HEALTH

Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding

A multicentre randomised controlled trial comparing laparoscopic supra-cervical hysterectomy with second generation endometrial ablation for the treatment of heavy menstrual bleeding.

PROTOCOL

A UK Collaborative Study funded by the
National Institute for Health Research
[Health Technology Assessment (HTA) Programme]
Project Number 12/35/23

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NHS
National Institute for Health Research

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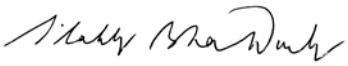
Signature

The CIs agrees to abide by this protocol

Siladitya Bhattacharya 

Date: 01 December 2016

Kevin Cooper 

Date: 01 December 2016

VERSION HISTORY

Amendment No.	Protocol Version No.	Description of Changes (*incl. Author(s) of changes*)	Date Effective
	Version 1	New Document	never used
	Version 1.1	Following initial REC review, added previous endometrial ablation to the exclusion criteria	6/1/14
AM01	Version 1.2	Neil Scott replaced Jonathan Cook as a grant holder. Removed size of uterine cavity and menstrual pain from minimisation criteria. Corrections to flow Diagram to; add baseline text box, SF-12 at 12 mths and delete acceptability of procedure at 12mths, all in accordance with 3.3.4 and Table1. Correction to Funder's title and programme details Addition names of TSC and DMC members	Approved 15/04/14
AM02	Version 1.3	Flow diagram and S3.2.2 - Exclusion criteria 'submucous fibroids distorting the uterine cavity' corrected to read; 'submucous fibroids >3cm distorting the uterine cavity'	Approved 24/04/14
AM03	Version1.4	Insert study office number Change contact details Dr KG Cooper Delete Hilary Denyer as member of TSC and replace with Isobel Montgomery Delete reference to Sexual Activity Questionnaire (SAQ) from text, Table 1, Flow chart and Abbreviations list. Included in error. Summary, S3 and S3.2, Flow diagram. Delete references to failed medical treatment as this is not part of inclusion criteria. Replace with 'eligible for endometrial ablation' consistent with inclusion criteria. Clarify timepoints for follow up as Baseline, day 1-14 after surgery, 6 weeks after surgery, 6 months after surgery and 15 months after randomisation, throughout document. S3. Insertion 'non-blinded' S3.1. Delete reference 'experimental technique' and	Approved 23/06/14

		‘standard technique’ S3.1.1. Correction title ‘Laparoscopic supracervical hysterectomy’ S3.1.1. Clarification of culdotomy as an alternative to morcellation in LASH. S3.2.2 & Flow Diagram. Exclusion criterion - ‘abnormal cytology’ added S3.2.2 & Flow Diagram. Exclusion criterion- Submucosal fibroids >3cm distorting the uterine cavity’ modified to ‘any fibroids >3cm’. S3.3.2. Delete words ‘the standard technique of’ preceding EA. S4.1. Addition bladder injury and voiding dysfunction to expected adverse events. S7.2. Insertion word ‘monthly’ to sentence ‘Recruitment at all sites is projected to be 50% of the projected total in the first month…’ S8. Add reference to separate statistical analysis plan. S8.1. Insert ‘presence or absence of fibroids’ to subgroup analysis. S17. Add TSC to approvals to be sought for satellite studies. S13. Quality Assurance, deletion duplicated text. S13. Addition ‘proportional’ in relation to monitoring. Corrections to grammar, spelling; P13, 16, 19, 23, 24.	
AM7-1	Version 1.5	S4.1, Addition of expected adverse events; Admission HTU/ITU, emergency hysterectomy, laparotomy, port site hernia, blood transfusion.	Approved 02/04/15
AM09	Version 1.6	S4.1, Addition of expected adverse events; Bowel Injury, ureteric injury	Approved 13/10/2015
AM10	Version 1.7	P5 correction of Protocol Version History	Approved 12/01/2016
AM11	Version 1.8	Correction to referencing throughout and addition of text message contact with participants (section 3.3.4)	Approved 22/07/2016

AM12	Version 1.9	Amendment to the recruitment period and end date of the trial (extended by 12 months)	

TABLE OF CONTENTS

PROTOCOL SUMMARY

Question addressed	Is laparoscopic supracervical hysterectomy (LASH) superior to second generation endometrial ablation (EA) for the treatment of heavy menstrual bleeding (HMB) in terms of clinical and cost effectiveness?
Considered for entry	Women < 50 years of age, with heavy menstrual bleeding (HMB) who are eligible for endometrial ablation.
Populations	Women presenting in secondary care with HMB for whom surgery is indicated.
Study entry	Eligible and consenting women.
Interventions	1. Laparoscopic supracervical hysterectomy (LASH). 2. Second generation endometrial ablation technology (EA) including thermal balloon ablation (Thermachoice and Cavaterm), or radiofrequency bipolar, Novasure® (Hologic Inc.).
Outcome assessment	All women who consent – a diary of pain symptoms at day 1-14 after surgery, postal questionnaires at 6-weeks and 6 months after the date of their surgery and at 15 months after the date of randomisation. Health care utilisation questions at 6-weeks and 6 months after surgery and at 15 months after randomisation.
Co-ordination	**Local**: by local lead Gynaecologist and Research Nurse. **Central**: by Study Office in Aberdeen (Telephone 01224 438163). **Overall**: by the Project Management Group, and overseen by the Steering Committee and the Data Monitoring Committee.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
AUC	Area under the curve
BNF	British National Formulary
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
EA	Endometrial Ablation
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HEALTH	Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding
HMB	Heavy menstrual Bleeding
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
LASH	Laparoscopic supra-cervical hysterectomy
LNG IUS	Levonorgestrel-intra uterine system
MMAS	Menorrhagia Mulit-Attribute QoL Scale
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NICE	National Institute for Health and Care Excellence
NIHR	National Institute Health Research
NRES	National Research Ethics Service
NRS	Numerical Rating Scale
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
PQ	Participant Questionnaire
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UK	United Kingdom

UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

TRIAL PERSONNEL

Chief Investigators

1 Siladitya Bhattacharya (Head of Division of Applied Health Sciences and Director Institute of Applied Health Sciences)

2 Kevin Cooper (Consultant Gynaecologist)

Grant Holders

Justin Clark (Consultant Obstetrician and Gynaecologist)

Jed Hawe (Consultant Obstetrician and Gynaecologist)

Kevin Phillips (Consultant Obstetrician and Gynaecologist)

