Version 1.1, 05 June 2023

Treatment options for women with heavy menstrual bleeding: A comprehensive systematic review, network meta-analysis, and health economic assessment

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Keywords: Heavy menstrual bleeding, Randomised controlled trial, Systematic Review, Prospective network meta-analysis

Version name	Date	Amendments made
HMB_NMA_Master_protocol_V1_0_9May2023.pdf	09/05/2023	Uploaded to REALMS system
HMB_NMA_Master_protocol_V1.1_05June2023.pdf	05/06/2023	1. Version control table added 2. Section 6_timelines: • specific dates replaced with month numbers (Table • updated timelines section to be consistent with project management plan 3. Acknowledged NIHR funding

1. INTRODUCTION

1.1. Rationale

Heavy menstrual bleeding (HMB) affects one in four women of reproductive age leading to significant impairment of their quality of life (1). Although the cause of HMB remains unknown in most affected women, about 50000 women in England and Wales seek specialist treatment at secondary care services annually (2), constituting approximately 20% of referrals to the National Health Service (NHS) gynaecology services (3). Around 28000 women eventually require surgery to manage their HMB (4). Several treatment options are offered for HMB including medical options (e.g., progestogen-releasing Intra-Uterine Systems (IUS), contraceptive pills, Danazol, Ulipristal acetate, nonsteroidal anti-inflammatory drugs, anti-fibrinolytic agents, gonadotropin-releasing hormone agonists) and surgical options (e.g. HMB is a chronic condition that affects otherwise healthy women at varied life stages (adolescents, pre-pregnancy, peri-menopause) adversely impacting their wellbeing and productivity in society. As such, it is important to consider women's evolving health needs (e.g., need for contraception vs the desire to get pregnant) and their treatment preferences to maximise the benefit and uptake of the varied HMB treatment options. For example, the treatment choice of women with HMB and uterine fibroids is likely to be influenced by their desire to get pregnant, thus opting for fertility-sparing treatments like hysteroscopic fibroid resection and Magnetic resonance-guided transcutaneous focussed ultrasound fibroid ablation, versus more radical treatments such as a hysterectomy or uterine artery embolization (6).

Precise evidence synthesis is therefore key to counselling affected women and informing their decision making and treatment selection process (6). Existing systematic reviews have tended to offer generic assimilation of data, and/or overviews of aggregate data from meta-analyses with head-to-head comparisons of individual treatments (7,8), potentially failing to make best use of the wealth of existing data with poor translation into clinical practice (9). Importantly, women's voices have been missing from these prior attempts to synthesize data.

With new treatments being introduced into clinical practice, as well as uncertainties and gaps in the existing recommendations in current guidelines, there is a need to re-examine the evidence to identify the most effective, acceptable and cost-effective treatments to be offered to affected women across NHS services. This is particularly relevant considering the rapid progress in surgical technology (e.g., novel endometrial ablation technology (10) and total laparoscopic hysterectomy (11)) which could play a key role in facilitating long term, reliable and safe treatments for certain women's subgroups (e.g. peri-menopause) with persistent HMB at a lower cost to the NHS (12,13). For example, NICE recommends the use of levonorgestrel-releasing intrauterine system (IUS) as the first line treatment option, reserving surgical options until medical treatments have failed or are undesirable (7). However, a recent pairwise Cochrane meta-analysis (25 Randomised Clinical Trials (RCTs), 2511 women) suggested that compared to surgery, women using IUS have less control of HMB, lower satisfaction, and more adverse events (mastalgia, weight gain, and acne) (14). Recent studies suggested reduced effectiveness for IUS in particular subgroups (e.g., women with uterine fibroids and adenomyosis) (15).

Similarly, several new pharmacological treatments are now offered to women with HMB and fibroids (e.g., Elagolix and Ulipristal acetate) which may offer more benefits, though their adoption is varied across NHS services (16). There is an apparent need for a clear, comprehensive and succinct evidence synthesis to address this uncertainty while taking into consideration the views and treatment preferences of women with HMB (17,18).

