HEALTH

Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding

A randomised comparison of laparoscopic supracervical hysterectomy with endometrial ablation for women with heavy menstrual bleeding - medium-term follow-up at a minimum of five years

A Longer-Term Follow-Up (LFTU) of the HEALTH trial

HEALTH LTFU PROTOCOL

Version 3, 01 November 2024

This Project is funded by the National Institute for Health Research (NIHR) HTA Programme [Project reference NIHR154434]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This Protocol has regard for the HRA guidance and order of content.

This protocol for the longer-term follow-up refers to the protocol for the HEALTH trial https://fundingawards.nihr.ac.uk/award/12/35/23; IRAS 139913. The end of study was declared for the HEALTH trial on 30th September 2018. Therefore, the protocol for the longer-term follow-up has a new IRAS number.

Sponsor/Co-Sponsors

Name:	University of Aberdeen
Address:	Health Sciences Building, First Floor, Foresterhill, Aberdeen AB25 2ZD
Name:	NHS Grampian
Address:	Health Sciences Building, First Floor, Foresterhill, Aberdeen AB25 2ZD
Sponsor number:	3-086-23

Chief-Investigator

Name:	Kevin Cooper
Address:	Department of Gynaecology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZD
Telephone:	01224 554800
E-mail:	kevin.cooper@nhs.scot

Trial Office

Address:	The HEALTH Study Office Centre for Healthcare Randomised Trials (CHaRT) 3rd Floor, Health Sciences Building University of Aberdeen, Foresterhill Aberdeen AB25 2ZD
Telephone:	01224 438xxx
Fax:	01224 438165
E-mail:	health@abdn.ac.uk
Website:	http://www.charttrials.abdn.ac.uk/health

Funder

Name:	Health Technology Assessment (HTA) Programme
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Signature

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Kevin Cooper 

Date: 1st November 2024

VERSION HISTORY

Amendment No.	Protocol Version No.	Description of Changes (*incl. Author(s) of changes*)	Date Effective
	Version 1	New Document	24th January 2024
	Version 2	Accommodate changes requested by REC	4th March 2024
	Version 3	Amendment to study end date	1st November 2024

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TRIAL SUMMARY

TRIAL TITLE		
Short title	HEALTH LFTU	
Rationale	In the HEALTH trial (NIHR HTA project 12/35/23; IRAS 139913) comparing laparoscopic supracervical hysterectomy (LASH) with endometrium ablation (EA) for heavy menstrual bleeding HMB), LASH was found to be clinically effective in terms of patient satisfaction at 15 months post randomisation but with higher immediate costs. Longer-term clinical and economic outcomes of LASH and EA, including further treatment rates, is required to address key uncertainties in our model-based estimates of cost-effectiveness that were extrapolated from the 15-month follow-up data and external literature. The need for longer term data on clinical and economic outcomes for EA and LASH are also highlighted in the Cochrane systematic review of EA and hysterectomy.	
Trial design	Medium-term follow-up (5-8 years post-randomisation) of a pragmatic, superiority, multi-centre randomised controlled trial comparing laparoscopic supra-cervical hysterectomy with second generation endometrial ablation for the treatment of heavy menstrual bleeding	
Eligibility criteria	All HEALTH participants who consented to be contacted about taking part in this medium-term follow-up study	
Planned sample size	648	
Duration of trial	18 months	
	Objectives	Outcome measures
Primary	To determine medium-term outcomes (5-8 years post-randomisation) in terms of: • Participant reported outcome measures • Safety and any late onset adverse events • Need for further treatment • Cost-effectiveness of LASH versus EA	• Patient satisfaction, measured at 5-8 years post-randomisation • Menorrhagia Multi-Attribute QoL Scale (MMAS) score, measured at 5-8 years post-randomisation. • Incremental cost per quality adjusted life year (QALY) gained at 8-years post-randomisation
Secondary	• Generic health-related quality of life [SF-12 and EQ-5D-3L] scores at 5-8 years post-randomisation • Need for further treatment within primary and/or secondary care for relevant symptoms (including surgery) • Late onset side effects of treatment • NHS care resource use costs up to 5-8 years post-randomisation	