Robert Hawthorne (Consultant Gynaecologist)

John Norrie (CHaRT Director)

Neil Scott (Methodologist/Statistician)

Graham Scotland (Health Economist)

Kirsty McCormack (CHaRT Research Manager)

Angela Hyde (Vice Chair RCOG Women's Network)

Project Management Group (PMG)

This group is comprised of the grant holders along with representatives from the HEALTH central study team:

1	Trial Manager	5	Trial statistician
2	Data co-ordinator	6	Trial health economist
3	Senior Trial Manager	7	Trial programmer
4	Senior IT Manager	8	Quality Assurance Manager

Trial Steering Committee (TSC) Members

This committee comprises of <<x>> independent members along with the Co-Chief Investigators (Siladitya Bhattacharya and Kevin Cooper). The other HEALTH grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Independent TSC Members

1	Professor Henry Kitchener	3	**Barbara Farrell**
2	Patrick Chien	4	Isobel Montgomery

Data Monitoring Committee (DMC) Members

This committee is comprised of <<x>> independent members (including an independent statistician) and the CHaRT statistician. The CIs or another trial member can contribute to the open session as appropriate.

1 Professor Jane Norman

2 Professor Peter O'Donovan

3 Mr Andy Vail

Trial Office Team

This team comprises of the CI, Aberdeen-based grant holders and central office team members

1. INTRODUCTION

1.1 Background

Heavy menstrual bleeding (HMB) is a common problem affecting approximately 1.5 million women in England and Wales. It accounts for a fifth of all gynaecology outpatient referrals and has a major impact on women's physical, emotional, social and material quality of life. The condition is initially treated in primary care =either by means of oral medication or insertion of the levonorgestrel-intra uterine system (Mirena®). If medical treatment fails, surgical treatment can be offered, either in the form of endometrial ablation (EA) which destroys the lining of the cavity of the uterus (endometrium), or hysterectomy i.e. surgical removal of the uterus. However, neither medical treatment nor EA can guarantee complete resolution of symptoms and up to 59% of women on oral drugs[1] and 13.5% of those using the levonorgestrel-intra uterine system (Mirena®)[2] require surgery within two years, while 19% of women treated by EA go on to have a hysterectomy for relief of their symptoms.[3]

1.2 Scale of the problem in the UK and use of NHS resources

Hospital Episode Statistics data indicate that a total of 136,921 hysterectomies and 128,434 endometrial ablations were performed in England and Wales for HMB between April 1997 and December 2009.[4] EA is commonly performed at the present time by means of second generation or non-hysteroscopic procedures including thermal balloon EA (Thermachoice and Cavaterm) and Novasure® (Hologic Inc).

1.3 Evidence explaining why this research is needed now

The NICE guideline on HMB recommends both EA as well as hysterectomy as options for women with HMB resistant to medical treatment[5] but a significant minority of women treated with EA are likely to need further EA or hysterectomy. A recent individual patient data meta-analysis[6] of results from randomised trials has shown that that, despite the greater invasiveness, longer hospital stay and prolonged recovery associated with conventional hysterectomy (removal of the uterus and the cervix), fewer women are dissatisfied with it in comparison with EA. Additionally, a cost effectiveness model based on these data also favouredhysterectomy.[7] An HTA evidence synthesis report[8] showed that a quarter of all women who undergo EA will require subsequent gynaecological surgery, with just under a fifth requiring hysterectomy. These findings, which are consistent with those of a relevant Cochrane review[9], suggest that the optimal surgical treatment for HMB unresponsive to medical treatment may well be hysterectomy but its effectiveness needs to be balanced against its invasive nature and increased short and long term morbidity.[3]

Unlike conventional hysterectomy, the more recent approach of **laparoscopic supra-cervical hysterectomy** (LASH) removes the body of the uterus which is primarily responsible for menstrual bleeding, but conserves the cervix and the uterosacral ligament complex. It is minimally invasive, quick, relatively easy to learn and associated with low risk of complications, short hospital stay (under 24 hours) and rapid recovery time[10,11] and could potentially provide the benefits of a conventional hysterectomy without its morbidity and prolonged recovery time.

Before this technique is incorporated into routine clinical practice, it is important that it is subjected to robust evaluation. Authors of two small randomised trials comparing LASH with a first generation EA - endometrial resection[11] or second generation EA - thermal balloon[10] suggest that laparoscopic supra-cervical hysterectomy could lead to a better quality of life profile, but have emphasised the need for larger evaluative studies to confirm this – a view endorsed by the relevant Cochrane and HTA reviews.

The last decade has seen widespread use of laparoscopic techniques in gynaecology due to increased familiarity with the procedures, more sophisticated instruments, better training and greater laparoscopic surgical skill. As a result of this, LASH could be delivered by most general gynaecologists with minimal morbidity to women who are currently being treated with EA. Advances in peri-operative care also means that, unlike conventional hysterectomy, hospital stay in women treated by this procedure may not be any longer than in those receiving EA.

HEALTH (Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding) is a multi-centre randomised controlled trial (RCT) comparing supra-cervical laparoscopic hysterectomy with second generation endometrial ablation (the current first line surgical treatment for HMB) in terms of clinical and cost effectiveness. The trial is relevant and timely, as a robust evaluation of this new surgical option will provide much needed high quality evidence to underpin any decision to offer it as a preferred treatment.

2. STUDY OBJECTIVES

The primary aim of this study is to compare the clinical and cost effectiveness of laparoscopic supra-cervical hysterectomy (LASH) with second generation endometrial ablation (EA) in women with heavy menstrual bleeding (HMB).

The **primary objective** is to compare a) condition-specific quality of life (QoL), measured using the Menorrhagia Multi-Attribute QoL Scale (MMAS), at 15 months after randomisation, and b) patient reported satisfaction measured on a six point Likert scale (from totally satisfied to totally dissatisfied). The corresponding economic objective is to estimate the incremental cost per QALY gained for LASH versus EA at 15 months after randomisation.

