NETSCC, HTA

24 November 2009

PROJECT PROTOCOL

PROJECT TITLE

Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): Systematic reviews, IPD meta-analysis and model based economic evaluation.

1. RESEARCH OBJECTIVES

- To determine the accuracy of various tests and test combinations for investigation of heavy menstrual bleeding and postmenopausal bleeding
- To determine the most cost-effective diagnostic testing strategy for the diagnosis and treatment of heavy menstrual bleeding
- To determine the most cost-effective diagnostic testing strategy for the diagnosis and treatment of postmenopausal bleeding

2. EXISTING RESEARCH

Abnormal uterine bleeding (AUB) affects women of both reproductive (pre-menopausal women) and post-reproductive (postmenopausal women) age, but the implications of diagnosis and need for treatment of abnormal uterine bleeding (AUB) are completely different according to menopausal status. Heavy menstrual bleeding (HMB) affects 1 in 5 women of reproductive age, with 5% of women aged 30-49 consulting their General Practitioner each year because of the condition and accounts for 12% of all gynaecology referrals. The number and cost of consultations and treatments impose substantial demands on health service resources[1-2] and a substantial adverse impact upon health-related quality of life (HRQL)[3-4]. Postmenopausal bleeding (PMB) is also a common clinical problem in both general practice and secondary care, hospital settings. Women are most likely to present with PMB in the sixth decade of life, where consultation rates in primary care are 14.3/1000 population[5]. Prompt referral to secondary care is recommended to exclude premalignant or malignant disease. Thus it is not surprising that abnormal patterns of uterine bleeding account for up to 50% of all gynaecological consultations in the peri- and post-menopausal years[6]. Guidelines have been produced for the diagnostic work up of women presenting with these problems[7-8], but the utility of these guidelines are limited for the following reasons.

Firstly the evidence guidance is based upon does not reflect real clinical practice because it does not take account of the accuracy of diagnostic testing in combination. This is because best evidence is limited to traditional systematic literature reviews / meta-analyses of diagnostic tests in isolation[9-16], rather than individual patient data meta-analyses which can provide data of tests used in combination[17], thereby reflecting the real clinical situation. One primary research trial from Scotland has compared three outpatient diagnostic tests (outpatient biopsy, ultrasound and hysteroscopy) for the evaluation of AUB in certain test combinations, but without regard for menopausal status. Thus, clinical inferences to influence decision making from this HTA [18] are limited. The aim of investigation of women with postmenopausal bleeding is to exclude endometrial cancer whereas it is to optimise management of benign uterine pathologies associated with AUB (i.e. selection of appropriate treatment modalities) in pre-menopausal women. The authors of this HTA

report[18] highlight this themselves by stating "…*in future research into the evaluation and management of AUB, postmenopausal women should be studied separately from premenopausal women with menstrual bleeding problems*".

Secondly, the basis of practice recommendations[7-8] takes little account of health economics because of the paucity of robust evidence examining cost-effectiveness of clinical approaches to diagnosis and subsequent treatment of AUB. Economic evidence, using decision analytical modelling, for the investigation of women with PMB for endometrial cancer has been published since the production of such guidance[19-21]. Although comprehensively and well conducted using best available data, the clinical utility of these health technology assessments are limited because they are based upon diagnostic testing in isolation i.e. taking no account of clinical practice where testing in combination is usually employed. The lack of an economic rationale to direct appropriate diagnostic work up is even starker in premenopausal women with AUB. The dearth of cost-effectiveness data in these women reflects the complexity of care pathways (i.e. the varied outpatient tests available, the range of uterine pathologies detected, the relatively recent introduction of minimally invasive and ambulatory treatments, and patient factors including co-morbidities and preferences).

Cost-effectiveness was examined in the randomised trial comparing outpatient biopsy, ultrasound and hysteroscopy alluded to above[18]. However, the primary outcome end-point defining 'effectiveness' was based upon the premise that a satisfactory diagnosis must have been reached once no further investigation had been carried out, as identified by retrospective case note review. Clearly such an indirect assumption of effective treatment, whilst expedient, is unlikely to be a reliable or valid measure of effectiveness and does not take account of patient-centred outcomes (e.g. satisfaction, reduction in bleeding, survival etc.). Moreover, as diagnostic testing generally precedes the institution of treatments, the use of this outcome measure does not account for all treatment costs when calculating cost-effectiveness. This is important, as most women with AUB have either no identifiable pathology ('dysfunctional uterine bleeding') or benign pathologies (e.g. polyps, fibroids), conditions, which are often amenable to less invasive, cheaper, and potentially outpatient treatments.

