PROTOCOL

Improving outcome**S** for **W**omen diagnosed with early breast cancer through adh**E**rence to adjuvant **E**ndocrine **T**herapy **(SWEET)**

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This protocol has regard for current HRA guidance and content

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Protocol Amendments:

Amendment number	Date of amendment	Protocol version	Type of amendment	Summary of changes
NSA03		3.0	Non-substantial	Clarification of eligibility criteria from 3months to 14 weeks. Update to stratification factors to encompass all CDK4/6i pathways Updates to reflect combination of QOL and health resource use questionnaire. Inclusion of example nudge messages Clarification about prescription record access across the devolved nations.

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TRIAL SUMMARY

Trial Title	Improving outcome**S** for **W**omen diagnosed with early breast cancer through adh**E**rence to adjuvant **E**ndocrine **T**herapy	
Internal Ref. Number (or Short Title)	SWEET	
Trial Design	Multi-centre, unblinded, pragmatic randomised controlled trial (RCT) of HT&Me intervention + usual care Vs usual care alone in (i) reducing poor adjuvant endocrine treatment (AET) adherence (defined as suboptimal implementation or early discontinuation) and (ii) improving cancer-specific HRQoL.	
Trial Participants	Women recently diagnosed with ER-positive invasive breast cancer, stages 1- 3 and treated with curative intent, who have been prescribed oral adjuvant ET within the past 14weeks.	
Planned Sample Size	1460	
Intervention Duration	Participants will have an initial consultation (consultation 1) with a SWEET study nurse/practitioner within 8 weeks of randomisation who will provide access and introduce the HT&Me web app. The participant will then receive a follow up consultation (consultation 2) 3 months later, but will continue to receive access to the HT&Me web app for the duration of the study (18 months).	
Follow-up Duration	Eligible women will be followed up to 18-months initially for analyses of primary outcome, further funding will be sought to monitor adherence and investigate recurrence in the longer term (up to 15years).	
Planned Trial Period	1st January 2024 – 18th November 2027 Recruitment over 24 months, 21 months allotted for follow-up and analyses for primary outcome, write up and dissemination.	
	Objectives	Outcome Measures
gPrimary	AET Adherence	Combined self-report (Medical Adherence Report Scale (MARS-5) [55] and prescribing records (e.g. Medication Possession Ratio (MPR)
	Cancer-specific HRQoL	Functional Assessment of Cancer Therapy scale-General (FACT-G) [56]

Secondary	AET-specific HRQoL	Breast Cancer Trialist Prevention Checklist (BCPT) [57])
	Cost-effectiveness	Within trial cost per quality-adjusted life year (QALY); QALYs; resource use and cost to NHS, patients and society, and EQ-5D-5L [58]
Additional Outcomes	Extent of adherence	MPR (continuous); encashment records and/or GP prescribing records.
	Suboptimal implementation	Self-reported: MARS-5 [55]
	Non-persistence	>180 days gap in AET prescriptions; self-report
Postulated Mediators (examples)	Improved self-efficacy for taking AET	Questions adapted from [60] [61]
	Self-efficacy	Self-efficacy for coping with symptoms, adapted from [62]
	Reduced cancer related distress	FACT-G emotional functioning subscale [63]
	More positive medication and illness beliefs	Illness Perception Questionnaire for breast cancer (IPQ-BCS) [64]; Beliefs about Medicines Questionnaire-endocrine therapy (BMQ-AET) [65]
	Satisfaction with information about AET	Satisfaction with Information about Medicines Scale (SIMS)[66]
	Increased physical activity	Godin-Shepard leisure-time physical activity questionnaire [67]
	Reduced practical barriers to adherence and increased self-efficacy for managing treatment	Cancer survivor self-efficacy scale (CS-SES), adapted from [68]
	Self-efficacy & Improved self-efficacy for taking AET	Questions adapted from [60- 61] and Self-efficacy for coping with symptoms, adapted from [62]

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
AET	Adjuvant Endocrine Therapy
BCT	Behaviour Change Techniques
BSO	Business Service Organisation
CI	Chief Investigator
CONSORT	*Cons*olidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
ER	Oestrogen Receptor
FPS	Family Practitioner Services
GCP	Good Clinical Practice
HSC	Health and Social Care
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
NHS	National Health Service
NHSBSA	National Health Service Business Service Authority
NICE	National Institute for Health and Care Excellence
NWSSP	National Health Service Wales Shared Service Partnership
MDT	Multi-disciplinary team
MRC	Medical Research Council
PCS	Primary Care Services
PHS	Public Health Scotland
PI	Principal Investigator
PPI	Patient & Public Involvement
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPPG	Strategic Planning and Performance Group
TMG	Trial Management Group
TNO	Trial Number
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

Fig 1: Definitions for each role involved in the study delivery:

Local/Site research team:

Research team at site responsible for the conduct of the study at site (ie PI, research nurses, trial co-ordinators).

SWEET study Nurse/ Practitioners:

Responsible for delivering the intervention and conducting the consultations. *This role may be delivered by a member of the local site team or nurses from Breast Cancer Now.*

Central research team/ SWEET trial office:

Team based at Warwick Clinical Trial Unit, Oxford Brookes University & University College London. Oversee the overall delivery of the study & coordinate HT&Me website.

1. BACKGROUND

1.1 Background

Breast cancer is the most common cancer in women in the UK [1]. Although survival rates are high, in 2016, 11,600 women died from the disease [1]. Most women with breast cancer (~80%) have oestrogen receptor (ER) positive disease. These women are usually recommended to take adjuvant endocrine therapy (AET) (tamoxifen or an aromatase inhibitor) in the form of a daily tablet following surgery and/or radiotherapy or chemotherapy. AET significantly reduces the risks of recurrence, death from breast cancer, and (hence) death from any cause when taken for five years [2-4]. Extending therapy beyond five years further reduces recurrences [5, 6]. In light of this, the recently published NICE breast cancer diagnosis and management guidelines recommend extending AET use beyond five years [4].

Despite these recognised benefits, there is good evidence that many women do not take AET as recommended. Suboptimal implementation (taking less than the recommended dose of a medication) and early discontinuation (stopping taking the medication before the end of the recommended treatment period) are forms of medication non-adherence [7]. Twenty to 40% percent of women display suboptimal implementation of AET, which is generally defined in this context as taking <80% of the recommended dose [8-14]. In terms of early discontinuation, around 20% of women stop taking AET completely by two years and up to 50% do so by five years [8, 11, 12]. In addition, our data indicate that women who display suboptimal AET implementation in the first year of therapy are more likely to discontinue therapy in the future [15].

There is strong evidence that AET non-adherence is associated with an up to 3-fold increased risk of breast cancer recurrence and mortality [8, 13, 16-19]. For example, the Breast International Triallists Group found that suboptimal implementation and early discontinuation were associated with significantly reduced disease-free survival (suboptimal implementation: HR=1.45, 95%CI 1.09-1.93; early discontinuation: HR=1.61, 95%CI 1.08-2.38, respectively) [19]. In Ireland, we found that women who stopped taking AET had significantly increased recurrence risk compared with women who persisted (OR=2.88, 95%CI 1.11-7.46) [16]. We have also shown that non-adherence is associated with significantly poorer cancer-specific health-related quality-of-life (HRQoL): women with reduced adherence have poorer scores in all HRQoL domains (physical, social, emotional, functional, and endocrine symptoms) [20]. Moreover, non-adherence results in reduced quality-adjusted life years, and significantly higher medical costs [21].

This programme will develop and test an evidence-based, theoretically-informed, intervention to support women with AET adherence. The intervention will target potentially modifiable factors associated with non-adherence previously identified by ourselves [11, 15, 22-33] and others [34-39]. Women's initial "necessity and concern" beliefs are particularly important; non-adherence is related to the way in which women judge their personal need to take AET, relative to their concerns about taking it. Beliefs about the risk of recurrence and concerns about side-effects commonly associated with AET (e.g. severe hot flushes, joint pain, weight gain, depression) influence women's willingness to take AET. Some women are also concerned about long-term effects and/or have a desire to move on and leave cancer behind (with daily medication preventing that); others have negative attitudes towards medicine-taking in general. Motivation to take AET is important, as is ability: poor coping skills, poor medication management techniques and forgetfulness are related to non-adherence. In addition, poor understanding of why it is important to take AET, both every day and long-term, frequently emerges as influencing non-adherence. In contrast, a good patient-health professional relationship (within which communication is person-centred and frequent and women feel supported) is positively related to adherence.