	• Medium-term cost effectiveness, based on extrapolation of the medium-term follow-up data. • Indirect costs related to participant reported time lost from productive activities due to heavy menstrual bleeding, its treatment, or associated complications
Methods	Medium-term follow-up of HEALTH participants at a minimum of five years post randomisation using the same questionnaires utilised for 15-month follow-up, supplemented with routinely collected clinical datasets. Analysis will be based on the intention-to-treat principle. Incremental cost-effectiveness will be determined by updating the exiting decision analytic model based on analysis of the observed rates and costs of further surgery and complications and observed health-related quality of life data at five to eight years. Indirect costs related to participant reported time lost from productive activities due to heavy menstrual bleeding, its treatment, or associated complications, will also be estimated from participant questionnaires.
Co-ordination	Central: by Trial Office in Aberdeen (Telephone 01224 43xxxx). Overall: by the Project Management Group and overseen by an independent Trial Steering Committee, with Data Monitoring Committee responsibilities.

GLOSSARY OF ABBREVIATIONS	
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
DMC	Data Monitoring Committee
EA	Endometrial Ablation
eDRIS	Electronic Data Research and Innovation Service
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
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ISD	Information Statistics Division
ISRCTN	International Standard Randomised Controlled Trial Number
LASH	Laparoscopic supra-cervical hysterectomy
MMAS	Menorrhagia Multi-Attribute QoL Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute Health Research
PI	Principal Investigator
PMG	Project Management Group
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SD	Standard Deviation
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UoA	University of Aberdeen

TRIAL PERSONNEL

Chief Investigator

1 Kevin Cooper
(Consultant Gynaecologist)

Grant Holders

1 Suzanne Breeman (Trial Manager)
2 Neil Scott (Methodologist/Statistician)
3 Graham Scotland (Health Economist)

Trial Office Team

1 Chief Investigator
2 CHaRT Director
3 Trial Manager
4 Data Co-ordinator
5 Senior Trial Manager
6 Senior IT Manager
7 Trial Statistician
8 Trial Health Economist
9 Quality Assurance Manager

Project Management Group (PMG)
This group is comprised of the grant holders along with representatives from the Trial Office team and a patient and public representative.

Trial Steering Committee (TSC) Members
The membership of this committee comprises independent members, which includes a patient and public representative, along with the Chief Investigator (Kevin Cooper) or a nominated delegate. The other HEALTH grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Role of the Trial Sponsor and Funder
The Sponsor (co-sponsor) has responsibility for the initiation and management of the trial as defined by the UK Policy Framework for Health and Social Care Research v3.3 07/11/17. This is further defined within a co-sponsorship agreement outlining the roles and responsibilities of the parties involved in the research. Specific responsibilities delegated to another party are formally agreed and documented by the Sponsor.

The funder has oversight of the study through regular reports from the trial office. The funder appoints the independent members of the Trial Steering Committee and receives minutes from these. The funder is made aware of all outputs from the study but does not have a role in the decision to publish results from the study. In any publications, the funder is acknowledged, and appropriate disclaimer used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

1. INTRODUCTION

1.1 Background

Heavy menstrual bleeding (HMB) affects 1 in 4 British women.[1] In the absence of an effective long-term medical intervention, many will require surgical treatment in the form of endometrial ablation (destruction of the lining of the uterus) or hysterectomy (removal of the uterus). Although endometrial ablation (EA) offers a less invasive surgical option, the uterine lining can regrow after the procedure; many women will need repeat EA and 1 in 5 will ultimately need hysterectomy for recurrence of their symptoms.[2] Whilst conventional hysterectomy guarantees amenorrhoea, it is invasive and associated with a higher risk of complications.

In the NIHR HTA funded HEALTH trial (HTA project 12/35/23; IRAS 139913) we compared a less invasive form of hysterectomy (laparoscopic supracervical hysterectomy or LASH) which removes all of the uterus except the cervix, with EA in 660 women seeking surgical treatment for heavy menstrual bleeding.[3] At 15 months post randomisation, women who underwent LASH reported statistically significantly higher levels of satisfaction (97% vs 87%, adjusted odds ratio (OR) 2.53, 95% CI 1.83–3.48) and more of them had the best possible Menorrhagia Multi-Attribute Scale (MMAS) score of 100 compared to women assigned EA (180 [69%] of 262 women vs 146 [54%] of 268 women; adjusted OR 1.87, 95% CI 1.31–2.67). While complication rates were low and similar across both groups, women who received LASH had a longer hospital stay and return to normal activities.[3]

Our economic evaluation showed that LASH cost an additional £1,604 per woman and produced 0.004 additional QALYs compared to EA at 15 months post-randomisation.[4] A model incorporating external data on anticipated rates of further surgery, suggested that the additional cost of LASH could be reduced to £1,362 per woman, for an expected QALY gain of 0.111 compared to EA at ten years; an incremental cost-effectiveness ratio of £12,314 per QALY gained.[4] However, due to the duration of the original HEALTH study we were unable to collect empirical evidence on the impact of emerging differences in quality of life and the need for further surgery over a longer time horizon, precluding a definitive conclusion on cost effectiveness.