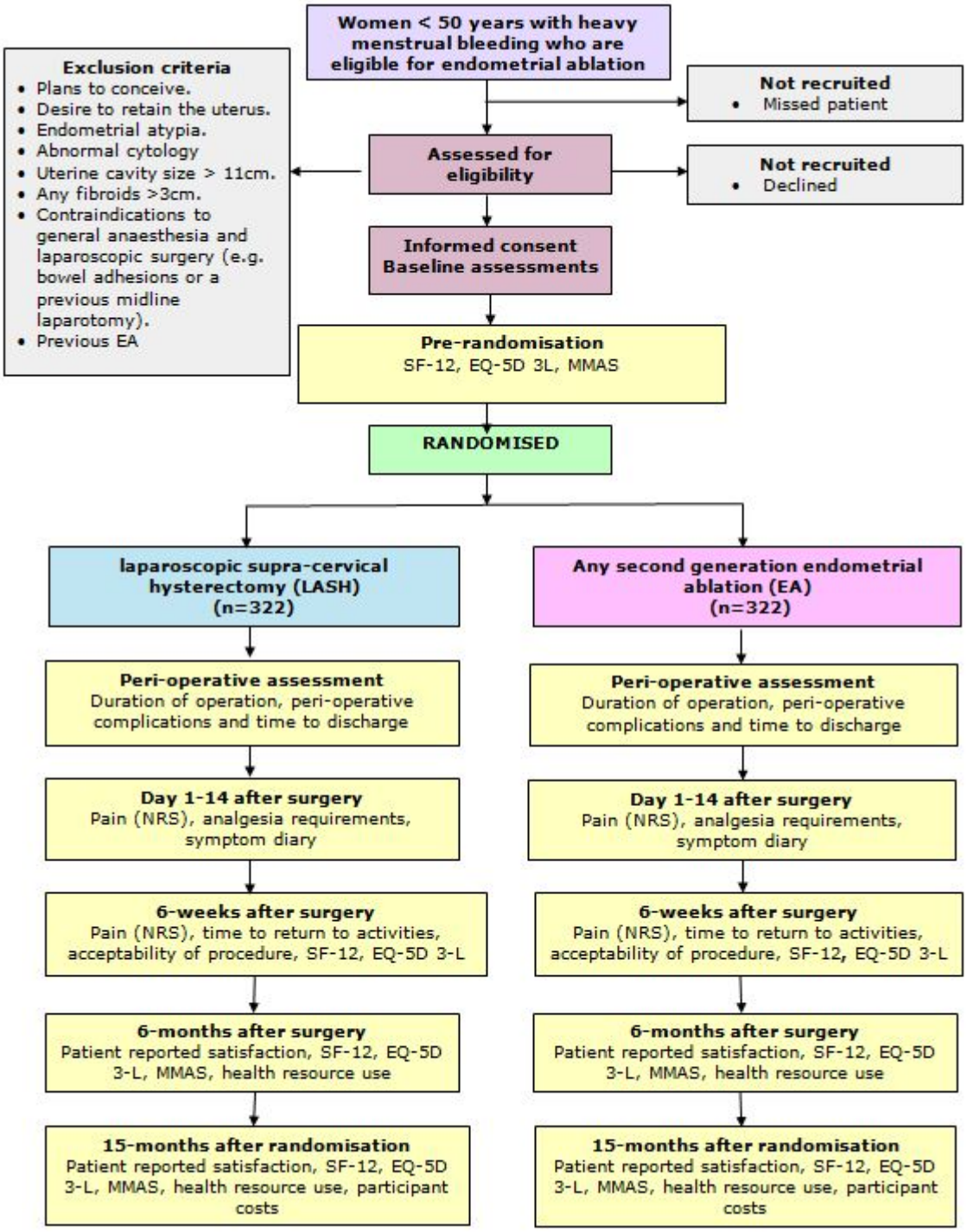
The **secondary objectives** are to compare the above in terms of MMAS and patient satisfaction at 6 months after surgery, other patient reported outcomes, complications, recovery details, further gynaecological surgery, and modelled long-term cost-effectiveness.

The hypothesis being tested is that laparoscopic supra-cervical hysterectomy is superior to second generation endometrial ablation for the treatment of HMB in terms of patient satisfaction, QoL and costs.

3. STUDY DESIGN

The study is a multicentre randomised controlled trial (RCT) of alternative surgical treatments for women with HMB. The trial structure is shown in Figure 1 (Flow Diagram). The rationale for our proposed trial design reflects the uncertainties in the evidence base in this clinical area. Current evidence suggests that endometrial ablation (EA) is a successful treatment in the short term, but around 20% of women who fail to benefit from this procedure will need further treatment such as repeat ablation or hysterectomy, and it is important to address the impact of these events on relative cost-effectiveness. Conventional hysterectomy (where the cervix is removed along with the body of the uterus through an open procedure) is a more definitive treatment - but is also potentially more morbid, with a longer post-operative recovery time. Laparoscopic supra-cervical hysterectomy (LASH) offers the permanence of a conventional hysterectomy by means of a less invasive procedure with a quick recovery time.

Figure 1: Flow Diagram



3.1 Intervention to be evaluated

This protocol addresses the comparison of two surgical operations for HMB; LASH and EA. The surgical procedures have been agreed and standardised by consensus within the research team and recruiting gynaecologists. EA will be performed using second generation techniques under either local or general anaesthetic.

3.1.1 Laparoscopic supracervical hysterectomy (LASH)

LASH involves removal of the upper part of the uterus or the body by means of keyhole surgery facilitated by use of morcellation or culdotomy to remove the uterine corpus. The uterine body contains the endometrial cavity lined with tissue which undergoes cyclic growth and shedding

each month thus causing menstrual bleeding. Increased access to specialised laparoscopic equipment and training means that LASH is quick and relatively easy to learn. It is associated with low morbidity, short hospital stay (under 24 hours) and rapid recovery time. Unlike conventional total hysterectomy, the cervix is not removed, thus removing the need for bladder dissection and extended surgery around the cervix and conserves the uterosacral ligament complex. These extra steps, necessary for the removal of the cervix, can lead to serious complications such as injury to the bladder, ureters and blood vessels. As the cervix is retained, cervical smears are still required and although most women will cease to have periods after the procedure, light menstrual loss can occur in 5-10% of cases.