1.2 Rationale

The proposed programme aligns well with current NHS priorities. National Institute for Health and Care Excellence (NICE) has highlighted an urgent need for systematic development of interventions to optimise adherence to appropriately-prescribed medications [40]. Supporting those living with and beyond a cancer diagnosis is a priority in the NHS Cancer Strategy for England [41], and AET adherence, and development of interventions to enhance the survivorship experience, are identified as key research gaps and translational priorities in breast cancer [42]. Moreover, the programme addresses the top priority for living with and beyond cancer research, published by the National Cancer Research Institute in partnership with the James Lind Alliance [43], by exploring an innovative, new model for delivering long-term cancer care.

It has been argued that 'increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments' [44].

In the UK, more than 55,000 women are diagnosed with invasive breast cancer annually [1], of whom around 80% (44,000) are prescribed AET. AET non-adherence is a significant problem, resulting in poorer breast cancer outcomes for women [8, 13, 16-19]. In addition, non-adherence incurs costs to the NHS associated with managing recurrence and the provision of end-of-life care. In 2009, the cost per recurrence was estimated to be £31,403 [45], while the total cost of providing hospital care to women with breast cancer in the 12 months before end-of-life in England in 2010 was £94 million [46]. In contrast, health economic models suggest that supporting women to adhere to AET could reduce breast cancer recurrences by 9.0% and deaths from breast cancer by 8.7% [21]. Assuming a willingness to pay threshold of £25,000 per quality-adjusted life year (QALY), the expected value of changing a woman from non-adherent to adherent with AET has been estimated to be £33,897 (95% CI: £28,322–£39,652) [21]. This suggests that interventions which support AET adherence may be highly cost-effective.

Breast cancer care is changing. Treatment is more personalised involving less use of chemotherapy and radiotherapy [47, 48]. The recently updated NICE guidelines, published in October 2018, recommend offering extended (i.e. >5 years) treatment with AET [49]. Roll-out of stratified follow-up pathways, through the Cancer Transformation Programme, is accelerating. This means that hospital-based follow-up is more often nurse (rather than consultant) led [50] and is typically of shorter duration. In addition, a significant (and growing) proportion of breast cancer patients are expected to self-manage [51]. These trends have accelerated recently, with the COVID-19 pandemic, which has changed the clinical landscape. There is now an even greater emphasis on early discharge of women with breast cancer from hospital, with remote (telephone/video) follow-up and more promotion of self-management and patient-initiated follow-up. There has also been an increasing move towards the use of digital solutions.

These developments make it increasingly important to support women with breast cancer to adhere to AET. Despite this, our empirical research and Patient & Public Involvement (PPI) work undertaken to inform this programme indicate that the support and monitoring women receive regarding AET is often inadequate [24, 25, 27, 28].

We intend to change this situation by providing women with a tailored multi-modal intervention which will commence soon after AET is prescribed and be augmented with light-touch follow-up to provide ongoing support, communicate the continuing priority of treatment, and address any emerging concerns/issues and barriers. We will address potentially modifiable determinants of adherence identified in our preparatory work including beliefs about necessity of taking AET, concerns about taking AET, motivation and self-efficacy to take AET, strategies for dealing with side-effects,

medication management techniques and AET knowledge and understanding [11, 15, 22-33]. By improving self-efficacy and supporting women to manage and/or cope with any AET-related concerns or bothersome side-effects, we hope to improve cancer-specific HRQoL. This will be the first AET adherence intervention study worldwide with the potential to examine impact of the intervention on clinical outcomes (namely breast cancer recurrence at 5-years) and, by following women for 5 years, to determine whether any impact of the intervention on adherence is sustained. This intervention will also offer real potential to improve breast cancer outcomes in the longer term (10 years and beyond), benefiting both women and the NHS.

The programme also has considerable wider implications and potential. NHS cancer services are overwhelmed. Since the first quarter of 2014, there has been consistent failure to meet the national operational standard for the 62 day target for the wait between urgent GP referral to first treatment [52]. Since late 2017, the operational standard for 62 day wait between National Screening Service referral and first treatment has also failed to be met. Therefore, an initiative that would result in fewer breast cancer patients requiring treatment for recurrence or end-of-life care could help ease pressures in the system.

In addition, over the past decade there has been dramatic growth in oral anti-cancer drugs. For example, currently, over 50 targeted therapies (many of which are taken orally) are licensed to treat various cancers, and that number is expected to increase rapidly in the future. Evidence is beginning to emerge of significant non-adherence with some oral antineoplastic drugs [53, 54]. This programme will provide the foundation for interventions to support adherence to these anti-cancer oral therapies with similar non-adherence issues. Similarly, it has the potential to inform development of interventions to support adherence with other long-term medications in other disease groups.

The overall aim of the programme of work is to develop and evaluate an intervention to reduce poor adherence to AET and improve health-related quality-of-life (HRQoL) and, in the longer-term, to reduce recurrence, in women with ER-positive invasive breast cancer.

The study will be conducted in a number of workstreams:

Workstream 1: Intervention development (months 1-22)

Workstream 2: Feasibility study (months 20-32)

Workstream 3: Evaluation of intervention effectiveness in reducing poor adherence and improving HRQoL in pragmatic RCT (months 32-74)

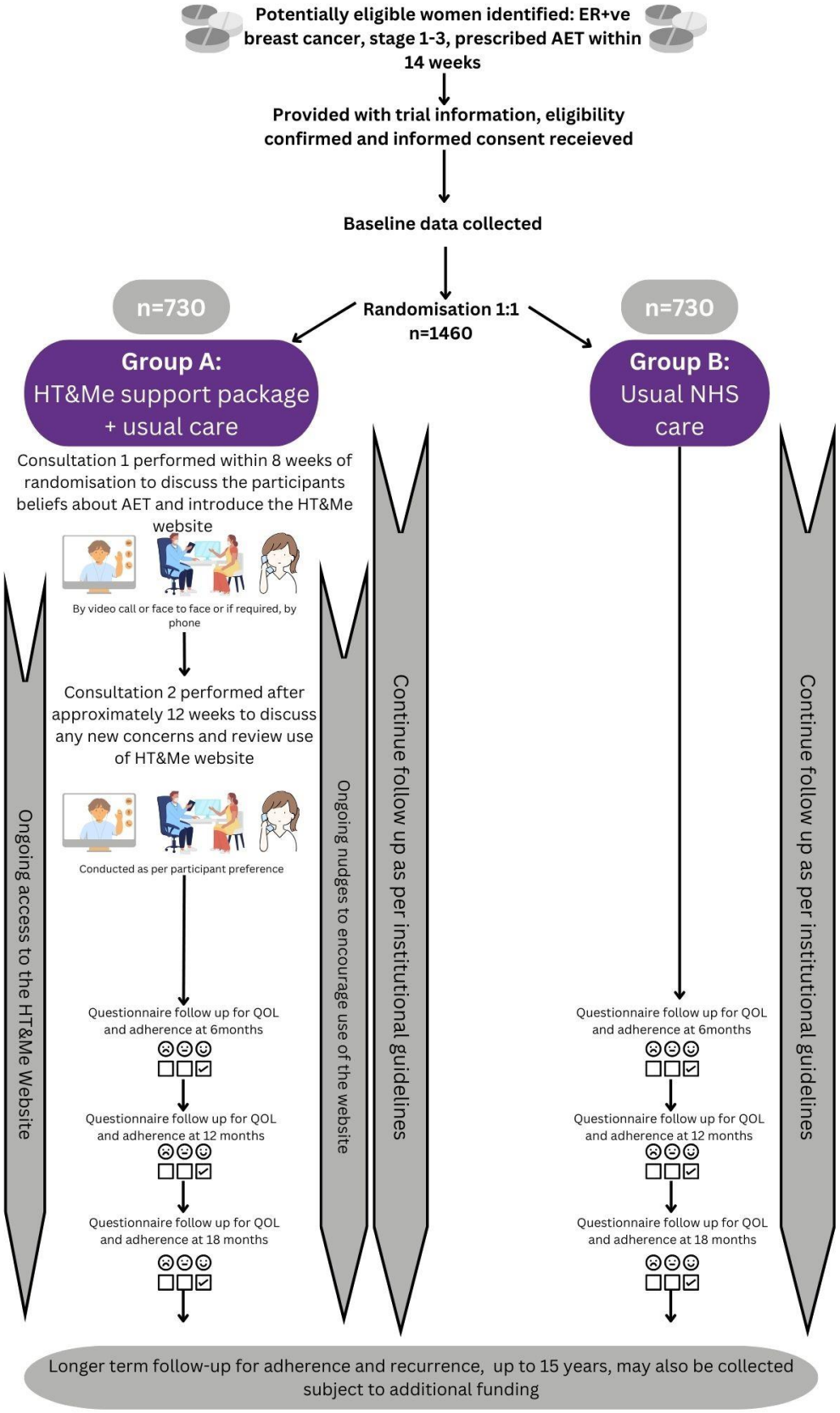
Workstream 4: Health economic evaluation (months 14-80)

Workstream 5: Pathway to impact and potential scale-up to NHS implementation (months 21-80)

This protocol is in regard to workstream 3- the randomised controlled trial.