Despite its greater effectiveness and comparable safety, higher immediate costs and lack of longer-term clinical and cost effectiveness data may have delayed the uptake of LASH. Thus, it is essential that the longer-term clinical and economic outcomes of LASH and EA, including further treatment rates, are compared through follow-up of the HEALTH trial. The need for longer term data on clinical and economic outcomes for endometrial ablation and LASH are also highlighted in the Cochrane systematic review of endometrial ablation and hysterectomy.[5]

1.2 Rationale for medium-term follow-up of the HEALTH trial

The National Institute for Health and Care Excellence (NICE) recommends that the options of total hysterectomy (removal of the uterus and the cervix) and subtotal hysterectomy (removal of the uterus and retention of the cervix) are both discussed with women being offered hysterectomy.[6] In a recent Cochrane library systematic review comparing hysterectomy and EA techniques, the implications for research section specifically points out the need for 'Trials with follow-up of four years or longer to adequately assess the cost differential between the two types of surgery and the requirement for further surgical treatment'.[5] The need for longer term follow-up of randomised trials comparing different techniques for hysterectomy was also highlighted in another Cochrane library review.[7]

A search of medical research databases has not revealed any new publications or evidence of ongoing trials comparing the two procedures that can otherwise provide this information which is essential for healthcare providers and purchasers to make evidence-based decisions or a patient to make an informed choice. Meanwhile, there are no new surgical techniques which are likely to replace or supersede LASH or EA. Also, as

supracervical hysterectomy is now recommended as part of sacrocolpopexy procedures for uterine prolapse,[8] relevant data on longer-term outcomes are essential but are not available. Longer-term follow-up of surgical techniques from randomised trials offer essential information to women and clinicians, which allow them to make fully informed choices. This makes longer-term follow-up of the HEALTH trial increasingly important.

Whilst the HEALTH trial showed LASH to be more clinically effective at 15 months post-randomisation, it was found to cost £1,604 more per woman compared to EA and produced only 0.004 additional QALYs over this short time-horizon.[4] A model based extrapolation suggested that the cost-effectiveness of LASH could improve over a longer time horizon, with expectation that more women will require further surgery following EA. In order to get an accurate estimate, however, it is essential that the longer-term costs and outcomes of LASH and EA are compared in a randomised setting. Given that the mean age of participants was 42 years at recruitment (2014-17), it is essential that follow-up is conducted over the next 2 years before the menopause impacts on menstrual symptoms.

2. TRIAL AIM AND OBJECTIVES

The aim of this follow-up study is to determine the medium-term clinical (including need for further treatment) and cost effectiveness of Laparoscopic Supracervical Hysterectomy (LASH) versus Endometrial Ablation (EA) for women with heavy menstrual bleeding randomised between May 2014 and March 2017.

The objective is to determine medium-term outcomes (5-8 years post-randomisation) in terms of:

- Participant reported outcome measures (satisfaction; condition specific QoL; generic QoL)
- Safety and any late onset adverse events
- Need for further treatment via participant reported data and routine datasets
- Cost-effectiveness of LASH versus EA at 5-8 years follow-up

3. TRIAL DESIGN

Medium-term follow-up (5-8 years post-randomisation) of a pragmatic, superiority, multi-centre randomised controlled trial (the NIHR HTA funded HEALTH trial (HTA project 12/35/23; IRAS 139913) comparing laparoscopic supra-cervical hysterectomy with second generation endometrial ablation for the treatment of heavy menstrual bleeding.