1.2. Aim and objectives

1.2.1. Aim

- To provide relevant, comprehensive, and up-to-date evidence on the clinical and cost effectiveness of available treatment options for women with HMB
- To better inform clinical recommendations and guidelines to improve outcomes for women overall, and within specific population subgroups.

1.2.2. Objectives

1. To identify all relevant randomised trials that evaluated any treatment option for HMB through comprehensive literature searches.
2. To evaluate the relative effectiveness and safety of all available treatment options for HMB overall and within key subgroups based on factors relating to the characteristics of affected women and their preferred treatment options.
4. To evaluate the cost-effectiveness and utility of identified treatment options for improving the quality adjusted life years of women with HMB within the National Health Service.
5. To produce a decision aid toolkit and overall ranking of evaluated treatments for their effectiveness and safety within specific population subgroups.

2. METHODS

2.1. Clinical effectiveness and safety

We will conduct a suite of systematic reviews of **randomised trials** with direct (pairwise) meta-analyses, network meta-analysis evaluating any treatment options for HMB compared to placebo, no intervention, or other treatment options. We define our **population** as any person of a reproductive age affected by HMB from any cause or due to unknown cause. The **interventions** will include the following categories:

a) Any hormonal treatment (including combined contraceptives, progesterone-only pills, combined vaginal ring, synthetic steroids, intra-uterine hormone releasing systems).
b) Any pharmacological non-hormonal treatment (including antifibrinolytics or haemostatic agents, anti-inflammatory agents, progesterone receptor modulator agents)
c) Surgical treatment options (including open (abdominal), vaginal or laparoscopic hysterectomy, endometrial ablation, hysteroscopic resection of fibroid, myomectomy, uterine artery embolization.

Based on the relevant clinical practice guidelines, Cochrane systematic reviews, and core outcomes sets (21–23) we identified key outcomes of importance to stakeholders.

We aim to evaluate the intervention effect primarily on the **change in menstrual blood loss** (using Pictorial blood loss assessment chart scores, or the Alkaline-Haematin method). The other outcomes of interest are the chance of post-treatment amenorrhoea, dysmenorrhoea, changes in haemoglobin, and adverse events (e.g., surgical complications or thrombosis while using contraceptive treatments). Where possible, we will aim to evaluate the effect the quality-of-life (assessed using EQ-5D, SF-36 and SF-12 questionnaires) and treatment satisfaction (assessed using dichotomous or Likert scale questionnaires).

2.1.1. Study selection

We will perform a bespoke multi-stage systematic search of the literature using the following steps:

a) **Electronic databases** (MEDLINE, EMBASE, CENTRAL): using a multi-stage search strategy combining MeSH terms and keywords using the Boolean operators AND/OR. No search filters or language restrictions will be employed.
b) **International clinical trials registries** (Clinicaltrials.gov, EU-CTR, ISRCTN): to identify any ongoing and/or recently completed trials.
c) **Grey Literature**: We will perform complementary searches in Google Scholar and Scopus to screen for potentially relevant citations in the grey literature.
d) **Hand searching**: Clinical Practice Guidelines on the management of HMB, relevant Cochrane reviews, and bibliographies of relevant articles to identify any missed citations.

In order to eliminate duplication of efforts and streamline the extraction of relevant data and maximise the use of published evidence for the studies published before 2019 we will use the summaries available from the previous evidence synthesis (Clinical Practice Guidelines and Cochrane Reviews on HMB). Consequently, our literature search will cover a period from **1 January 2019 and will be updated quarterly until** 6 months before the end of the project (**June 2024**). We will exclude quasi and non-randomised studies, reviews, and animal studies. Articles in non-English languages will be translated.