2. TRIAL DESIGN

Figure 1 Trial flow diagram


Potentially eligible women identified: ER+ve breast cancer, stage 1-3, prescribed AET within 14 weeks
Provided with trial information, eligibility confirmed and informed consent receieved
Baseline data collected
Randomisation 1:1
n=1460
n=730
n=730
Group A:
HT&Me support package + usual care
Group B:
Usual NHS care
Consultation 1 performed within 8 weeks of randomisation to discuss the participants beliefs about AET and introduce the HT&Me website
By video call or face to face or if required, by phone
Consultation 2 performed after approximately 12 weeks to discuss any new concerns and review use of HT&Me website
Conducted as per participant preference
Questionnaire follow up for QOL and adherence at 6months
Questionnaire follow up for QOL and adherence at 12 months
Questionnaire follow up for QOL and adherence at 18 months
Questionnaire follow up for QOL and adherence at 6months
Questionnaire follow up for QOL and adherence at 12 months
Questionnaire follow up for QOL and adherence at 18 months
Ongoing access to the HT&Me Website
Ongoing nudges to encourage use of the website
Continue follow up as per institutional guidelines
Continue follow up as per institutional guidelines
Longer term follow-up for adherence and recurrence, up to 15 years, may also be collected subject to additional funding

2.1 Aims and objectives

The aim of the RCT is to determine the clinical effectiveness of the trial intervention in reducing poor adherence to AET and improving cancer specific HRQoL.

2.2 Objectives and Outcome measures

2.2.1 Primary objectives and outcomes

- Adherence using combined self-report (Medical Adherence Report Scale (MARS-5) [55] and prescription encashment records (e.g. Medication Possession Ratio (MPR).
- Cancer-specific HRQoL: Functional Assessment of Cancer Therapy scale- General (FACT-G) [56]

2.2.2 Secondary outcomes

- AET-specific HRQoL: Breast Cancer Trialist Prevention checklist (BCPT) [57]
- Cost-effectiveness: Within trial cost per quality-adjusted life year (QALY); and EQ-5D [58]

2.2.3 Additional outcomes:

- Extent of adherence: MPR (continuous); encashment records
- Suboptimal implementation: self-reported: MARS-5 [55]
- Non-persistence: >180 days gap in AET prescriptions; self-report

3. ELIGIBILITY CRITERIA

Patients are eligible to be included in the trial if they meet the following criteria:

3.1.1 Inclusion criteria

1. Aged 18+
2. Female
3. Diagnosis of ER positive invasive breast cancer, stages 1-3 and treated with curative intent
4. Completed surgery for breast cancer
5. Within **14 weeks of first oral Adjuvant ET prescription** (tamoxifen or aromatase inhibitor) post breast cancer completion surgery
6. Completed chemotherapy (if applicable)
7. Able to access the internet
8. Has access to an email address
9. Are willing to use a support package with a web-based component.

The following women will also be eligible providing they fulfil the above criteria:

- *Women undergoing, or planned to receive radiotherapy,*
- *Women receiving anti-HER2 therapies,*
- *Women receiving ovarian suppression drugs,*

- *Women receiving, or planned to receive an adjuvant CDK4/6i (e.g. abemaciclib)*
- *Women who received neo-adjuvant ET*
- *Women who have had a previous primary breast cancer (as long as they did not have AET to treat that first cancer).*

3.1.2 Exclusion criteria

1. Male
2. Evidence of metastatic disease i.e. stage 4 disease (M1 regardless of T and N status)
3. Previous AET for another previous breast cancer
4. Have cognitive impairment sufficient to preclude participation, as judged by the clinical team
5. Are unable to read and understand English

4. STUDY PROCEDURES

4.1 Participant identification

Potentially eligible women will either be identified via multi-disciplinary team meetings (MDT) or hospital records. A member of the local research team will review the women's medical records to assess eligibility. Any staff reviewing participants records to screen for eligibility prior to consent should be embedded within the participants clinical care team (which is inclusive of the site research team).

A Participant Information Sheet (PIS) will then be provided by the local research team, either in person or by post or email, and patients should be given 24 hours where possible to consider their participation, prior to obtaining informed consent. A letter of invitation has been designed and can be used to support the remote approach of potential participants if needed.

All women considered as potentially eligible and approached regarding the study should be added to the screening log, as well as their outcome in terms of trial entry.

4.2 Informed consent

It is the responsibility of the local Principal Investigator (or trained designee as listed in the Site Signature and Delegation Log) to obtain informed consent in compliance with international requirements from each patient prior to entry into the trial. Discussions about trial participation may take place during an in-person consultation or remotely. **In all settings, either in person or following the remote consent process, the patient will be provided with a copy of the PIS.** The patient will be given the opportunity to ask questions and to be satisfied with the responses prior to consent being given. The right of a patient to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time without giving reasons and without prejudice to any further treatment. Patients will also be provided with a contact point where they may obtain further information about the trial.

Where possible, to reduce digital exclusion technical equipment (and technical support) such as tablets will be provided to participants that do not have the required technology to take part in the trial.

Full written consent (in person): The local Principal Investigator or designee receiving consent must countersign the consent form. The consent form should be signed and dated before conducting any trial related activities. A copy of the signed consent form must be provided to the participant.

Remote verbal consent: For participants who do not attend site to provide written consent, verbal consent can be taken by telephone/videocall. The local Principal Investigator or designee or study team researcher receiving consent must read out each point on the consent form individually and must initial each box to confirm the participant agrees to each point. The consent form must be signed by the local Principal Investigator or designee and countersigned by a witness. A copy of the signed consent form must be provided to the participant (either by post, email or in person).

The PIS and Consent Form will be available in electronic format to facilitate printing onto local headed paper. Current versions of the PIS and ICF will be uploaded on the trial website. Signed original consent forms will be retained on site and should be stored in the investigator site file with a copy filed in the patient's hospital notes. Completed Consent Forms will not be sent to the SWEET Trial Office at Warwick Clinical Trials Unit (WCTU).

A copy of the fully signed consent form will be given to the patient. Copies may be on paper or electronic format according to site standard procedures. Sites will ensure that patients' participation, and result of randomisation in the trial is recorded in the patient notes and is communicated to the patient's General (or family) Practitioner using the relevant study specific GP letter. If the PIS and/or Consent Forms are modified during the course of the trial, sites will be notified of any required procedure to follow for patients already consented.

4.3 Baseline

Participant demographics and medical history will be collected prior to randomisation. A participant questionnaire, with questions on adherence, health-related quality of life and other topics, must also be completed prior to randomisation.

4.4 Randomisation

4.4.1 Randomisation

Before randomising a participant, informed consent must have been obtained and confirmation of trial eligibility documented in the patient's medical notes.

Sites will log on to the SWEET randomisation portal to randomise the participant via the link below:

Patients can be randomised via the SWEET database:

https://ctu.warwick.ac.uk/SWEET

In the unlikely event the randomisation portal is not available, sites should contact the dedicated WCTU registration/randomisation line on 02476150402 (Mon-Fri 9am-5pm) excluding bank holidays & Christmas closure.