As well as economic data from effectiveness studies, an alternative approach to assessment of cost-effectiveness of diagnostic testing is to employ decision-analytic modelling. One economic evaluation of diagnostic testing in heavy menstrual bleeding (HMB) using decision analytic modelling has been published[22]. This analysis compared pelvic ultrasound, saline infusion sonography (SIS) and outpatient hysteroscopy and found a diagnostic strategy based upon initial evaluation with SIS to be the most cost-effective strategy for 'cure' of HMB. However, study weaknesses limit the validity and stability of these findings. These included problems with construction of the decision model (e.g. use of outmoded and restricted medical and surgical treatments)[23] and data assumptions employed (e.g. failure rates of testing unaccounted for, precision and validity of data sources used for test accuracy and therapeutic effectiveness). Moreover, the findings were sensitive to changes in the key assumptions limiting the robustness of clinical inferences.

So what is the most appropriate methodology to determine cost-effectiveness of diagnosis in women with AUB? Whilst randomised diagnostic trials must be

considered, the complexity and rapidly changing nature of care pathways, particularly in pre-menopausal women with AUB described above, makes the practicality of such primary research difficult. Decision analysis may overcome these obstacles, but modelling needs to be based upon rigorous data of test performance and decision trees built to reflect comprehensive up to date clinical practice. Thus we propose to answer the important questions of cost-effectiveness of diagnostic testing strategies in AUB using decision analytic models that can capture the intricacy of contemporary practice populated with accuracy data derived from high quality IPD data.

It is therefore clear that cost-effectiveness data addressing the important question of how best to investigate women with AUB is lacking. Gynaecologists are uncertain about the relative performance criteria of diagnostic tests available to them[18]. Moreover, AUB is a common condition associated with high resource use in both primary and secondary care and the morbidity and costs in terms of adverse impact on women's health related quality of life (and mortality in the case of endometrial cancer in the 10% of women with PMB) is substantial to both the sufferer, her family and society at large[1-8]. Effective treatments can only be optimally and safely employed once an accurate and timely diagnosis has been arrived at. Thus we overlook the importance of diagnostic accuracy of available testing strategies at our peril. A robust economic examination of contemporary practice is urgently required to direct practice, improve the care of these women and avoid unnecessary use of scarce resources.

2.1 Pilot work undertaken by applicants leading to the proposal

The applicants have independently (University of Birmingham and University of Amsterdam) produced the only economic analyses published in the field of investigating women presenting with AUB. Two cost-effectiveness analyses based upon economic decision analytic modelling using data derived from systematic reviews have been published for PMB[19-21] and one for women of reproductive age with HMB[22]. Whilst these analyses represent the only robust economic data available to practising gynaecologists, the limitations of the research, particularly the issue of accuracy of tests used in combination and the lack of incorporation of comprehensive, contemporary therapeutic options for AUB restrict the utility and generalisability of their findings. An HTA of two types of endometrial ablative technology for the treatment of HMB has been published[24] and the applicants are currently undertaking a rigorous HTA of endometrial ablation based on systematic quantitative reviews using individual patient data (05/45/02). Electronic databases have been compiled for treatment outcomes in abnormal uterine bleeding (Birmingham Women's Hospital, University of Birmingham) and in post-menopausal bleeding (Amsterdam Medical Centre, University of Amsterdam).

3. RESEARCH METHODS

3.1 Design

Decision analytic model based economic evaluation using individual patient data meta-analyses for producing cost-effectiveness analyses to determine the most parsimonious testing strategy for the diagnosis and treatment of abnormal uterine bleeding (both pre- and post-menopausal bleeding)