3.1.2 Endometrial ablation (EA)

Endometrial ablation aims to treat HMB by destroying the endometrium (lining of the womb) which is responsible for heavy periods. Historically, a number of methods have been used to achieve this. Initially, in operations involving so called "first generation" techniques , the interior of the uterine cavity was visualised endoscopically and the endometrial lining resected or ablated using electric diathermy or laser energy. More recently, "second generation" techniques which did not require hysteroscopic visualisation of the uterine cavity became popular. Current second generation procedures used in the UK include two forms of thermal balloon EA (Thermachoice and Cavaterm) and a device known as Novasure® (Hologic Inc). Thermal balloon EA is undertaken by means of a silicone balloon which is introduced through the cervix into the uterine cavity. Hot fluid circulating within the balloon ensures endometrial destruction and the temperature and duration of treatment is carefully controlled electronically by means of a computer attached to the device. Novasure uses radiofrequency energy delivered through an intrauterine mesh electrode which expands on insertion through the cervix to fit the shape of the uterine cavity. All three treatments significantly reduce menstrual loss and result in complete cessation of bleeding in 40 -50% of women.[5] Second generation endometrial ablation procedures can be performed either under general or local anaesthetic, costing the NHS £995 per procedure carried out as a day case in 2011/2012.[12]

3.2 Study population

Women under 50 years of age with HMB who are eligible for endometrial ablation.

We aim to recruit women from approximately 30 active secondary care NHS hospitals in the UK which can carry out both surgical procedures. Discussions at meetings facilitated by the relevant professional organisation, the British Gynaecological Endoscopy Society, and an online survey of members of this Society have confirmed that minimal access surgeons from these centres are willing to randomise women to either option.

3.2.1 Selection of participants

As standard practice, clinicians will assess patients likely to require surgery for HMB. A log will be taken of all patients assessed in order to document the reasons for non-inclusion in the study (e.g. reason they were ineligible, or declined to participate) to inform the CONSORT diagram.

3.2.2 Planned inclusion and exclusion criteria

Inclusion criteria:

1. Women less than 50 years of age with heavy menstrual bleeding eligible for endometrial ablation
2. Women who are willing to be randomised between laparoscopic supra-cervical hysterectomy and endometrial ablation.

Exclusion criteria:

1. Women with plans to conceive, endometrial atypia, abnormal cytology, uterine cavity size greater than 11 cm, any fibroids >3cm, contradictions for laparoscopic surgery (e.g. midline lower abdominal incision or known intrabdominal / pelvic adhesions) and previous endometrial ablation (EA).
2. Women who are unable to give informed consent or complete trial documentation.

3.3 Recruitment and Study Procedures

3.3.1 Identifying participants

All eligible women referred from primary care for consideration of surgery for HMB will be identified by their consultant gynaecologist, dedicated research nurse, or designated team member at outpatient gynaecology clinics and pre-assessment clinics in each recruiting centre. Local procedures at the participating hospitals are different and the timing and mode of approach to women and the consent process may vary in order to accommodate both the specific circumstances at each site and the needs of the women. Each eligible woman will be given or sent a Patient Information Leaflet (PIL) describing the study and will have the opportunity to discuss the study with her gynaecologist. Women will also have the opportunity to discuss all aspects of the proposed research with the local clinical team (staff at pre-admission clinics and ward staff while admitted), the Research Nurse, family and friends and, if appropriate, with their GP before admission. Women may make a decision to participate during an initial consultation with their gynaecologist, during a subsequent visit to hospital (e.g. a clinic appointment, a pre-assessment visit or when they are admitted for surgery), or alternatively at home. If the woman agrees to be contacted at home (recorded on the Surgical Assessment Form), she may receive a telephone call from the local Research Nurse to discuss any queries. Women who decide to participate following telephone counselling can either send their completed documents (consent form and baseline questionnaire) through the post to the local team at their treating hospital or bring it with them if they are returning to hospital for another consultation or surgery.

The PIL and consent form refer to the possibility of long term follow up to determine the incidence of future operations.

All women who enter the study will be assigned a unique Study Number.

3.3.2 Informed consent

The PIL explains that the trial is investigating the use of either LASH or EA for the surgical management of HMB in women. Signed consent forms will be obtained from the participants in all centres. Participants who cannot give informed consent (e.g. due to incapacity) will be not be eligible for participation. The participant's permission will be sought to inform their general practitioner that they are taking part in this trial.

3.3.3 Randomisation and allocation

Eligible and consenting participants will be randomised to one of the two study groups in a 1:1 allocation ratio using the randomisation application at the trial office at the Centre for Healthcare Randomised Trials (CHaRT). This randomisation application will be available 24 hours a day, 7 days a week as both an Interactive Voice Response (IVR) telephone system and as an internet based application. The randomisation will use a minimisation algorithm based on centre and age.

3.3.4 Follow-up procedures

Eligible patients that have given signed informed consent to participate in the study will be asked to complete the SF12, MMAS and EQ5D at baseline before being randomised to either LASH or EA. A self-completed diary will be used between days 1 and 14 post surgery to record pain scores and the use of analgesics. At 6-weeks after surgery, participants will be asked to complete a questionnaire to measure Pain Numerical Rating Scales (NRS), time to return to normal activities and acceptability, EQ5D and SF12. At 6 months after surgery and at 15 months following randomisation, participants will complete the SF12, MMAS, EQ5D, satisfaction with treatment and questions about health care utilisation. Up to two reminders will be sent to participants by post, email, phone or text message, taking into account any preferences they may have for mode of communication.

3.3.5 Change of Status/Withdrawal procedures

Participants will remain in the trial unless they chose to withdraw consent or if they are unable to continue for a clinical reason. If a participant withdraws consent, participant questionnaires will

not be collected; however permission will be sought for the research team to continue to collect outcome data from their health care records (via the case report forms). All other changes in status with the exception of formal withdrawal of consent will mean the participant is still followed up for all study outcomes wherever possible.

3.3.6 Subsequent arrangements *(if applicable)*

Informing key people

Following formal trial entry:

The Study Office will:

i) Inform the participant's General Practitioner (by letter enclosing information about HEALTH and Study Office contact details).

The local Research Nurse will:

i) File the Hospital Copy of the Consent form in the hospital notes along with information about HEALTH.
ii) Use the HEALTH internet database to enter data regarding the participant, including data required to complete randomisation
iii) Return all study documentation to the Study Office in Aberdeen after database entry of essential data.

Notification of/by GPs

GPs are asked to contact the Study Office if one of the participants moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the Study Office may contact the GP.

4. SAFETY

The HEALTH trial involves procedures for the surgical management of HMB in women which are well established in clinical practice. Adverse effects may occur during or after any type of surgery.