As part of the randomisation process, the participant will be assigned a unique trial number (TNO) that will be used to identify the participant and be recorded on all CRFs and on any correspondence with the SWEET Trial Office. This TNO will also be used to track patient participation, data, questionnaires, etc. throughout the trial to avoid transfer of patient identifiable data.

Automated confirmation of the participant's randomisation details, TNO and trial arm allocation will be sent by email to the PI, randomising practitioner, and main contact for the site research team.

4.4.2 Method of Implementing the Trial Arm Allocation

Participants will be randomised on a 1:1 basis to the HT&Me intervention + usual care, or to usual care alone. Trial arms will be allocated randomly using a computer minimisation algorithm held centrally at the WCTU and stratified by the following variables:

1. Age: <50, 50+
2. AET: Tamoxifen/AI
3. Treatment complexity
    i. No chemotherapy, no anti-HER2, no CDK4/6i (e.g., abemaciclib)
    ii. Chemotherapy, no anti-HER2, CDK4/6i (e.g., abemaciclib)
    iii. Chemotherapy, anti-HER2, no CDK4/6i (e.g., abemaciclib)
    iv. Chemotherapy, no anti-HER2, no CDK4/6i (e.g., abemaciclib)
    v. No chemotherapy, no anti-HER2, CDK4/6i (e.g., abemaciclib)

4.4.3 Post-randomisation withdrawals, exclusions and moves out of region

Participants may be withdrawn from the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. Should a participant withdraw their consent, their access to the HT&Me intervention may be revoked (if applicable) depending on their level of withdrawal.

For patients who are lost to follow-up, follow-up data should continue to be collected from hospital or GP records where possible, these patients should not be automatically withdrawn from the trial.

Patients moving away from the region of the local site will NOT be withdrawn from the trial. Every effort should be made to obtain the participants new address and continue to collect follow up information remotely; local research teams should contact the SWEET trial office for more information.

4.5 Trial treatments / intervention

4.5.1 HT&Me intervention (Arm A)

Participants randomised to the HT&Me intervention, will have a consultation with the SWEET study nurse/practitioner that will last approximately 30 minutes. Where possible, these consultations should take place within 4 weeks post randomisation, however an allowance of up to 8 weeks post randomisation is permitted in the event of any delays. This consultation should take place face-to-face or remotely by videoconferencing. If required, this consultation may take place by telephone call, but this should be reserved as a last resort. For sites using the Breast Cancer Now (BCN) model, these consultations will always be performed remotely by dedicated nurses at Breast Cancer Now. If a woman does not attend the consultation, up to two further appointments will be sent, with the option to reschedule again if the date or time does not suit. The date and time of the consultation will be confirmed by email or letter, and this will also include details on how to access the HT&Me animation so participants can watch this prior to the consultation. The animation (approximately 6 minutes) addresses necessity for AET and common AET concerns and supports self-efficacy, motivation, goal-setting and developing an adherence habit. The animation can be viewed here:

https://welcome.htandme.co.uk/

Prior to this consultation, the SWEET trial office will pre-register the woman with an account on the HT&Me web-app using their email address.

i. **Consultation 1:** This consultation will follow the consultation 1 guide, and using elicitation, will be tailored to the women's beliefs, concerns and AET behaviours. The SWEET study nurse/practitioner will also introduce the woman to the web-app, confirm log-in information and a contact number in event of any IT problems. A sample of consultations will be audio-recorded for the purpose of assessing fidelity. If they have not already accessed it, where possible, women will view the animation at the consultation. Following the consultation**,** the woman will be provided (by email or post), a copy of the "how to" guide for the web-app and the helpline number. The SWEET study nurse/practitioner should also complete a Consultation 1 appointment checklist.

For sites using the BCN model- this consultation will be performed remotely by a dedicated nurse at Breast Cancer Now.

i. **Access to the HT&Me Web app:** At consultation 1 with the SWEET study nurse/practitioner, the participant will receive access to the HT&Me web-app. They will continue to have access to this for the duration of their time in the study. The web app contains tools and information to support adherence to AET. Features of the web-app include information on the importance of taking AET, supportive information on common side effects and coping strategies, how to talk to family members as well as signposting to further support. It also contains interactive facilities to set daily reminders to take endocrine therapy and order repeat prescriptions, as well as facilities to record side effects of hormone therapy and their severity and impact which can be used to support ongoing conversations with medical professionals.

ii. **Consultation 2:** Approximately 12 weeks after consultation 1, a 15-20 minute consultation with the SWEET study nurse/practitioner will take place by telephone, or video call, or face-to-face if that is the women's preference. This consultation will follow the Consultation 2 guide and communicate the continuing importance of treatment and address any emerging AET-related concerns or issues. The consultation will be tailored around the woman's current necessity and concerns beliefs about AET. A sample of consultations will be audio-recorded for the purpose of assessing fidelity. If a woman does not attend consultation 2, up to two

further appointments will be sent, with the option to reschedule again if the date or time does not suit.
The SWEET study nurse/practitioner should also complete a Consultation 2 appointment checklist following the consultation.

For sites using the BCN model- this consultation will be performed remotely by a dedicated nurse at Breast Cancer Now.

Participants may be asked to provide brief feedback, using an automated SMS service, rating the value of these appointments using a numerical scale. This will help to capture some feedback on the intervention which may not easily be recalled at the point of the follow up questionnaire.

iii. **Web-app analytics:** App/website analytics will be collected in order to determine whether women use the web-app and, if so, how often and which elements.

iv. **Motivational messages:** At regular intervals during follow-up women will be sent an email or text message (according to individual preference) which will provide tailored prompts for adherence, reinforce the importance of continuing therapy, and indicate support is available if needed via the web-app. These will be interspersed with messages encouraging them to visit the web-app to access tailored information and support.

The motivational messages will be timed as follows:

- 2 weeks - message encouraging recipient to complete My Personal Support
- 1 month - motivational message
- 2 months - motivational message
- 3 months- motivational message
- 4 months- motivational message
- 5 months - message encouraging recipient to complete My Personal Support
- 6 months- motivational message
- 7 months- motivational message
- 8 months- motivational message
- 9 months- motivational message
- 10 months- motivational message
- 11 months - message encouraging recipient to complete My Personal Support
- 12 months- motivational message
- 13 months- motivational message
- 14 months- motivational message
- 15 months- motivational message
- 16 months- motivational message
- 17 months - Message encouraging recipient to complete My Personal Support
- 18 months- motivational message

A selection of the motivational messages are in Appendix 2.

4.5.2 Usual care alone (Arm B)

Participants randomised to usual care alone will continue to access AET as per institutional guidelines and will continue to be followed up (either at site or through their GP) as per institutional guidelines and follow up processes.

As breast cancer follow up varies across sites, usual care will be documented prior to site opening.

4.6 Follow-up assessments

Participants will be followed up at 6 months, 12 months and 18 months by means of questionnaires (completed on paper, or online) and linked prescription encashment/prescribing data. It is the responsibility of the site research team to distribute these questionnaires. Up to two reminders (by phone or email) to complete the questionnaires may be sent if needed. Subject to additional funding, longer term follow-up data will be collected for up to 15years to monitor adherence and recurrence.

4.7 End of trial

The end of study will be defined as last data capture for the last participant, allowing three months after this to return CRFs and answer data queries. The CI will notify the Sponsor, participating sites, and REC within 90 days of the end of study, or within 15 days if the study is ended prematurely. The clinical study report will be written within 12 months of the end of study. Further funding will be sought for longer term follow up and consent for this will be obtained at recruitment.

4.8 Parallel process evaluation

A parallel process evaluation will be undertaken, using a mixture of qualitative and quantitative methods. The aims of the process evaluation are to:

- Explore fidelity of the intervention as delivered, received and enacted
- Assess whether the intervention worked as hypothesized by the logic model
- To identify any moderating contextual factors and/or unintended consequences of the intervention.

Semi-structured telephone interviews will be conducted throughout the trial with participants (Arm A, n=25-30; Arm B, n=10-15). Participants will be purposively selected to ensure maximum variation of characteristics (including socio-demographic and socio-economics, AET type, site). At the time of recruitment, participants will be given the option to consent for the purpose of undertaking an interview.

