities associated with outpatient treatment as an advantage.

## Implications for health care

Outpatient polyp treatment is effective, acceptable and cost-effective. The current situation, for which the majority of NHS providers of gynaecological services are unable to routinely offer women the choice of outpatient surgical treatment for symptomatic uterine polyps, is unsustainable. Diagnostic outpatient hysteroscopy facilities and practitioners are widely available within most NHS hospitals, so that little additional infrastructure and training would be required to begin offering therapeutic services. Contemporary health service development needs to take into account the views of patients; the demand for the outpatient setting demonstrated in recruitment to the OPT preference study further support the clinical and economic argument for change. In addition to developing modern diagnostic and therapeutic 'ambulatory units' within hospitals, providers should consider the possibility of setting up or expanding community-based services, which may be more convenient to service users and potentially more cost-effective.

The results of this research should inform the consenting process so that contemporary written material and counselling is succinct, valid and relevant. This will enable patients to acquire realistic expectations of the likely outpatient treatment experience, especially regarding pain, acceptability and treatment failure. The provision of timely written and verbal information is therefore of prime importance to allow women to make informed choices regarding treatment setting, especially where 'see and treat' approaches to diagnosis and treatment are to be offered.

### Recommendations for future research (numbered in priority order)

1. Within gynaecological practice and other surgical disciplines, technology and patient expectations will drive the development of convenient and rapid outpatient interventions to resolve commonly encountered conditions that currently necessitate traditional inpatient surgery. Further RCTs, similar to the OPT Trial, should be conducted to evaluate the effectiveness and cost-effectiveness of such practices.
2. RCTs comparing uterine polypectomy compared with (1) medical management (e.g. the levonorgestrel intrauterine system) and (2) expectant management may be warranted, subject to preliminary feasibility studies, for the treatment of abnormal bleeding (stratified by bleeding pattern). Similar trials should be considered in subfertility.
3. RCTs should be conducted to delineate the optimal surgical approach and identify the best technologies in terms of feasibility, acceptability and effectiveness to treat common uterine pathologies, such as uterine polyps, in an outpatient setting.
4. RCTs designed to evaluate approaches to minimising pain and enhancing both recovery and acceptability of outpatient, ambulatory interventions. Environmental and procedural interventions, such as local anaesthetic, analgesic and sedative regimens, and variations in surgical technique, should be conducted.
5. Studies are needed to identify clinical factors, for example patient characteristics, anatomic, surgical and pathological indicators that are predictive of poor patient experience and adverse outcomes, including complications, with outpatient surgery. A prospective, centralised database of outpatient surgical procedures in gynaecology should be considered.

### Trial registration

This trial is registered as ISRCTN65868569.

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