3.1 Interventions to be evaluated

We will determine the medium-term effectiveness and cost-effectiveness of the following two randomised interventions for the treatment of heavy menstrual bleeding:

- Laparoscopic supra-cervical hysterectomy [removal of the uterine corpus (body) by means of keyhole surgery]
- Second generation endometrial ablation [destruction of the endometrium (lining of the womb) by means of a silicone balloon containing hot fluid or radiofrequency energy delivered through an intrauterine mesh electrode]

4. TRIAL RECRUITMENT

4.1 Trial population

HEALTH involved the recruitment of 660 women presenting with heavy menstrual bleeding across 31 secondary/tertiary hospitals in the UK. During the consent process the HEALTH participants agreed, or not, to be contacted about medium-term follow-up.

The target population for this medium-term follow-up study will therefore include the 648 women who consented to being contacted about medium-term follow-up and who did not withdraw from receiving further study questionnaires or die during the initial 15-month post-randomisation period.

4.2 Setting

In this medium-term follow-up phase, we will collect participant-reported outcomes using participant questionnaires. Need for further surgery will use a combination of participant-reported accounts and routine data sources.

4.3 Inclusion and exclusion criteria

Inclusion criteria: Women who participated in the HEALTH trial, consented to being contacted about medium-term follow-up and who have not withdrawn from completing further questionnaires or died during the initial follow-up period (15-months post-randomisation).

Exclusion criteria: Women who did not consent to be contacted about medium term follow-up are excluded.

5. OUTCOME MEASURES

During the extended follow-up phase, we aim to collect the same participant-reported outcome measures as in the initial HEALTH trial.

5.1 Primary outcome measure

The co-primary clinical outcome measures in the medium-term follow-up phase are:

- Patient satisfaction, measured on a six-point scale (from 'totally satisfied' to 'totally dissatisfied'), at 5-8 years post-randomisation
- MMAS) score, a condition specific QoL outcome,[9] ranging from 0 (worst possible health state) to 100 (best possible health state), based on six items, measured at 5-8 years post-randomisation.

The primary economic outcome will be incremental cost per quality adjusted life years (QALY) gained at 8-years after randomisation.

5.2 Secondary outcome measures

The secondary outcome measures include:

- Generic health-related quality of life [Short Form questionnaire-12 items (SF-12) and EuroQol-5 Dimensions, three-level version (EQ-5D-3L)] scores at 5-8 years post-randomisation
- Need for further treatment within primary and/or secondary care for relevant symptoms (including surgery)
- Late onset side effects of treatment
- NHS care resource use costs up to 5-8 years post-randomisation
- Medium-term cost effectiveness, based on extrapolation of the medium-term follow-up data.
- Indirect costs related to participant reported time lost from productive activities due to heavy menstrual bleeding, its treatment, or associated complications

6. DATA COLLECTION AND PROCESSING

6.1 Participant reported outcomes

HEALTH participants will be asked to complete one additional questionnaire at 5-8 years post-randomisation. The questionnaire will be issued by the trial office at the University of Aberdeen, either by post or by email with a link to complete the questionnaire online.

The participant questionnaires will collect information on patient satisfaction with treatment; condition specific (MMAS) and generic (SF-12 and EQ-5D-3L) QoL; need for further treatment for HMB and other relevant symptoms (including surgery); late onset adverse effects of treatment; and NHS and participant related indirect costs.

Reminder letters or emails will be sent three weeks after the original questionnaire is issued and not returned, followed by a phone reminder for continuing non-responders to ensure questionnaire response rates are maximised. A small token of appreciation (£15 gift voucher) will also be included with the first reminder to compensate them for this time in completing the questionnaire. This is the same approach used in the original HEALTH trial, which received ethical approval. If we are unable to retrieve information from a participant, for example, the participant has moved address, we will try to re-establish contact with the participant. If that re-establishment involves a GP or any other health care professional, we will amend the protocol and seek R&D approval.

6.2 Routine data

Relevant readmissions, reoperations, and further treatment in secondary care for HMB and other relevant symptoms will be identified through a combination of participant-reported accounts and routine data sources. Record linkage applications will be submitted to NHS England and the Electronic Data Research and Innovation Service (eDRIS) in Scotland requesting relevant data covering the period from randomisation to point of contact for the medium-term follow-up study.

6.3 Change of Status/Withdrawal procedures

Participants will remain on the trial unless they choose 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. A member of the trial team will complete the “change of status form” which includes the participant’s instructions on what parts, or whole, of the study they may wish to withdraw from. 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.

7. SAFETY REPORTING

Both interventions delivered in the initial phase of the HEALTH trial (LASH and EA) are NICE recommended treatments for the management of HMB and have been widely used in the NHS for many years. Women received their intervention during the initial phase of the HEALTH trial and no further trial intervention is offered as part of the medium-term follow-up study. Therefore, there will be no safety reporting within the medium-term follow-up of the HEALTH trial participants.