Interviews with SWEET study nurses/practitioners (n=20-25) will also take place. These interviews will explore:

- Views and experiences of the trial, intervention, and Behaviour Change Techniques (BCTs) (as appropriate)
- Intervention fidelity and quality
- Potential contamination
- Contextual factors

In addition, the interviews with the SWEET study nurses/practitioners will discuss what would need to be in place (i) to maintain the intervention as a part of usual care in the absence of the trial/research team; and (ii) to provide the intervention to women who do not speak English. SWEET

study nurses/practitioners who are approached to take part in process evaluation interviews will undergo a consent process with a researcher from the central team, the site PI or their trained delegee. PIS will be provided and will be available in electronic format and can be printed. The SWEET team will ensure any consent forms completed by the central team researcher are returned to the recruiting site where possible or stored securely at the SWEET trial office based at WCTU.

These interviews will be spread across participating sites and throughout the duration of the study. Interviews can be conducted face-to-face,by telephone, or via a conferencing platform such Microsoft Teams or Zoom as the interviewee prefers. They will be audio-recorded (with consent), transcribed, anonymised, coded inductively, and subject to thematic analysis using a framework approach [69]. Standard approaches to the rigorous analysis of qualitative data [70] will be used throughout. To further assess contamination, at a sample of sites, the research team may observe a sample of relevant usual care appointments (e.g. post-surgery, end-of-treatment, follow-up appointment; n=5) within a one-week time window. They will then compare usual care during the trial with that documented before the trial commenced. To understand mechanisms of action of the intervention, structural equation modelling approaches [71] will be used estimate the proportion of the intervention effect on the primary outcomes that occurs via the putative mediator variables that are the target of the intervention. This analysis will inform understanding of whether and to what extent the mediator variables were influenced by the intervention and, hence, how the intervention “worked”.

4.9 Schedule of assessments

Visit	**1**	**2**	**3**	**5**	**6**	**7**	**8**
Visit Window (No. Weeks ± No. Days)	**Baseline**	**Week 4** (+4 weeks)	**Week 16** (+4 weeks)	**6 months** (+/- 1 month)	**12months** (+/- 1 month)	**18 months** (+/- 1 month)	**Long term follow-up** *Annually up to 15years**
Informed consent	x						
Medical history	x						
Inclusion/exclusion criteria	x						
Questionnaire booklet	x			x	x	x	
Randomisation	x						
Consultation 1 with SWEET study nurse/practitioner		x ***(ARM A ONLY)***					
Access to the HT&Me web-app		x ***(ARM A ONLY)***					
Text or email motivational nudges		x ***(ARM A ONLY)***					
Consultation 2 with SWEET study nurse/practitioner			x ***(ARM A ONLY)***				
HT&Me automated text feedback		x ***(ARM A ONLY)***	x ***(ARM A ONLY)***				
Encashment data linkage				x	x	x	x
Survival status				x	x	x	x
Disease recurrence assessment				x	x	x	x

**Subject to additional funding*

4.10 Site staff training

PIs may be drawn from a range of health care professionals at participating sites. Nurses/allied healthcare professionals (NAHPs) with experience in breast cancer, and/or oncology are also actively encouraged to act as local PIs. Staff specific trial training will be provided to all staff.

A bespoke standardised, one day training package will also be provided for nurses/practitioners for undertaking the SWEET consultations.

4.11 Contamination

To reduce contamination, where possible, staff members conducting the SWEET consultations should not be routinely involved in providing AET support available at their site.

Availability of dedicated AET services will be explored with all new sites as part of the feasibility assessment, level of services will be recorded, and any decisions made by the Trial Management Group (TMG) as to whether or not these sites are included in the study. The research team may observe a sample of relevant usual care appointments (e.g. post-surgery, end-of-treatment, follow-up appointment) at a sample of sites to assess contamination.

4.12 Co-enrolment into other trials

As a non-CTIMP, it is expected that co-enrolment to SWEET will be permitted. Patients randomised into SWEET can be enrolled into other studies as long as this has been agreed with the TMG and they do not affect the SWEET outcomes. Once agreed, these trials will be added onto a rolling list of trials permitted for co-enrolment.

5. ADVERSE EVENT MANAGEMENT

All treatment administered to participants is identical to the treatment given in normal clinical practice, for which there is extensive safety data already available. Due to the low-risk nature of the intervention, adverse event reporting will not be required for this trial.

6. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the current UK GDPR.

6.1 Data collection and management

The (CRF) will comprise of a set of forms capturing details of eligibility, baseline characteristics, treatment(s), and outcome details. This trial will use an electronic data capture (EDC) system which will be used for completion of the CRF. Access to the EDC system will be granted to approved site personnel via the Trial Office. If the use of a paper CRF is required, then original forms should be sent to the co-ordinating team at WCTU and copies retained on site. CRFs are expected to be completed within 4 weeks of their due date. Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. Missing and ambiguous data will be queried in line with the WCTU data management plan, which will outline the requirements for CRF completion and return.

To obtain prescription encashment data, a file containing details required for matching (name, date of birth, NHS number (or equivalent e.g. Scottish CHI number, Northern Ireland H&C number), study number, and address (partial postcode)) will be provided to the appropriate Data Controller(s) and/or Data Processor(s) for application and data release. These Data Controllers/Processors will be as follows:

- NHS England (England)
- Public Health Scotland (PHS) (Scotland);
- NHS Wales Shared Services Partnership (NWSSP) Primary Care Services (PCS) on behalf of Health Boards in Wales under a Service Level Agreement. Please note that NWSSP are the Data Processor of the data held rather than the Data Controller for the prescribing element of the Welsh component of the SWEET study (Wales).
- Family Practitioner Services (FPS) in Health and Social Care (HSC) Business Services Organisation (BSO) and the Strategic Planning and Performance Group (SPPG) within the Department of Health (Northern Ireland).

The datasets to be accessed for each devolved Nation are as follows:

- Medicines Dispensed in Primary Care NHS Business Service Authority (NHSBSA) Dataset (England)
- NHS Wales Prescribing Dataset (Wales)
- Prescribing Information System (Scotland)
- Enhanced Prescribing Dataset (Northern Ireland)

Identifiable patient level data of endocrine therapy and other prescriptions encashed for each woman at baseline, and throughout the RCT will be requested to enable linkage to clinical and demographic details recorded at initial RCT recruitment. However, linked datasets for analysis will be pseudonymised. It is anticipated that such data requests will occur twice for each nation (initial data access request and at the end of the RCT). Where it is not feasible to obtain encashed prescription data or in instances where additional prescription information would prove useful, GP prescribing data for participants with a focus on breast cancer prescriptions will be sought directly from GPs..

6.2 Source data

Source documents are where data is first recorded, and from which participants' CRF data is obtained. These include, but are not limited to, hospital records (from which medical history and previous and concomitant medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, GP prescription records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the TNO, not by name. Investigators should keep records of all participating patients, all original signed ICFs and copies of any paper CRFs. It is necessary for investigators to provide access to source document for monitoring and audit purposes to WCTU, Sponsor, any monitoring or regulatory authorities as deemed necessary.

6.3 Data Handling and Record Keeping

The database will be developed and managed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff. The database will meet industry standard security criteria and only be accessible to authorised personnel. Within the database, participants will be identified by the TNO only.

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

Personal data (including name, email and contact information) entered onto the HT&Me web app will be securely stored online on Microsoft Azure (hosted in the UK) within a two-layer encrypted folder. The information collected on use of the website ("analytics") will be anonymous and will be stored securely on Microsoft Azure cloud which is hosted within the UK. IP addresses will not be collected.

Interviews and SWEET consultations (where applicable for the purpose of assessing fidelity) will be recorded using encrypted audio devices or using a conferencing platform such Microsoft Teams or Zoom. Recordings will be securely sent to WCTU using a secure file transfer system and downloaded as soon as possible to encrypted university laptops and subsequently to the secure study area on the university servers. Once downloaded, recordings should be deleted from their original source. Any data that are transferred out of the secure environment (for example audio files of consultations for transcription) will adhere to University of Warwick SOPs. Any transcription service used will be subjected to the University of Warwick's approved supplier review processes. Study participants TNO will be used to label any recordings.

6.4 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

6.5 Access to data

Direct access will be granted to authorised representatives from the Sponsor, the WCTU monitoring team, host institution and the regulatory authorities to permit study-related monitoring, audits, and inspections. The co-CIs, those responsible for analysis and the WCTU administrator (or delegate) will have access to the final study data set.