3.2 Setting

The perspective adopted is that of a UK National Health Service Hospital

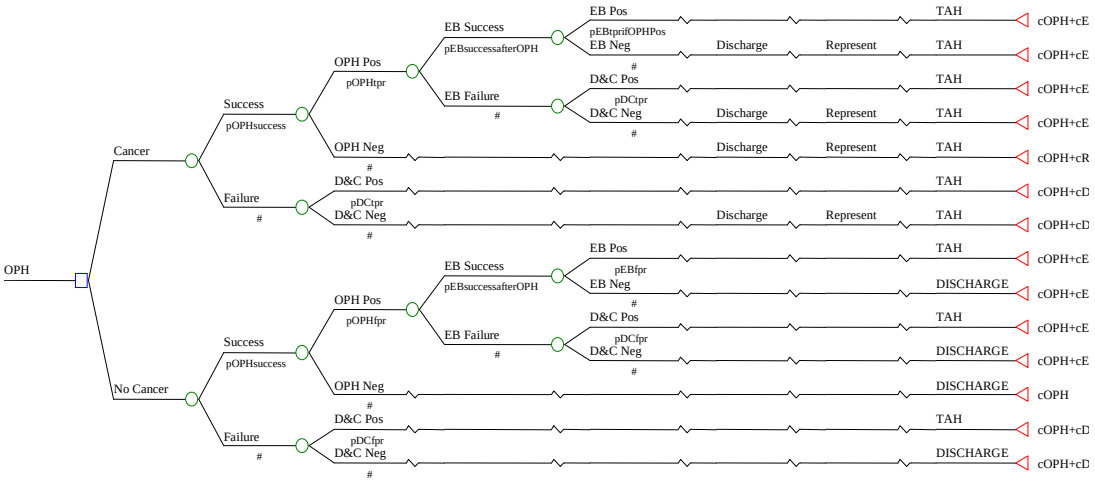
3.3 Overview

The cost-effectiveness analysis will be based on modelling the costs and outcomes of patients with AUB investigated using various diagnostic strategies. Analyses will be conducted separately according to menopausal status because the implications of genital tract bleeding are different in women of reproductive age (presenting complaint sometimes abnormal and invariably benign pathology) as compared to postmenopausal women (presenting complaint always abnormal and potential for malignant pathology). Thus in premenopausal women with AUB the clinical outcome measured will be (i) cure of symptoms and (ii) avoidance of hysterectomy whereas in postmenopausal women survival in terms of life years gained (LYG) will be the clinical outcome measured. Cost-effectiveness will therefore be assessed according to cost per case cured / cost per hysterectomy avoided in premenopausal women and cost per LYG in postmenopausal women.

3.4 Economic modelling

A decision model will be constructed to reflect current service provision. As there is no consensus regarding how best to investigate premenopausal women with HMB and women with PMB for endometrial cancer, initial investigation utilising all currently utilised tests (pelvic ultrasound, saline infusion sonography, outpatient endometrial biopsy and outpatient hysteroscopy) either alone or in combination will be included in the model. Figure 1 provides an extract from a sample model[20]. Subsequent clinical treatment pathways of women will be based upon published guidance for both HMB[7] and PMB[8,25].

Figure 1



3.4.1 Data sources and modelling assumptions for decision analysis

The initial investigation(s) used in each strategy will be assumed to take place in a 'one stop' setting (i.e. one initial consultation only with no planned follow up unless test(s) failed or abnormal results were found). It will be assumed that a consultant grade specialist will perform all diagnostic and subsequent therapeutic procedures. Expert clinical opinion will be obtained independently about decision-making conditional upon positive or negative test results (i.e. the need for any further testing or therapeutic intervention). An expert clinical panel will be convened to reach

consensus in cases of disagreement. In this manner a representative body of opinion will be obtained regarding current management pathways in the diagnosis and treatment of women of all ages with AUB.

Tests
Data estimates of test performance (feasibility and accuracy) will be derived from IPD meta-analyses for women presenting with PMB or HMB.

Treatment
Recommended treatments will be used in the model based upon existing contemporary guidance (NICE / SIGN) and where guidance is unavailable expert clinical opinion (consensus from a convened panel). Estimates of effectiveness in terms of cure rates, avoidance of hysterectomy and survival rates will be derived from sources including published literature[25] as well as unpublished prospectively collected datasets collected by the applicants (compiled for treatment outcomes in abnormal uterine bleeding (Birmingham Women's Hospital, University of Birmingham) and test combinations / treatment outcomes in post-menopausal bleeding (Amsterdam Medical Centre, University of Amsterdam). In addition, the applicants are currently undertaking a rigorous HTA of minially invasive treatments for heavy menstrual bleeding (endometrial ablation and Mirena^{TM}) based on systematic quantitative reviews using individual patient data (HTA grant 05/45/02). These data of treatment effectiveness will be used also.

3.4.2 Cost data collection
Costs will be estimated from the perspective of a United Kingdom National Health Service (NHS) hospital and from NHS data provided by the Department of Health[26-27]. The analyses will include all direct medical costs in UK pounds sterling. Data for the base case and subsequent sensitivity analyses will be obtained from local sources (Birmingham Women's Hospital data for uncomplicated procedures 2007-8) and national sources (Department of Health, National Schedule of Reference Costs for the United Kingdom 2007[26] and Unit Costs of Health and Social Care 2007/8[27]. Drug costs will be obtained from the British National Formulary 2008[28].