As part of the secondary outcome data collection, women will be asked about need for further treatment and late onset complications of treatment. These will be reported as outcomes of the study rather than as safety events.

8. SAMPLE SIZE

The original HEALTH trial [NIHR HTA 12/35/23] was powered to detect a difference in total satisfaction rate of 8% (87% vs 95%), using a two-sided continuity-corrected chi-squared test. This also allowed >90% power to detect a 10-point difference in MMAS scores [assuming a standard deviation (SD) of 33 units]. Actual rates of total satisfaction at 15 months post randomisation were 75.9% (LASH) vs 56.4% (EA), and MMAS had a skewed

distribution with 68.7% (LASH) and 54.5% (EA) of women reporting the maximum score of 100.

Assuming data for 264 women in each group at the 5-8 years follow-up time-point (20% attrition) and a significance level of 5%, we would have >90% power to detect absolute group differences of at least 13% in either total satisfaction or MMAS 100, assuming proportions in the LASH group of 75%. We conservatively assumed a binary split of outcomes, however the actual analysis of both co-primary outcomes will likely use an ordinal model as in the 15-month follow-up analysis, improving precision/power.

9. STATISTICAL ANALYSIS

Analysis will be based on the intention-to-treat principle. The data from the 15-month follow-up will be combined with this medium-term follow-up outcome data to increase precision. Clinical outcomes will be analysed using mixed effects generalised linear models with link functions suitable for the distribution of the outcome (most likely ordinal regression for the co-primary outcomes as in the previous analysis) adjusted for the baseline score (if applicable), as well as time since randomisation to reflect the varying follow-up measurement time, minimisation variables (age as a fixed effect and centre as a random effect), and a random effect for participant. Full details may be found in the separate statistical analysis plan.

10. ECONOMIC EVALUATION

Data from this medium-term follow-up will be combined with the 15-month follow-up data and used to update the economic model previously developed.[4] The model will simulate short-term differences in costs and outcomes (based on 15-month data), the incidence of recurrence and/or complications requiring further surgery, and the impact of these events on costs and health-related quality of life. Cost estimates based on the on the original 15-month data used a combination of micro-costing (initial procedures) and routine units costs. These will be updated to current prices[10-12] and re-analysed to inform revised model inputs. Parametric survival analysis of time to further surgery and complications, combined with data on types of procedure, will inform the medium-term probability and cost of these further events by allocated treatment arm.

The medium-term follow-up data on health care resource use, from routine sources and patient questionnaires, will inform background health state costs associated with medical treatment and related primary/secondary care use. The analysis of medium-term EQ-5D data will better inform the health state utilities applied in the model. This updated analysis will enable a more robust assessment of cost-effectiveness for informing future health care decision making.

Cost-effectiveness will be assessed in terms of the incremental cost per QALY for LASH versus EA at eight years post-randomisation. Further analysis will assess the impact on cost-effectiveness of reducing the time horizon to five years or extending it further based on extrapolation of the medium-term follow-up data. We will address uncertainties around the cost-effectiveness of LASH relating to the alternative approaches (morcellation in a bag and culdotomy) that can be used to remove tissue from the abdominal cavity during the procedure. This will be achieved by applying expected differences in equipment costs and theatre time with these alternative approaches relative to simple morcellation and any potential differences in perioperative complication rates. Parameter uncertainty relating to model inputs will be addressed using probabilistic sensitivity analysis, and structural uncertainties will be explored using scenario analysis.

11. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 Trial office

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) is based within the Health Services Research Unit, University of Aberdeen. The Trial Manager in CHaRT will take responsibility for the day-to-day transaction and coordination of study activities, including liaising when needed with the other members of the project team to ensure smooth study processes. The Data Coordinator 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-based data entry portal). The programmer will maintain and update all applications for the trial, including all administrative and analysis databases.

The Trial Office Team will meet formally monthly during the course of the trial to ensure smooth running and troubleshooting.

11.2 Project Management Group (PMG)

The trial is supervised by its Project management Group (PMG). This consists of the grant holders, representatives from the Trial Office and a patient and public representative. Observers may be invited to attend at the discretion of the PMG. The PMG will meet approximately quarterly over the duration of this study.