6.6 Data access and quality assurance

The study will be conducted in accordance with the current UK General Data Protection Regulation (UK GDPR). The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. To preserve anonymity, participants will be identified on all study specific documents (except for the informed consent form and enrolment log) by only the TNO. This identifier will be recorded on documents and the database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

All documents will be stored securely with access restricted to study staff and authorised personnel.

To support the intervention delivery, the participant will be asked for their consent to provide their name and contact details (email address and telephone number) and for this to be shared with the central research team for the purpose of creating HT&Me accounts, and the BCN team (where BCN will be responsible for conducting the SWEET consultations), and the research team (based at UCL and OBU) responsible for conducting the process evaluation interviews. Personal data, including name, NHS number (or individual devolved nation equivalent), contact details will be stored securely on the database and security roles would be applied to ensure only those people who require access to participant identifying data are granted access. Participants should be assured that their confidentiality will be respected at all times.

Linked datasets obtained from NHS England or equivalent (and/or GP's) will be pseudonymised and securely stored to enable analysis.

Newcastle upon Tyne Hospitals NHS Foundation Trust and the University of Warwick will act as joint data controllers for this study.

6.7 Archiving

At the end of the study, following completion of the end of study report, NuTH and WCTU will securely archive all centrally held study related documentation for a minimum of 10 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of 10 years after the end of study, and in accordance with national legislation. WCTU will notify sites when study documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request. Trial documentation and data will be archived for at least 10 years after completion of the trial.

7. STATISTICAL ANALYSIS

7.1 Power and sample size

We have powered the trial to detect differences in the primary outcomes (poor adherence & cancer-specific HRQoL). The "decision-making framework" which we will adopt is that the intervention will be considered efficacious if it has effects on both primary outcomes. Therefore, no adjustments will be made to control the Type I error rate, which will be 0.05 throughout.

In total, approximately 2920 eligible patients will be approached for inclusion within the trial. Based on acceptance rates in other early breast cancer trials, we assume 50% of those eligible will consent to trial participation, thus leading to a sample size of 1460 participants. Of these, 730 will be randomised to intervention + usual care and 730 to usual care alone.

In terms of assessment of adherence, based on our experience, we assume 15% loss to follow-up in both arms and thus the final sample size with adherence data available will be 620 per arm. Based on reported data, we assume 10% of women in the usual care alone arm will have poor adherence at 18 months. There is no evidence on how high adherence needs to be to maintain the full clinical benefit

of AET for an individual woman, so the clinically important difference is unknown. However, reducing poor adherence across the patient population to around 5% is considered achievable. With a 5% two-sided significance level, 620 women in each arm will provide 90% power to detect as statistically significant a difference of 5% in poor adherence rates (e.g. consistent with a reduction from 10% to 5%).

In terms of assessment of cancer-specific HRQoL, higher FACT-G scores indicate better quality of life. The minimally important difference (i.e. the smallest difference in score that patients perceive as important, either beneficial or harmful, and that would lead the clinician to consider a change in the patient's management) is 3-7 points. Based on our own data, we assume that the mean FACT-G score will be 83.9 in the usual care arm (sd=15.9). Allowing for up to 20% non-completion/lost-to-follow-up, randomising 730 women to each arm will provide at least 99% power to detect a difference of 4 points in FACT-G scores between arms; and at least 89% power to detect a difference of 3 points (α=0.05, two-sided test).

In addition to the assessment of the primary outcomes, the current sample size could also provide sufficient power to detect, as significant, a plausible difference in risk of breast cancer recurrence at five years. However, this would require additional funding to be sought for longer follow-up than is currently within this project's remit.

7.2 Statistical analysis of efficacy and harms

7.2.1 Statistics and data analysis

A detailed statistical analysis plan (SAP) will be drafted by the trial statistician, which will be finalised and approved by the CIs and an independent statistician before the final data analysis.

All statistical analyses will be undertaken on an intention to treat basis where possible to preserve randomisation, avoid bias from exclusions and preserve statistical power. Hence all participants randomised into the trial, regardless of whether they received their randomised intervention, will be analysed according to their randomised group using data collected up to their final follow-up in the trial (18 month time point, or the last timepoint prior to their withdrawal or loss to follow-up).

The primary endpoint of poor adherence will be determined for each woman using, as recommended as best practice, a combination of an objective measure (prescription encashment records or, if not available, prescribing records) and a subjective measure (self-report using the MARS-5).

Prescription encashment records, although considered a good measure of adherence, slightly over-estimates adherence as people may collect medication but not use it. Self-report is highly specific for non-adherence and its use will reduce misclassification in adherence measured using encashment data. We will obtain participants' individual prescription refill records from prescribing datasets (such as Medicines Dispensed in Primary Care NHSBSA Dataset and equivalents in devolved nations, or primary care prescribing records). Accuracy of the Medicines Dispensed in Primary Care NHSBSA dataset processed prescriptions exceeds 99.7%. A measure of medication adherence, e.g. Medication procession ratio (MPR) will be computed for each woman; this is a measure of medication availability calculated as the proportion of prescribed days' supply obtained during the specified observation period. We, and others, have previously successfully used routine encashment records to measure AET adherence. Convention is that a MPR<80% is considered poor adherence: this is the level of (non)adherence to AET which is associated with increased risks of recurrence and breast cancer

mortality. For each woman, we will categorise MPR as ≥80% or <80% (i.e. <80% of the doses required to complete 18 months of AET measured from randomisation or, for women who are advised to cease AET, relapse, die or withdraw, <80% of the doses required in the time from randomisation to end-of-follow-up).

The MARS-5 [55] consists of five general statements about suboptimal adherence behaviour answered on a 5-point scale where 1 represents always and 5 represents never. It has been widely used, including by ourselves, to measure self-reported AET adherence. Our own data (co-applicant Hughes, suggests that a MARS-5 score of ≤23 (out of a possible 25) represents poor adherence to AET.

For the primary endpoint of poor adherence, women will be classified as having poor adherence if they have a (MPR<80%) OR (a MPR ≥80% and a total MARS-5 score of ≤23). Women who have a MPR ≥80% AND a total MARS-5 score of >23 will be classified as having adequate adherence.

For the primary endpoint of cancer-specific HRQoL, the FACT-G [56] questionnaire contains 27 statements; respondents indicate the extent to which each has applied over the past 7 days on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much) and question responses are summed.

Poor adherence rates at 18 months will be assessed across randomised arms using logistic regression methods to adjust for stratification variables. For the cancer-specific HRQoL assessment at 18 months, each randomised arm's point estimate (and 95% confidence interval) will be reported, and linear regression methods used to assess across randomised arms, with adjust for stratification variables. Appropriate longitudinal analyses will also be utilised for assessment of AET adherence and HRQoL over time.

Breast cancer recurrence free interval (RFI) will be calculated to the date of first invasive breast cancer relapse (local or distant). Patients without a recorded breast cancer relapse at time of analysis will be censored at date last seen, for patients alive and relapse-free, or date of death for those dying of other causes. Survival curves will be plotted using the Kaplan-Meier method and the HR between the two groups estimated using a Cox's proportional hazards model including randomised arm and the stratification variables.

The stratification variables, used at randomisation and to be included within the multivariable analyses specified above, are:

1. Age: <50, 50+
2. AET: Tamoxifen/AI
3. Treatment complexity
    i. No chemotherapy, no anti-HER2, no CDK4/6i (e.g., abemaciclib)
    ii. Chemotherapy, no anti-HER2, CDK4/6i (e.g., abemaciclib)
    iii. Chemotherapy, anti-HER2, no CDK4/6i (e.g., abemaciclib)
    iv. Chemotherapy, no anti-HER2, no CDK4/6i (e.g., abemaciclib)

v. No chemotherapy, no anti-HER2, CDK4/6i (e.g., abemaciclib)

Additionally, pre-specified sub-group analyses defined by these stratification variables will be undertaken using appropriate modelling techniques. These exploratory sub-group analyses will have lower power than the main whole trial analysis but are hypothesis-generating and results will be scrutinised graphically via forest plots.