3.4.3 Clinical Outcomes
Baseline values of the probabilities of each test result and treatment outcome, together with associated costs will be estimated and incorporated into the decision tree. The overall cost and effectiveness for all strategies will be calculated. The cost-effectiveness of each competing diagnostic strategy will be determined by comparing costs and outcomes using cost per case cured / cost per hysterectomy avoided (premenopausal women with HMB) and cost per life year gained (postmenopausal women). Incremental cost-effectiveness ratios will then be generated using the ratio of cost compared to change in clinical outcome relative to the cheapest strategy. In this way improvements in outcome per extra pound spent can be determined.

3.4.4 Sensitivity Analyses
The robustness of the results will be explored using sensitivity analysis. These analyses will explore uncertainties in the study based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Extensive sensitivity analyses will be performed for all strategies found to be potentially cost-effective following the base case analysis. One-way analyses will be

performed over ranges of age at presentation, disease prevalence, test failure rates, estimates of diagnostic accuracy, upstaging of endometrial cancer due to delayed diagnosis (postmenopasul women only) to explore the robustness of the analytic model (Appendices 6 and 7). Probabilistic sensitivity analysis will be employed to take account of the statistical uncertainty in the data used to populate the model.

3.5 Planned inclusion and exclusion criteria

Women with abnormal uterine bleeding referred to secondary care for further investigation and management.

Inclusion criteria:

Women presenting for the first time with postmenopausal bleeding
Women presenting for the first time with heavy menstrual bleeding

Exclusion criteria:

Premenopausal women presenting with non-menstrual bleeding

3.6 Proposed outcome measures

- Cost per life year saved (women with postmenopausal bleeding)
- Cost per case cured (women with HMB and postmenopausal bleeding)
- Cost per hysterectomy avoided (women with HMB)

3.7 Statistical analysis

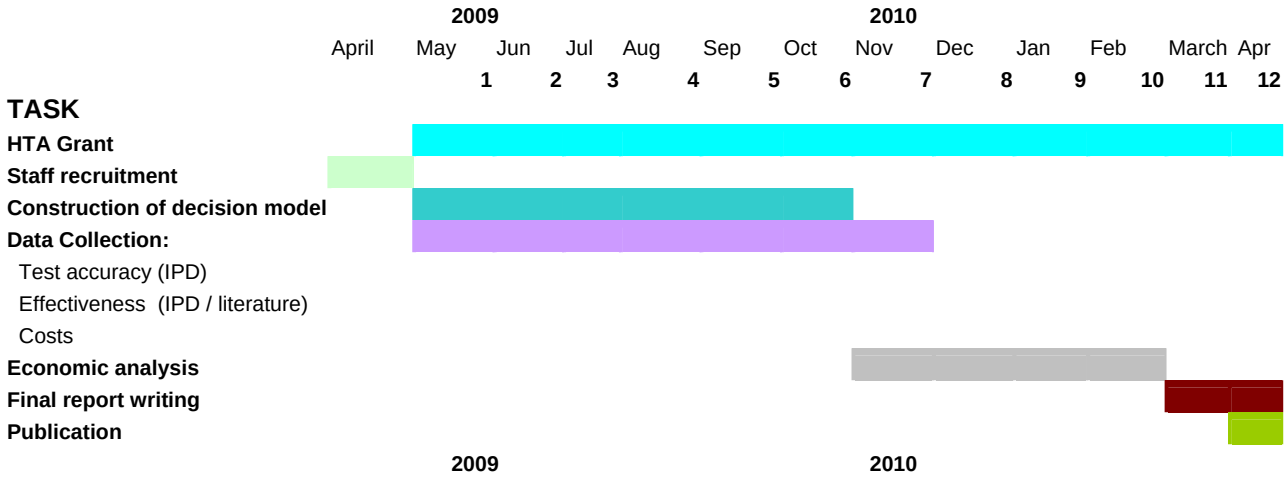
Analysis of the statistical uncertainty in the data will be incorporated within the decision model as part of the probabilistic sensitivity analysis referred to in section 3.4.4 above.

3.8 Ethical arrangements

Local ethics committee approval will be sought. As the study does not involve obtaining primary data from patients then we do not anticipate any problems from an ethical perspective.

4. PROJECT TIMETABLE AND MILESTONES

The research study will take 12 months to complete.



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