The research team has the expertise to cover the clinical and methodological aspects of the research.

11.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, which includes a patient and public representative, will oversee the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC. This Charter is filed in the Trial Master File (TMF).

11.4 Data Monitoring Committee (DMC)

A DMC is not required for this medium-term follow-up of the HEALTH trial cohort. This is because the participants will not be receiving trial treatment during the follow-up.

11.5 Patient and Public Involvement (PPI)

The current extended follow-up application also includes a patient and public representative on the PMG and the TSC to ensure continued patient and public input into the management of the research, developing participant information resources, contributing to the reporting of the research and dissemination of research findings.

12. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

12.1 Research Governance

CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance and the principles of GCP, and provides centralised trial administration, database support and economic and statistical analyses. CHaRT SOPs are followed.

The CI and Sponsor ensure that adequate systems are in place for monitoring the quality of the trial and that reports are prepared to a level appropriate to the risk assessment of the trial.

12.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team. Data may be looked at by individuals from the Sponsor organisation where it is relevant to the participant taking part in this trial.

The CI and trial staff involved with this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The CI and trial staff based in Scotland will also adhere to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate trial staff.

Computers used to collate the data will have limited access measures via usernames and passwords. Remote access to the network will be subject to robust authentication, and VPN (Virtual Private Network) connections to the network are only permitted for authorised users, ensuring that use is authenticated, and data is encrypted during transit across the network. No personal data will be downloaded or stored on local hard drives. All data input/access will be via the VPN and/or secure website.

Published results will not contain any personal data that could allow identification of individual participants.

We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses (see https://www.abdn.ac.uk/hsru/what-we-do/trials-unit/data-sharing-1115.php).

12.3 Sponsorship

The University of Aberdeen and NHS Grampian will continue to act as the co-sponsors for the medium-term follow-up study

13. ETHICS AND REGULATORY APPROVALS

The London Chelsea Research Ethics Committee has reviewed this longer-term follow-up 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 The London Chelsea Research Ethics Committee within the timelines defined in the regulations.

All HEALTH participants were informed about the intention to carry out medium-term follow-up and they consented to be contacted regarding medium-term follow-up when they first joined the study between May 2014 and March 2017 (consent obtained under NIHR HTA project 12/35/23; IRAS 139913, REC 13/NS/0155).

14. MONITORING AND AUDIT

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

14.1 Risk assessment

An independent risk assessment has been carried out by the sponsor.

15. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The University of Aberdeen and Grampian Health Board are Co-Sponsoring the study.

Insurance: The University of Aberdeen will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study. Grampian Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Grampian in relation to the study.

Indemnity: The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

16. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

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

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

17. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Questionnaires returned by post to the trial office will be entered there. Extensive range and consistency checks will further enhance the quality of the data.

Responsibilities for archiving are documented in the co-sponsorship agreement. All essential data and documents (electronic and hard copy) are retained for a period of 10 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. All data (electronic and hard copies) will be archived by UoA.

18. AUTHORSHIP AND PUBLICATION

Please refer to the Appendix 1 (Authorship policy) for full details on authorship.

18.1 Other Dissemination

Once the main trial findings have been published, a lay summary of the findings will be sent to participants.

Trial findings will also be disseminated to professionals involved in the trial, including GPs of participants, PIs at sites, dentists, site staff, pharmacy etc and will be considered and developed with input from PPI partners.

References

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Appendix 1: Authorship Policy

AUTHORSHIP POLICY FOR HEALTH LONGER-TERM FOLLOW-UP STUDY

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria.[1]

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-author.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT trials should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other. However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to “The HEALTH longer-term follow-up group” or “Jane Doe, John Doe, John Smith, Ann Other and the HEALTH longer-term follow-up trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

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 byline would read 'Jane Doe *for* the Trial Group')[2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all

individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].
Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group (PMG). Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].
The acknowledgements should also reflect any agreed acknowledgements (for example with suppliers) that were documented in supply agreements (or equivalent).

4. DISCLAIMERS

All papers arising from CHaRT must include the full title of the Health Services Research Unit (HSRU) and the appropriate disclaimer specified by the Chief Scientist Office (CSO). For the current disclaimer please see Q-Pulse.
Authors should also ensure they include the trial funder's disclaimer: refer to the funders website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the HEALTH longer-term follow-up study, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial, should be peer reviewed by the PMG. The PMG will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the trial team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

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