2.1.2. Data collection

We will screen relevant citations using the COVIDENCE systematic review software, using Cochrane methodology to select trials. We will map out all the selection steps through a study flow diagram. For all retrieved trials, we will record whether they match our eligibility criteria and the reasons for exclusion. Two of the review authors will extract data, including from multiple intervention arms and subgroups from each study using a bespoke form and upload data onto COVIDENCE database.

Following a collaborative approach to meta-analysis (20,46,47), we will maintain open communication with trial investigators throughout, to facilitate thorough data checking and querying and to ensure that data on all outcomes and subgroups of importance are collected for each trial, even when not directly available from trial reports. This approach has facilitated rapid evaluation of the effects of various treatments, overall and in relevant subgroups (46,47).

2.1.3. Risk of bias assessment

We will assess the risk of bias for each study using the criteria of the Cochrane Risk of Bias 2 tool, outlined in the Cochrane Handbook for Systematic Reviews of Interventions (48). Risk of bias will be assessed in the following specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding (low risk if at least double blinded), incomplete

outcome data (low risk of bias if less than 10% missing data), selective reporting, and other sources of bias, such as conflict of interest and method of measuring blood loss (objective, subjective or not specified)(48). Each domain will be assigned a judgment relating to the risk of bias for that study: low risk, high risk, and unclear, except for blinding where an intermediate risk will be assigned if at least the outcome assessor was blinded.
We will assess the trustworthiness of identified studies using the Cochrane Pregnancy and Childbirth Group screening tool (49). Where measures of quality are unclear, we will work proactively with relevant trialists to gain additional information and refine the risk of bias assessment of included studies (20).

2.1.4. Pair-wise meta-analysis

We will assess the potential for additional direct (pairwise), indirect, and mixed (network) evidence synthesis across all treatment comparisons and the network geometry within prespecified populations, subgroups, and outcomes. We will evaluate statistical heterogeneity and the global network consistency using the design-by-treatment model. We will also investigate inconsistency by comparing the direct and indirect evidence within the network using the node-splitting approach. We will test for treatment effect modification (covariate interaction) using a "within-trial framework" (19). That is, we will test for subgroup differences within each trial and then pool across trials, to avoid the risk of aggregation bias. Where significant interaction effects are found, we will proceed to estimate subgroup specific pooled treatment effects consistent with the interaction effects ("floating subgroup-specific treatment effects") (19). We will assess the certainty of evidence using the Confidence In Network Meta Analysis (CINeMA) approach (50). All analyses will be performed using Stata V.17 (StataCorp).

For dichotomous data, the main outcome is likely to be the number of patients experiencing an improvement in menstrual bleeding. Since only randomised controlled trials are eligible, confounding factors may be assumed to be balanced across arms, so that we may synthesise data appropriately using raw count data. We will compare the statistical fit of models that fit log-odds ratios and log relative risk estimates for the primary outcomes. The best-fitting effect measures for the primary outcomes will be used for all primary and secondary outcomes. If there is no statistical reason to prefer one over the other, we will use estimates of relative risk for ease of interpretation. Reported results will be the posterior median relative effect estimate with 95% confidence intervals.

For continuous data, we will report the posterior mean difference with 95% confidence intervals. Where the target parameter is the effect of treatment on the change in continuous variable between baseline and follow-up, we will check whether the trial methodology correctly accounted for the within patient correlation between baseline and follow-up estimates. If not, we will apply an approximate correction using methods described in the Cochrane Handbook (48).

The main continuous outcome is likely to be the mean (with standard deviation) improvement in menstrual bleeding. By communicating with trial authors, we will aim to collect mean improvement data using a consistent definition across trials. If this is not possible, disparate continuous outcome measures would be pooled after applying standardization, and pairwise results presented overall and by trial subgroups defined by the underlying outcome measure. Since only randomised

controlled trials are eligible, confounding factors may be assumed to be balanced across arms, so that we may synthesise data appropriately using raw means and standard deviations.