7.2.2 Planned recruitment rate

Recruitment will take place in up to 80 NHS hospitals across the UK (England, Wales, Scotland, and Northern Ireland) with a track record of delivery on clinical research, in order to facilitate enrolment of the required number of participants and ensure relevance to the wider NHS. Assuming a sample size of 1460 participants, participants will be recruited over a planned 24 months duration.

7.2.3 Summary of baseline data and flow of patients

Descriptive statistics will be used to summarise the distribution of baseline variables across each of the randomisation arms. Continuous variables will be reported with means and 95% confidence intervals, if normally distributed, or medians and Interquartile Ranges (IQR) otherwise. Categorical variables will be reported using frequencies and percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram [72] will be produced, showing the frequency of participants:

- Assessed for eligibility
- Excluded prior to randomisation (and the frequency of each reason for exclusion)
- Randomised
- Allocated to each randomisation arm
- Receiving or not receiving their randomised treatment
- Followed-up at each protocol specified timepoints
- Lost to follow-up at each protocol specified timepoints (and the frequency of each reason for loss to follow-up)

7.3 Health Economic Evaluation

Workstream 4 (WS4) will include; 'within-trial' analysis to determine intervention cost-effectiveness; a budget impact analysis; and modelling of long-term cost-effectiveness. The base case analysis will adopt an NHS and Personal Social Services perspective, with a sensitivity analysis exploring the societal perspective.

Data on resource use that women considered related to their breast cancer or side effects/complications will be collected directly from women in the RCT at baseline, 6, 12 and 18 months. This will include medications, follow-up primary care consultations, hospitalisations, chemotherapy, radiotherapy, surgery, costs incurred by patients and their families/carers and days lost from work/usual activities due to ill health. The EQ-5D-5L [58] will be administered at baseline, 6, 12 and 18 months. Supplementary information on key non-AET medication data will be obtained from linked prescription record datasets. Intervention costs will be estimated during WS3. Within-trial cost and QALY differences between intervention + usual care and usual care alone will be reported and explored alongside measures of adherence within a cost-consequences framework. Incremental cost-effectiveness (cost per QALY) will be estimated, with robustness of results evaluated

in sensitivity analyses. The incremental cost-effectiveness ratio (ICER) will be compared against thresholds used to establish value for money in the NHS (currently £20,000-£30,000 per QALY) [73].

Resource events and corresponding costs will be scaled-up to ascertain national NHS cost/budget impact.

If the trial meets its primary endpoint, to account for longer-term economic consequences and patient benefits (including effects on survival), a cost-effectiveness model will developed de-novo or based on previous models such as McCowan et al [74] and adapted using RCT data and results. Expected costs and QALYs for the intervention + -usual care and usual care alone will be estimated and compared using ICERs, across a lifetime horizon, assuming AET treatment for the recommended period (5-10+ years). Cost-effectiveness is likely to be influenced by key model variables including efficacy, patient age, disease stage, and adherence. The impact of these with other variables will be explored in sensitivity and subgroup analysis.

8. TRIAL ORGANISATION AND OVERSIGHT

8.1 Sponsor and governance arrangements

Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) are the sponsor for this study. The trial will be conducted in accordance with the principles and guidelines of the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) [75], UK legislation and relevant SOP's. GCP-trained personnel will conduct the trial.

8.2 Ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of Capacity and Capability (CC&C) is received by NuTH and WCTU.

8.2.1 Amendments

All amendments will be documented by the SWEET Trial Office. Substantial amendments will be submitted for HRA Approval, which includes NHS REC review, prior to communication to relevant participating NHS Organisations. Non-substantial amendments will be submitted to the HRA, and the applicable national coordinating functions in the devolved administrations, for review. Each trial site must ensure that they are using the most up to date version of the protocol, the PIS and ICFs. All previous versions of the protocol, and other trial documents should be crossed out and marked as 'superseded', initialled and dated on the cover page.

8.2.2 Annual Reports

SWEET Trial staff will send an annual trial update report to the NHS REC within 30 days of the anniversary date on which favourable opinion was given. This will be distributed to the local research team at each trial site. It is the responsibility of the local research team at each site to send a copy of this report to the research management function (e.g. R&D Office) in accordance with local requirements and recommendations made by the NHS REC. Any additional local information required

must also be submitted. Additional data required by NHS Trusts is available from the SWEET Trial Office on request.

NHS REC will be notified at the end of the trial, either at the planned end of study or prematurely. NHS REC will be notified within in writing within 15 days if the trial has been concluded or terminated early. The CIs will submit a final report to NHS REC with the results and any study publications within one year of the end of trial.

8.2.1 Peer review

This study has been independently peer reviewed as part of the NIHR's programme grant application process.

8.3 Trial Registration

SWEET is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register: ISRCTN24852890

8.4 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or

(b) The scientific value of the study.

If a serious breach is confirmed by clear and unequivocal evidence, the study Sponsor must notify the REC within 7 days of the matter coming to their attention. The Corrective and Preventative Actions Report template, supplied by WCTU, may be used for this purpose.

8.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

8.6 Trial timetable and milestones

Month	**1-6**	**7-16**	**17-24**	**25-31**	**32-49**	**50-55**
Trial set up: protocol development						
Approvals						
Patient recruitment						
Data collection & Patient follow-up						
Data cleaning						
DMC/TSC meetings						
Data analysis						
Dissemination						
Trial close down						

8.7 Administration

The trial co-ordination will be based at WMS/WCTU, University of Warwick.

8.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

8.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the Data monitoring committee (DMC)
- Informing and advising on all aspects of the trial

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members. The TSC responsible for oversight during the feasibility study is expected to continue oversight for the main RCT.

8.10 Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (DMC) will be established for this trial.

DMC meetings will also be attended by the Co-Chief Investigators and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members. The trial will meet prior to commencement and then annually thereafter or more frequently if requested, The DMC will review the main trial for trial progress, recruitment, protocol compliance and interim assessment of outcomes, annually or more frequently if requested. The DMC will advise the TSC whether the trial should continue, be amended or stop prematurely based on the trial data monitored and any future publications or emerging worldwide evidence.

8.11 Essential Documentation

A Trial Master File will be set up according to Warwick SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

8.12 Financial Support

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9. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment. It is anticipated that monitoring activity will be predominantly central with remote visits scheduled if required.

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or equivalent local regulatory bodies for international centres. Authorised representatives of the Sponsor may visit the participating sites to conduct audits/ inspections.

All forms will be checked for completeness and consistency and any anomalies will be queried with the site. The trial staff will maintain regular communication with sites through routine calls, mailings and meetings. In the event of persistent issues with the quality and /or quantity of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. A representative from the Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and to determine the site's future participation in the trial.

10. PATIENT AND PUBLIC INVOLVEMENT (PPI)

PPI have been actively involved from the start in planning meetings and commenting on iterations of the proposal. They have also consulted widely with members of local support groups, their own social networks, colleagues on the NCRI Consumer Forum and through Independent Cancer Patient Voices and have actively fed views back into the development process.

A Patient Advisory Group (PAG) was established at the outset of the study, which includes a diverse group of 11 women with a range of experiences of AET. The PAG meet regularly and have been closely involved in co-designing the intervention web-app and in developing the scripts for consultations 1 and 2. They have also reviewed the patient-facing documents and provided input to the choice of questionnaires for assessing outcomes and mediators. The PAG will also provide a patient perspective on the write-up of papers, will help produce lay summaries, and with presenting the study findings results at conferences, support groups and charity group open days. The PAG also form part of the programme monitoring committee (PMC)

We also established a wider PPI group called a Community of Interest (CoI)**.** The CoI includes 28 women with breast cancer who have been recommended AET. The CoI is consulted, mainly by email, on an ad hoc basis, as and when needed. They were extensively consulted in the development of content for the web-app and several members of the group pre-tested the web-app.

Beyond PPI, we have also engaged with a wide range of stakeholders. In developing the programme, we sought advice from consultants in breast cancer, breast cancer nursing groups (e.g. Pan London Breast Care Nurses) and the third sector (BCN, Macmillan Cancer Support). The programme has the support of the NCRI Breast and Psychosocial and Survivorship Groups and Breast Symptoms Working Group.

During the programme, we have established a Clinical Reference Group which includes breast cancer surgeons, oncologists, GPs, pharmacists, cancer specialist nurses, community nurses, and a clinical psychologist and a dietitian with expertise in breast cancer. We consult with this group regularly, including on eligibility criteria, clinical aspects of the intervention content, and the content of the navigator appointments.