4.1 Definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

A **serious adverse event** (SAE) is any AE, that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

HEALTH specific expected adverse events:

In this trial the following events are potentially expected:

Admission high dependency unit/intensive care unit, emergency hysterectomy, laparotomy, port site hernia, blood transfusion, wound infection, lower urinary tract infection, endometritis, blood stained vaginal discharge, anaesthetic complications, low grade pyrexia, blood loss, haematoma, constipation, pelvic discomfort/pain, internal bleeding or injury, pulmonary

embolism (PE), deep vein thrombosis (DVT), injury to the wall of the uterus, bladder injury, bowel injury, ureteric injury and voiding dysfunction.

4.2 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

4.2.1 Detecting AEs and SAEs

Non-serious events will be recorded in the case report forms (CRFs). Planned primary care or hospital visits for conditions other than those associated with HMB or consequence of surgery will not be collected or reported. Hospital visits (planned or unplanned) associated with further interventions due to heavy menstrual bleeding (eg further surgery) will be recorded as an outcome measure, but will not be reported as serious adverse events.

Any SAEs related to the participants' HMB treatment that are not further interventions (eg if a participant is admitted to hospital for treatment of infection) will be recorded on the serious adverse event form. In addition all deaths for any cause (related or otherwise) will be recorded on the serious adverse event form.

Within HEALTH, 'relatedness' is defined as an event that occurs as a result of a procedure required by the protocol, whether or not it is either a) the specific intervention under investigation or b) it is administered outside the study as part of normal care.

4.2.2 Recording AEs and SAEs

Depending on severity, when an AE/SAE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or delegate) should then record all relevant information in the CRF and on the SAE form.
Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

4.2.3 Evaluating AEs and SAEs

All adverse events will be assessed in respect of seriousness, relationship to study intervention, whether expected or unexpected, and therefore, whether constituting a Serious Adverse Event (SAE) by the local PI, CI or their deputies.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 4.1.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to any of the research procedures according to the following definitions:

- **Related**: resulted from administration of any of the research procedures
- **Unrelated**: where an event is not considered to be related to any of the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 4.1)

4.2.4 Reporting AEs and SAEs

Reporting responsibilities of the CI

When an SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification. The sponsor will provide an assessment of the SAE.

The CI (or Trial Manager) will report any related and unexpected SAEs to the main REC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

5. OUTCOME MEASURES

This RCT will assess and compare laparoscopic sub-total hysterectomy (LASH) with standard technique of endometrial ablation (EA) in respect of: condition-specific quality of life (QoL); patient reported satisfaction; and other patient reported outcomes (complications, recovery details, further gynaecological surgery, and modelled long-term cost-effectiveness).

5.1 Primary outcome measure

The **co-primary (clinical) outcomes** will be a) MMAS, a condition-specific QoL outcome[13] ranging from 0-100 based upon 6 domains, measured at 15 months after randomisation, and b) patient satisfaction, measured on a six point scale (from "totally satisfied" to "totally dissatisfied") measured at 15 months after randomisation. These two co-primary outcomes will be addressed in a hierarchy – first, the patient satisfaction will be considered, and if this shows a statistically significant difference using $p<0.05$, then the disease-specific QoL MMAS outcome will be considered. Both will need to achieve statistical significance at $p<0.05$ for the study endpoint to be considered to have been achieved. By specifying this hierarchy we do not need to apply any adjustment for multiple comparisons, since the overall false positive error is controlled at an alpha of 0.05. Together these measures are comprehensive, intuitive and accepted by patients and the clinical community, and have been used in previous trials and studies by the Aberdeen group and others in the field.[14-16]

The primary economic outcome is the incremental cost (to the health service) per QALY gained (LASH versus EA). This will be calculated from within-trial health service costs (resource use collected via case report forms and patient questionnaires, and valued using standard unit prices) and generic quality adjusted life years (derived from responses to the EQ-5D). The incremental cost per QALY gained for LASH versus ablation will be derived from generalised linear regression models adjusting for baseline health status and other important covariates.

5.2 Secondary outcome measures

Patient reported: MMAS at 6 months after surgery; patient reported satisfaction at 6 months after surgery; acceptability of procedure measured at 6 weeks after surgery; severity of post-operative pain using a pain Numerical Rating Scale (NRS) measured at 1-14 days and 6 weeks after surgery, symptom diary days 1 to 14 after surgery (including analgesic use); generic health related quality of life (SF-12, EQ-5D 3-L) measured at 6 months after surgery and at 15 months after randomisation.

Clinical: duration of operation; peri-operative complications and recovery details including analgesia requirements; time to discharge; further gynaecological surgery by 15 months after randomisation.

Economic: wider societal costs associated with changes in productivity based on information on the time taken to return to normal activities (following intervention) combined with questions on work productivity delivered during the follow-up period. Further, a simple Markov model, based on within trial data supplemented by available published data on the requirement for further gynaecological surgery over time (following the alternative procedures) will be developed and used to extrapolate cost-effectiveness beyond 15 months after randomisation.

While the analyses within this application are based upon an initial 15 months after randomisation follow up, we also anticipate collecting long-term information on further gynaecological surgery by utilising Hospital Episode Statistics for England and Wales and Information Services Division (ISD) data for Scotland. These data will be used in the future to revise the extrapolated longer-term estimates of cost-effectiveness for LASH versus EA.

6. DATA COLLECTION AND PROCESSING

6.1. Measuring outcomes

Outcome data will be collected throughout the trial from consent until 15 months following randomisation.

6.2. Schedule of data collection

The components of follow-up are shown in the Table 1 below:

Table 1 Measurement of outcomes: components and timing

	Pre Randomisation		**Post-Surgery**			**Post Randomisation**
	Baseline	**Surgery**	**Day 1-14**	**6-weeks**	**6-months**	**15-months**
Baseline CRF	X					
Surgical details		X				
Pain NRS symptom diary			X			
Pain NRS				X		
Time to return to normal activities				X		
Acceptability				X		
Satisfaction					X	X
MMAS,	X				X	X
EQ-5D 3-L, SF-12	X			X	X	X
Health care utilisation					X	X
Participant costs						X

6.3. Data processing

Research Nurses will enter locally-collected data in the centres. Staff in the Study Office will work closely with local Research Nurses to ensure that the data are as complete and accurate as possible. Follow up questionnaires to participants will be sent from and returned to the Study Office in Aberdeen. Extensive range and consistency checks will further enhance the quality of the data.

7. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

7.1 Sample size

The specification of the target difference was driven by two criteria: i) what target difference would be important if it existed, and ii) what would be a realistic difference[17] given the interventions under evaluation. With regards to ii), the observed rates in the recent IPD meta-analysis of abdominal hysterectomy versus first generation endometrial ablation,[6] would lead to a target difference of odds ratio of 2.84 (95% versus 87%) for patient satisfaction. Such an odds ratio also equates to a medium sized standardised effect (Cohen's d). This requires 292

participants per group for a 2-sided test with 90% power. This size would also be more than sufficient to allow a small to medium sized (0.3, Cohen's d) standardised effect in the co-primary outcome, MMAS, to be detected; this is a target difference for MMAS that can be viewed as important and has observed in other areas for similar outcomes. This would equate to being able to detect a target difference of 10 points on the 0-100 scale, given a standard deviation of 33 points or less. Given these assumptions for the co-primary outcomes, and additionally allowing for 10% missing data, 648 participants in total are required.

7.2 Recruitment rates

The original recruitment projection was based on 25 active centres participating, with the expectation that they will contribute a minimum of 26 women per centre, and 21 months of recruitment (months 6-26 inclusive). We expected a staggered recruitment of centres with all centres active by the end of month 12. Recruitment at all sites was projected to be 50% of the projected monthly total in the first month and reduced recruitment in the peak holiday months of August and December.

7.3 Revised recruitment rates and milestones

At steady state the recruitment rate was assumed to be approximately 62 women per month, although recruitment was actually slower than anticipated. This occured for a number of reasons, principally patient preference, lack of equipoise among clinical colleagues and organisational issues at the recruiting centres.

The revised projections for the extension period are based on a conservative estimate of the recruitment trend observed over a six month period from September 2015 to February 2016 inclusive, resulting in an expected recruitment rate of 25 participants per month. As a result, a 12-month extension to the recruitment phase is necessary to achieve the original target sample size (648 participants in total).

The original and revised recruitment projections together with the revised project timetable and milestones (Gantt Chart)can be found in Appendix 1.

8. STATISTICAL ANALYSIS

All analyses will be based on the intention-to-treat principle, analysing women in the groups to which they are randomised. All study analyses will be conducted according to a statistical analysis plan that will be agreed in advance by the Trial Steering Committee. Analyses will be conducted at 2-sided 5% significance level with corresponding 95% confidence interval generated as appropriate. Full details may be found in the separate statistical analysis plan.

Analysis of the two co-primary outcomes (Patient satisfaction and MMAS) will be conducted independently. Patient satisfaction ("totally satisfied" versus others) will analysed using a logistic regression model with adjustment for minimisation factors. Sensitivity analyses will assess the impact of varying the dichotomisation cut-off and adjusting for clustering at centre and surgeon levels. Sensitivity analyses (such as using a multiple imputation approach) will also explore what influence missing data might have on the robustness of our findings and where feasible modelling non-ignorable (informative) missing data mechanisms. A further analysis of patient satisfaction will use a proportional odds model utilising the underlying ordinal (Likert) scale (Ologit function, Statacorp, 2012). MMAS will be analysed using linear regression adjusted for baseline and minimisation factors or an ordinal model if the data are found to be skewed. Secondary outcomes will be analysed using generalised linear models adjusted for minimisation factors (and when appropriate, a baseline measure).

8.1 Planned subgroup analyses

Exploratory subgroup analyses will be performed for the following groups: uterine cavity length (8cm≤ versus >8cm, menstrual pain (dysmenorrhoea) at baseline ("severe" versus non-"severe" - determined using a 5-point Likert scale), fibroids (present or absent), patient age < 40 or > 40 years old. The pre-specified subgroup analyses will be conducted by including the corresponding treatment by subgroup interaction term in the corresponding regression models

for the co-primary outcomes (patient satisfaction and MMAS). No other subgroup analyses are planned. Subgroup analyses will be stated as exploratory and evaluated at the 5% 2-sided significance level.

8.2 Proposed frequency of analyses

A single statistical analysis will be performed when 12-month follow up data have been collected. An independent Data Monitoring Committee will review confidential interim analyses of accumulating data at its discretion but at least annually.

9. ECONOMIC EVALUATION

The economic analysis will consist of a trial based analysis of individual patient level cost and effect (QALY) data, and a decision modelling component to inform cost-effectiveness in the longer term.

For the within trial analysis, total costs to the health service, wider costs to society associated with lost productivity, and QALYs will be estimated for each individual patient enrolled in the RCT. Costs of the initial intervention procedures will be estimated from resource use data recorded on the case report forms of each individual patient (including time in theatre, staff present, any perioperative complications, and length of stay in hospital post treatment) coupled with routine unit cost data. [12,18] Any subsequent contacts with primary and secondary care (collected from patient questionnaires at 6 months after surgery and 15 months after randomisation), will also be valued for each patient using nationally accepted sources of unit costs. Since the EQ-5D is the recommended instrument for deriving QALY weights by the National Institute for Health and Care Excellence (NICE) (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9), participant responses to this instrument (at baseline, 6 weeks and 6 months after surgery and 15 months after randomisation) will be used to derive QALYs. The SF-12 is being included as another potentially more sensitive measure of general health related quality of life, and will provide an alternative means for estimating QALYs via the SF-6D scoring algorithm. This will be carried out as a sensitivity analysis at 12 months. Productivity losses will be estimated based on the reported time taken to return to normal activities (assessed at 6 weeks after surgery) and responses to work productivity questions at 6 months after surgery and 15 months after randomisation. Time lost from paid employment will be valued using national age/sex specific average gross wage rates. [19] The value of time lost from alternative non-paid activities will be valued using appropriate shadow prices.

Analysis of the patient level cost and QALY data will use appropriately specified generalised linear regression models adjusted for baseline EQ-5D score and minimisation factors applied during randomisation.[20]. From these analysis models, the co-efficient for the treatment allocation group will provide estimates of the incremental costs and QALYs associated with LASH versus EA. Uncertainty surrounding the joint estimates of incremental costs and effects will be characterised by running the regression models on a large number of bootstrapped samples obtained, with replacement, from the original trial sample. This process will generate a large number of estimates of the incremental costs and effects, capturing any correlation between them. These results will be plotted on the incremental cost-effectiveness plane, and used to derive a cost-effectiveness acceptability curve; indicating the probability of LASH being cost-effective (at 12 months) given different notional values of decision makers' willingness to pay per QALY gained. The primary analysis will assess cost-effectiveness from the health service perspective, but a secondary analysis incorporating wider costs to society will also be conducted. As a further step to help present the 12 month findings in a meaningful way for decision makers, we will present all costs and outcomes within a cost-consequence balance sheet. This will summarise all the costs and trial outcomes by treatment allocation group, and indicate which treatment group each outcome favours.