As described under "Data collection", via open communication with trial authors we aim to limit missing data as far as possible and carry out analyses on an intention-to-treat basis, i.e., we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether they received the allocated intervention. For included studies, we will note levels of attrition and if necessary, conduct sensitivity analysis.

For our primary analysis, we will analyse the available data without imputation. However, if there is substantial missing data for an analysis of specific clinical interest, we may conduct sensitivity analyses where data are imputed using methods described in the Cochrane Handbook. (48)

2.1.5. Subgroup and sensitivity analyses

Subgroup analysis and investigation of heterogeneity: We will work to refine and prioritise comparison subgroups with relevant stakeholders and lay patient representatives. Where possible, we will explore the varied treatment effect across the following subgroup categories:

- Treatment characteristics: class (Medical vs Surgical), type (e.g., Hormonal vs non-Hormonal), mode of delivery (oral, vaginal, injection), dose.
- Participant characteristics: age group (adolescent, pre-pregnancy, perimenopausal), prior treatment (naïve, pre-treated), desire for pregnancy, uterine anomaly (e.g., Fibroids, Adenomyosis).

If we identify substantial heterogeneity in the pairwise analysis of the main outcome, we will investigate it using trial-level subgroup analyses and sensitivity analyses. For patient-level subgroups, we will test for differences in effect (covariate interactions) within each trial and then pool these across trials, and a related the "within-trial framework" (51) to estimate subgroup-specific pooled treatment effects.

Sensitivity analyses will be conducted according to the quality of the studies, trial publication date (before and after 2000), trial size (excluding small studies, in recognition of the greater likelihood for small studies than large or multi-centre studies to suffer publication bias) and whether an objective method of outcome assessment was employed. On the quality assessment, studies will be labelled to have a low, medium, or high risk of bias as per the Cochrane Risk of Bias 2 tool. (48) We consider protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses because protocol publication only became widespread in recent years (post 2000). Sensitivity analyses will be restricted to the primary outcome.

2.1.6. Network meta-analysis

If sufficient data are available, and assuming pairwise analyses do not suggest that trial estimates should not be combined (e.g., very large unexplained heterogeneity), then we will carry out a network meta-analysis by fitting consistency random-effects models for the primary outcome assuming the same between-study variance. With pairwise meta-analysis, fixed- and random-effects methods may both be reasonably justified. However, with a network of multiple contrasts, the fixed-effect assumption becomes less justifiable, and a random-effect network model (assuming the same between-study variance across all contrasts) is the 'standard' approach.

For relative risk, the model will be based upon log-ratio estimates and standard errors. For continuous measures, the model will be based upon mean differences and standard errors. Between-studies heterogeneity will be assessed by consideration of the between-study variance parameter. We will also fit inconsistency models and determine sources of inconsistency within the network (if present) using loop splitting. As a sensitivity analysis, we will also fit a model allowing a different between-study variance parameter per contrast. For all secondary outcomes including side effects we will fit the same model that was chosen for the primary outcomes. For continuous variables we will fit linear mixed effect regression models as described above.

If there is evidence that the inconsistency model has better predictive properties, then we will report this and carefully consider whether it is appropriate to conduct a network meta-analysis (bearing in mind that chance results are possible given the number of secondary outcomes). If poor fit is detected in both the consistency and inconsistency models, then we will assess the fit of a model that allows the between studies variance to be different for each contrast. In addition, individual contributions to the residual deviance from each study will be examined to identify outliers.

2.1.7. Presentation of the findings

In addition to pooled effect estimates we will calculate the probability, conditional on the model and the parameterisation for vague prior beliefs, that each treatment is the most clinically effective. We will also calculate the probability that each treatment holds each rank and the cumulative probabilities that each treatment is of a specific rank or higher for all ranks where rank indexes from one to the number of treatments. Between studies heterogeneity will be assessed by consideration of the between study variance parameter and assessment of model fit of the fixed and random effects models. We will use the GRADE (52) or alternative approach (53) to rate the certainty of the evidence for the overall effect of across the included trials for the primary outcome.