We also work closely with BCN, who are partners in the programme.

11. DISSEMINATION AND PUBLICATION

Our dissemination strategy includes conference presentations, scientific papers, regular social media and lay communications, and briefings (paper, digital and events) for clinical teams, patient groups and commissioners.

We are establishing a SWEET programme website. The website will contain information for both scientific and lay audiences, including the study protocol and a final study report. We will also design a twitter handle so that we can post key information, share progress and encourage engagement and debate throughout the programme.

For scientific dissemination, the research findings will be presented at relevant national and international meetings (e.g. National Cancer Research Institute conference, UK Society of Behavioural Medicine conference, UK Interdisciplinary Breast Cancer Symposium, European Breast Cancer Conference). Papers will be submitted to journals, for example, in cancer survivorship (e.g. The Breast, J Cancer Survivorship, Support Cancer Cancer), and psycho-oncology/behavioural science (e.g. Psycho-Oncol, Implement Sci, Patient Educ & Counselling). Papers and conference presentations will be publicised on the project website.

For lay dissemination, research participants will be given the option of receiving a lay summary of the findings once the study is completed. To reach patient and general populations, updates will be posted on the project website, with key messages (crafted together with the PPI Panel) highlighted. We may hold a dissemination event for breast cancer survivors and healthcare professionals. If there is sufficient interest, we will live stream this event to other locations (e.g. collaborating centres). We may also record parts of the event and post on the website.

11.1 Data Shared with Third Parties

The Trial Management Group supports the sharing of outcome data with other researchers wishing to undertake additional analyses such as meta-analysis once the primary analysis of the trial has been published. Any requests for access to the trial data should be sent to the CI and should describe the

purpose, scope, data items requested, analysis plan and acknowledgment of the trial management team. Any data transfer would be in accordance with NuTH & University of Warwick SOPs and require data sharing/processing agreements to be in place.

Appendix 1: Background and overview of the HT&Me intervention

Approach to development

Our intention was to develop an intervention that is evidence-based, theoretically-informed, effective and sufficiently flexible to adapt to local health-provider circumstances, thus potentially scalable and implementable in the NHS. We addressed shortcomings of previous research by building on our preparatory work to systematically develop, test and evaluate the intervention, following MRC guidance throughout.

We have worked in collaboration with service users and primary and secondary care stakeholders, using the Person-Based Approach, which prioritises and incorporates user perspectives wherever possible, while ensuring the intervention retains all the elements that theory and evidence suggest will be effective in supporting AET adherence.

The version of the intervention which is being used in the study has gone through extensive pre-testing with the SWEET PAG, and through two optimisation studies (IRAS 293238), and a feasibility study (IRAS 307011). Thus the intervention is based on evidence, theory and extensive user input and testing.

Underpinning principles & theory

The overarching principle of the HT&Me intervention is that it will support women to self-manage their AET. Self-management interventions seek to equip people with the skills and confidence to manage a chronic condition and are predicated on improving self-efficacy. Therefore, Bandura's social cognitive theory underpins the intervention.

In terms of AET adherence, the underpinning is provided by the Perceptions and Practicalities Approach (PAPA). The NICE Medicines Adherence Guidelines [40] recommends PAPA as an overarching framework for developing, and providing, adherence support. PAPA views adherence as a variable behaviour rather than a trait characteristic. It takes a 'no-blame' approach to non-adherence that encourages honest disclosure and then tailors support to address specific perceptions (e.g. beliefs about the treatment and condition) and practicalities (e.g. capabilities and resources) influencing the patients' motivation and ability to start and continue with treatment [76]. The core principle is that adherence support must take account of the patient's evaluation of the treatment addressing two adherence-related beliefs: necessity and concerns (The Necessity Concerns Framework (NCF)) [77]. The NCF and Leventhal's Common Sense model [78] can be applied to address salient adherence-related perception. Alongside this, it is also important to address practical issues that might impact on an individual's ability to adhere (e.g. having an adequate supply of the medication).

Focus and elements of intervention

The focus of the HT&Me intervention is on preventing non-adherence. Starting AET is a potential teachable moment when women may be more receptive to adherence support shaping their AET beliefs. We will create a common-sense rationale early on in a woman's course of AET for why it is important to take the medication and continue long-term. The intervention addresses practical issues that inhibit adherence, and women's perspectives of AET, from the outset of treatment; this means that support can be provided to overcome misconceptions and barriers and address specific concerns that would otherwise lead to non-adherence.

Informed by our preparatory work, the intervention comprises two elements: front-loading and lighter-touch (nudge-like) follow-ups, supplemented with a web-app. Within these two elements, the intervention will have five components which are described above in detail:

i. Consultation 1 with a SWEET study nurse/practitioner
ii. Access to the HT&Me Web app
iii. Consultation 2 with a SWEET study nurse/practitioner
iv. Web-app analytics
v. Motivational messages

Appendix 2: Example Nudge Messages

Nudge example 1:

Hello <name>,

Making a plan can help you build taking your hormone therapy into part of your daily routine. Why not try taking your tablet before or after something you do every day like brushing your teeth? This can help make taking it become an automatic process. This will make it less likely that you'll forget.

To make your plan to take your hormone therapy, go to the **Taking Hormone Therapy** section of the HT&Me website.

To go to the HT&Me website please click this link https://htandme.co.uk/#home/taking-ht/my-plan. If clicking on this link doesn't work, please type htandme.co.uk into your browser *(the bar at the top of your screen where you can type things in to search for them).*

Remember, the HT&Me website includes lots of other information, such as hints and tips for managing side-effects, advice on how to be more active, and experiences of other women with breast cancer.

If you have any problems at all accessing the website please contact HTandMesupport@warwick.ac.uk

The HT&Me Team

Nudge example 2:

Hello <name>,

Knowing how hormone therapy works can really help you to understand why it's important to keep taking it every day.

If you haven't already done so, you can watch a video about hormone therapy in the **Taking Hormone Therapy** section of the website. It explains how hormone therapy can help to protect you from cancer coming back. There is lots of other useful information in this section – including answers to some of the questions you might have about hormone therapy.

To go back to the HT&Me website click on this link https://htandme.co.uk/#home/taking-ht.

If clicking on this link doesn't work, please copy and paste or type the link into your browser *(the bar at the top of your screen where you can type things in to search for them).*

Remember, the HT&Me website includes lots of other information, such as advice on how to live a healthier life, tips on dealing with difficult emotions and access to a side-effect diary.

If you have any problems accessing the website please contact HTandMesupport@warwick.ac.uk

The HT&Me Team

Nudge example 3:

Hello <name>,

Some women do not experience any side-effects of breast cancer treatment, but others experience significant side-effects. Side-effects can also change over time - you may find that you are experiencing side-effects now that you weren't before. There are many things you can do to help with side-effects. Why not take another look at the **Dealing with Side-effects** section of the HT&Me website for a range of hints and tips for managing these.

To go to the HT&Me website please click this link https://htandme.co.uk/#home/dealing-se.

If clicking on this link doesn't work, please type htandme.co.uk into your browser *(the bar at the top of your screen where you can type things in to search for them).*

Remember, the HT&Me website includes lots of other information, such as advice with talking to healthcare professionals more effectively, tips to be more active, and access to a side-effect diary.

If you have any problems at all accessing the website please contact HTandMesupport@warwick.ac.uk

The HT&Me Team

Nudge example 4:

Hello <name>,

Although hormone therapy is the most effective way to reduce the chance of breast cancer coming back, being active and having a healthy diet can help too. The **Healthy Living, Healthy Mind** section on the HT&Me website has suggestions, hints and tips for making changes to your lifestyle and looking after your physical and mental health. You can also make plans and set goals, such as being more active.

To go to the HT&Me website please click this link https://htandme.co.uk/#home/healthy-living.

If clicking on this link doesn't work, please type htandme.co.uk into your browser *(the bar at the top of your screen where you can type things in to search for them).*

Remember, the HT&Me website includes lots of other information, such as advice for dealing with difficult emotions, tips for talking with healthcare professionals more effectively and advice for managing side-effects.

If you have any problems at all accessing the website please contact HTandMesupport@warwick.ac.uk

The HT&Me Team

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