While the within trial analysis will be useful for informing cost-effectiveness in the short term, previous research suggests that a longer time horizon may be required to determine the relative cost-effectiveness of LASH versus EA ;[8] as a result of EA being less costly and effective in the

short term but associated with higher failure rates and subsequent surgery beyond 12 months. Therefore, we will develop a simple Markov model to simulate the recurrence of symptoms and need for subsequent treatment over time, in order to estimate cost-effectiveness in the longer term. The model will be constructed in consultation with clinicians and based on a review of existing decision models developed in the field. Input parameters will initially be informed by the within trial analysis (to determine initial treatment costs and outcomes, and the probability of any subsequent treatment events/complications occurring within 12 months). This will be supplemented with published data on recurrence and the need for further gynaecological surgery (repeat EA, LASH, or conventional total hysterectomy) following EA and LASH. The model will incorporate the initial health service costs of treatment, ongoing costs associated with successful and unsuccessful treatment, and costs associated with subsequent surgery. Utility weights (obtained from the trial data) will be applied to the alternative states in the model, allowing modelled QALYs to be estimated. The model will be run over a five year period (the time point by which most women would be expected to have completed any subsequent required treatment), though the impact of adopting longer time horizons will also be explored. Linkage of participants' records to health episode statistics will allow future quantification of the incidence of repeat gynaecological surgery, providing a means for validating/updating initial model based predictions.

Probabilistic and deterministic sensitivity analysis will be carried out to characterise the uncertainty surrounding the model based estimates of incremental costs and effects of LASH versus EA. For the Probabilistic Sensitivity Analysis (PSA), an appropriate distribution will be assigned to each model input parameter (reflecting the degree of uncertainty surrounding it due to sampling variation) and the model will be analysed a large number of times, each time randomly drawing a value for each input parameter from its assigned distribution .[21] This process will generate a large number of estimates of the incremental costs and effects. Cost-effectiveness acceptability curves will be used to summarise the findings from the PSA. Further deterministic analysis will assess the sensitivity of the model based estimates to further choices over sources of parameter estimates and any structural assumptions required when constructing the model.

10. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 Study Office in Aberdeen

The Study Office is located in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of study activities. The Data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the study web data entry portal).
The HEALTH Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting. Finally, we intend to produce a yearly HEALTH Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

10.2 Local organisation in sites

The Local PI and research nurse will be responsible for all aspects of local organisation including identifying, consenting, and randomising the participants, along with facilitating the delivery of the intervention and notification of any problem or unexpected developments for the duration of the trial. The research nurse will be responsible for ensuring that study data is collected for baseline assessments, collecting and recording participant study data on study specific Case Report Forms and will log details onto the remote web-based data capture system.

10.3 Project Management Group (PMG)

The study will be supervised by a Project Management Group (PMG). The chair of this group will alternate between the Co-Chief Investigators (Siladitya Bhattacharya and Kevin Cooper) and will consist of representatives from the Study Office and grant holders. The PMG will meet

face-to-face in month 1 and month 6 in the first year. It is expected that, once the project is underway, the majority of these meetings will be held by teleconference; however, the PMG will also meet face-to-face at least annually. In addition, the PMG will also meet at the annual Trial Steering Committee meeting.

10.4 Trial Steering Committee (TSC)

The study is overseen by a Trial Steering Committee (TSC). This committee is comprised of four independent members along with the Co-Chief Investigators (Siladitya Bhattacharya and Kevin Cooper). The trial sponsors, other HEALTH grant-holders and key members of the central office (eg the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. CHaRT recommends to TSCs that they adopt the MRC CTU template to form the basis for each individual trial's charter. Details of the membership of the TSC can be found at the start of this protocol.

10.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be convened. The DMC will be made up of members listed at the start of this protocol, one of whom is an experienced statistician. After the trial has been initiated the DMC will initially meet to agree its terms of reference and other procedures. CHaRT has adopted the DAMOCLES Charter for DMCs and suggests to the independent DMC members that they adopt the Terms of Reference contained within.

The committee will meet regularly to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

11. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

11.1 Research Governance

The trial will be run under the auspices of CHaRT based at the Health Services Research unit (HSRU), University of Aberdeen. This will ensure compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The two Aberdeen based co-Chief Investigators will ensure, through the TSC that adequate systems are in place for monitoring the quality of the study (compliance with the principles of GCP) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the study.

11.2 Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details will be stored on a secure database under the guidelines of the 1988 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

11.3 Sponsorship

The University of Aberdeen and NHS Grampian are the co-sponsors for the trial.

12. ETHICS AND REGULATORY APPROVALS

The North of Scotland Research Ethics Service has reviewed this study. The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Annual progress reports and a final report at the conclusion of the trial will be submitted to North of Scotland Research Ethics Committee 2 within the timelines defined in the regulations.

13. QUALITY ASSURANCE

The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations.

13.1 Risk assessment

An independent risk assessment has been carried out by the sponsor. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate and proportional to the risk assessment of the study.

14. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme.

The necessary trial insurance is provided by the University of Aberdeen.

15. END OF STUDY

The end of the study is defined as the end of funding.

The end of the trial will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the trial is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial will be provided to the REC and Regulatory Authority within 1 year of the end of the trial. An end of trial report should also be issued to the funders at the end of funding.

16. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the local investigator and/or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The co-sponsors are responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 10 years following close of study.

17. SATELLITE STUDIES

It is recognised, that the value of the study may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advance with the Project Management Group. TSC and REC approval will be sought for any new proposal, if appropriate.

18. AUTHORSHIP PUBLICATION

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer- reviewed medical/scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the collective title of ‘the HEALTH Trial Group’. If one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the HEALTH Trial Group.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the HEALTH Trial Group.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the study by publication of HEALTH newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final HEALTH Newsletter to all involved in the trial.

Further details on the publication policy can be found in Appendix 2.