2.2. Health economics

2.2.1. Economic perspective and data collection

We will evaluate the costs and health benefits associated with using each treatment option and their combinations in the NHS by reporting on the quality-adjusted life years (QALYs) reflecting a cost-utility analysis. We will report on the net monetary benefit (NMB) for a range of cost-effectiveness thresholds for each treatment. Uncertainty will be explored using deterministic and probabilistic sensitivity analysis as per established methodology for time-horizon, cost perspective, calculating QALYs and discounting.

The choice for the most effective treatment for HMB should incorporate both the patient preference (e.g., medical vs surgical), risk profile, and potential cost implication in the health care sector. For example, undergoing a total hysterectomy would offer the maximum effectiveness in stopping HMB, however, this option won't be favoured by nulliparous younger women planning for pregnancy and would certainly come with increased health cost in the short term.

Furthermore, the potential for cost saving that might be implied by some short-term medical treatment (e.g., hormone-releasing intrauterine systems) might be offset by additional costs of repeated failed treatment, prolonged morbidity and adverse impact on quality-of-life measures in the long-term.

A model-based economic analysis is ideally suited to collate the appropriate evidence from a range of sources and explore alternative scenarios and the uncertainty surrounding a range of possible results including subgroup analysis. Thus, if available data allow, the economic evaluation will be based on an outcome of cost per QALY and/or cost per morbidity free survival post-event (this latter is an outcome we have used in our previous analysis due to the paucity of quality-of-life data).

We will also include analyses based on a range of other outcomes including treatment satisfaction, adverse events, days missed of work/school and other outcomes identified as important by women with evidence in the literature. The analysis will adopt a health service perspective. Therefore, data collection required for the model-based economic evaluation will include:

- Total treatment costs (based on dose, route and regimen of administration, other resource use and costs associated with reducing HMB including staff involved in the intervention and duration of their involvement).
- Specialist equipment used in the procedure (e.g., total laparoscopic hysterectomy).
- Knock-on costs associated with additional and failed treatments including length of inpatient stay, level of care received during inpatient stay and readmission to hospital.
- Satisfaction and quality of life outcomes associated with HMB.

Once the clinical evidence has been synthesised to provide the relative effectiveness and side-effects with the ranking of each treatment for resolution of HMB, the relevant studies will be examined for their data on costs and resource use. We will also search the wider literature for costs of event data. These data will be subjected to relevant quality criteria including GRADE and guidance set out by NICE Decision Support Unit and The Professional Society for Health Economics and Outcomes Research (ISPOR). Additional cost data will be available from other sources such as the National Schedule for Reference Costs and the British National Formulary. If necessary, primary cost and resource data will be collected from University College London Hospitals to complete any gaps in the information required for the modelling process.

The evidence found in the systematic reviews will provide most of the parameters required to carry out the model-based economic evaluations of evaluated treatment options. Additional searches as part of a wider pragmatic review will be undertaken to help structure and populate the decision model. We will consult relevant stakeholders to identify the model questions. These questions may relate to preference-based health related quality of life associated with HMB or analogous conditions; costs and duration associated with inpatient stay or side-effects of the treatments or morbidity as a result of treatment for HMB. Information to answer these questions will be provided by focused searching of appropriate databases, including reference cost databases, statistical sources and other sources of relevant information.

2.2.2. Economic model and analysis

We will develop a decision model using data from the systematic review considering the structure of women's health services in the NHS. The model will be developed in consensus with relevant stakeholders (e.g., clinicians and patient representatives) to reflect the current patient journey to access treatments. We will search the literature for evidence of existing model-based analyses for this clinical area and use these to inform our model structure as far as appropriate. Given the relatively short-term impact of the intervention and treatment, the most appropriate model

structure will be a simple decision tree, although we will explore other model structures including Markov models.

We will leverage data from our evidence synthesis to construct the model based on the cost per QALY. However, experience from similar research suggests that appropriate data on QALY outcomes are likely to be limited. As such, we will not attempt to model a whole lifetime and we will look for data and information that are related specifically to post-treatment outcomes with no specific time limit. Where we are not able to find suitable parameters from the published sources to populate the model, we will make assumptions based on expert opinion and after the consultation with relevant stakeholders. A modelling framework is ideally suited to demonstrate and explore the importance of the inherent uncertainty: we will conduct and report the results of deterministic and probabilistic sensitivity analysis. An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from the current treatment to resolve HMB to an alternative treatment. Net-monetary benefit (QALYS multiplied by a cost effectiveness threshold) will be reported to allow comparisons across a range of treatment options. Costs and benefits will be discounted in line with NICE guidance.

2.2.3. Presentation of economic results and sensitivity analysis:

The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties for a range of cost-effectiveness thresholds. Deterministic sensitivity analyses will be used to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used and to consider the broader issue of the generalisability of the results.

2.2.4. Discrete Choice Experiment

We aim to produce a health economic model that reflects the true health needs of women with HMB and incorporates their treatment preferences to inform health policy. Given the evolving health needs and priorities of women across different life stages, it is not clear if QALYs would sufficiently capture the outcomes of interest for women being treated for HMB.

As a result, we will first conduct a few focus groups (n= 10-20 lay patient representatives) to determine the key outcomes of interest and treatment attributes for women with HMB. These focus groups will be run in partnership with our PPI-co applicants to ensure inclusive and representative sampling for a range of different ages, ethnicities and conditions.

We will then use the treatment rankings from our evidence synthesis and the patient input from the focus groups to construct treatment choice sets within a Discrete Choice Experiment that would help us to model the treatment preferences of women with HMB. We aim to recruit 200-500 lay patient representatives (depending on the number of evaluated choices) who will be recruited over social media and key contracts of our lay collaborators (Katie's Team and the Co-Production Collective). We will internally pilot the Discrete Choice Experiment within our lay collaborators' membership to ensure the choice sets are understood by a lay audience and hold face and content validity. Participants will be asked to choose from treatment choice sets (each including scenario A or B) and select their preferred option. This task will be repeated by varying the values for the key outcomes of interests. Participants' responses will be analysed using methods of increasing complexity to determine which variables best explain treatment preferences. We will seek input from our lay patient representatives to assess the feasibility of including a cost variable that would allow us to

calculate willingness to pay for different treatment outcomes. The results and final weightings of the Discrete Choice Experiment will be then incorporated to inform the design and decision of the planned model.

3. Project management

The project will be managed within the framework of the MRC clinical trials unit - UCL which will provide access to the required infrastructure, quality management, and data hosting services. The project co-Cis (BHA and CV) will hold joint responsibility for overseeing the conduct and delivery of the project outputs as per the scheduled activities. The Co-CIs will chair regular team meetings (in person and virtual) and submit regular progress reports to the funder. A dedicated research fellow will be responsible for day-to-day project activities working under the supervision of (ER) and (BHA).

A Project Steering Committee with an independent chair and lay patient representatives (selected from the membership of Katie's Team, the Co-Production Collective, and other relevant charities and lay service user groups) will be constituted to govern and monitor the project conduct. The Committee will have a specific advisory role to ensure sufficient representation of lay service users and other relevant stakeholders as per the planned PPIE strategy.

We will adopt an Agile Project Management Methodology to drive efficiency and minimize tasks interdependency. Where possible we will use cloud-based software (e.g., COVIDENCE) and share regular task e-updates to set short and long-term delivery targets for team members. E-communication software (e.g., Slack and ASANA) will be used to share precise asynchronous updates and tasks with team members. Risk analysis and contingency planning will be performed by the Co-CIs quarterly in view of reported progress and in consultation with the Project Steering Committee. Regular progress reports capturing key performance indicators, contingency planning, and forecasted activities will be submitted to the funder at set milestones.