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APPENDIX 1
Figure 1 Recruitment projections

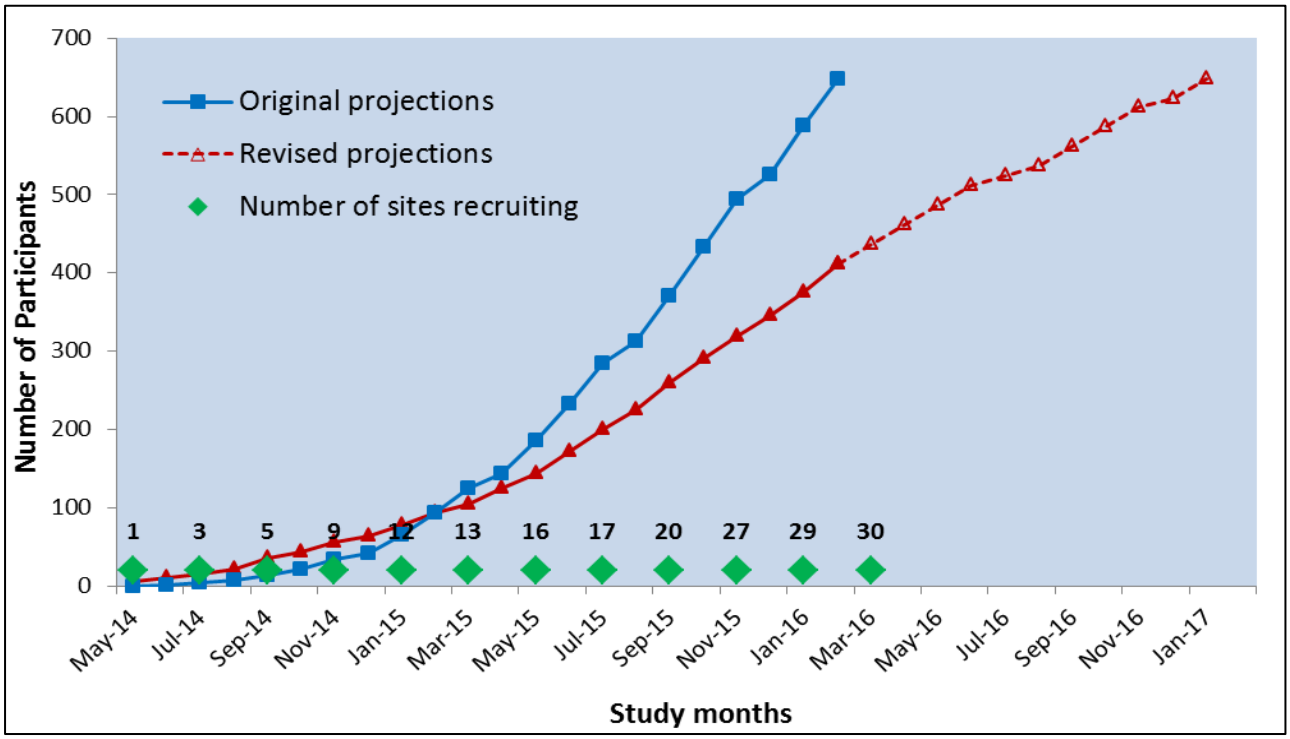
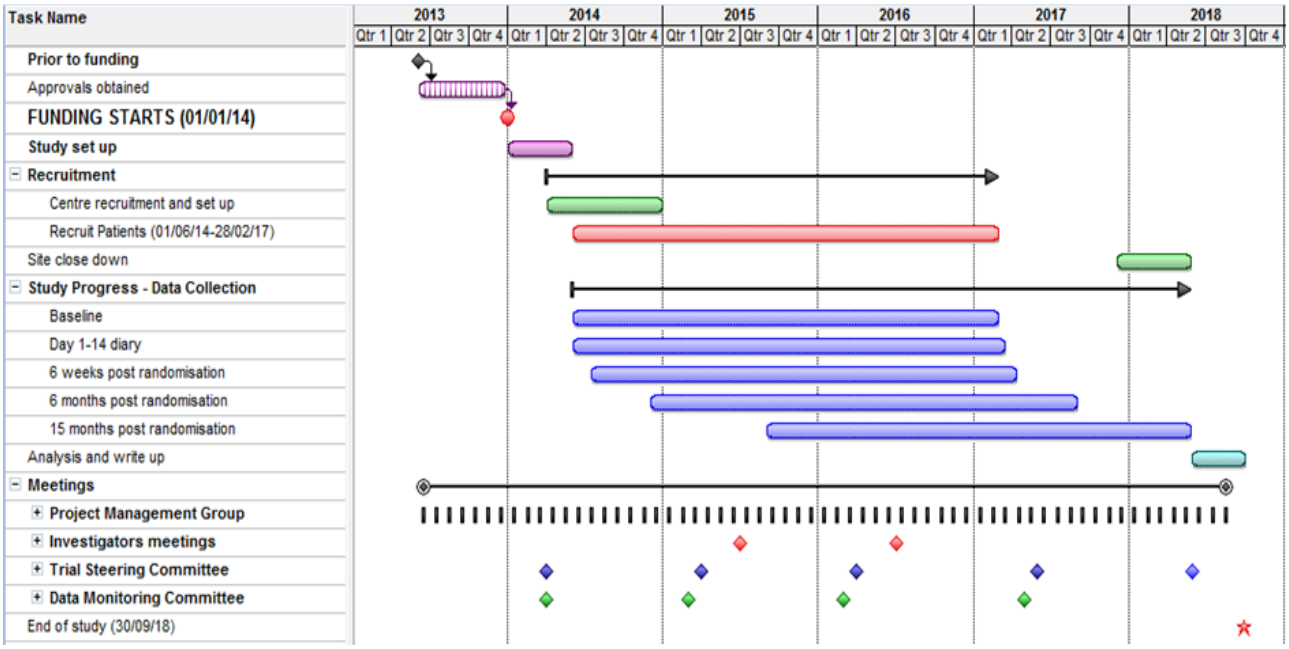


Figure 2 GANTT CHART



Appendix 2: Authorship Policy

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the international Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The HEALTH Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the by-line 'Jane Doe *and* the Trial Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by-line would read 'Jane Doe *for* the Trial Group').[2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. participation must include three steps:

- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself. Those contributors who do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible.[1] These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM HEALTH

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the HEALTH trial and its associated projects:

i. *Reports of work arising from the main HEALTH trial*

If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The HEALTH Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the HEALTH Trial Group'.

ii. *Reports of satellite studies and subsidiary projects*

Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the Trial Group in the development

and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the HEALTH trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the HEALTH Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the HEALTH trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the HEALTH project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertakes to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

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