4. Ethics

The planned evidence synthesis is exempt from NHS REC approval as s a secondary research project. We plan to involve volunteering lay patient representatives who are not under active treatment. We will not collect personal identifiable data and we will seek HRA approval where relevant (e.g., Discrete Choice Experiment). We will ensure all research activities are in line with the principles of GDPR, GCP and the Department of Health Research Framework.

5. Dissemination plan

The research question is inherently of high impact given the expressed institutional interest in this health topic from NICE, Royal College of Obstetricians and Gynaecologists, the Government initiative for women's health, several charities and lay service user groups. We plan to disseminate the project outputs across the following mediums:

Conferences: The findings will be disseminated among health professionals via oral and poster presentations at the annual conferences of the Royal College of Obstetricians and Gynaecologists, Royal College of General Physicians, British Fertility Society, British Society for Gynaecological

Endoscopy, British Society for Paediatric and Adolescent Gynaecology, The European Society of Human Reproduction and Embryology, European board & college of obstetrics and gynaecology, and the International Federation of Gynecology and Obstetrics (FIGO) conference. We aim also to present at lay conferences dedicated for women's health in the UK and abroad to raise awareness on the issue of HMB and available treatment options.

Peer-reviewed publications: We aim to publish in high impact peer-reviewed journals and an HTA monograph detailing the effectiveness, cost-effectiveness and side-effect profile of each HMB treatment option. We will disseminate the completed paper to the Department of Health, the NICE guideline development writing committee, the Scientific Advisory Committees of the relevant Royal Colleges and professional societies (e.g., British Fertility Society and the British Society for Gynaecological Endoscopy).

Protocol registration: The master research protocol will be registered prospectively with OSF and protocols for individual clinical questions with PROSPERO. We will also publish the master protocol under Open Access policy in a peer-reviewed journal.

Guidelines: We will communicate our findings with NICE to inform further updates of their HMB guideline (7). We aim to produce a decision toolkit and evidence-based rank-o-gram to aid health professionals and patients in choosing the most appropriate treatment options. Where relevant, we will work with relevant professional societies (e.g., British Fertility Society and The British Society for Paediatric and Adolescent Gynaecology) to aid the production of relevant evidence-based guidelines (e.g., management of fibroids, and HMB in adolescents).

Other copyright: We aim to produce a decision toolkit and evidence-based rank-o-gram to aid both health professionals and patients in choosing the most appropriate treatment options. We will make this toolkit freely available online under creative commons license.

Cochrane reviews: We will continue our collaboration with the Cochrane Gynaecology and Fertility Group to maximise impact and ensure continued knowledge generation beyond the lifetime of this proposal. We will share data summaries to facilitate the update of existing reviews and the commissioning of new reviews where needed.

Media outputs: We will produce lay media outputs to engage wider community focusing on patients and lay service users such as lay press releases, blog posts, Tweets, short videos, and infographics.

6. Timelines

We forecast a total project duration of 18 months to execute the following steps:

Activity	Time
• Research fellow is appointed, the project master protocol is finalised and uploaded to OSF. • First suits of protocols for individual research questions registered on PROSPERO. • The first update of the literature search is completed, and the findings are migrated to COVIDENCE database	1-3
• Completion of data extraction/collection and study risk of bias assessment. • Correspondence with primary trials authors for additional outcomes and subgroups information.	2-10

• Health economic modelling and literature retrieval initiated.	
• Data cleaning and credibility check. • Initiate statistical analysis. • Health economic data extraction completed. • Focus groups and Discrete Choice Experiment underway.	9-11
• Statistical analysis finalised, and the final economic modelling completed.	12-16
• Write up and dissemination of manuscripts and the final report.	13-18

7. Acknowledgements

This study is funded by the NIHR Health Technology Assessment Programme (NIHR 153187). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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