SWEET

SUPPORTING WOMEN WITH ADHERENCE TO ADJUVANT ENDOCRINE THERAPY FOLLOWING BREAST CANCER

STUDY PROTOCOL: SWEET FEASIBILITY STUDY

FULL TITLE OF THE STUDY
Improving outcomes for Women diagnosed with early breast cancer through adherence to adjuvant endocrine therapy.

SHORT STUDY TITLE (ACRONYM)
Supporting Women with adhErence to hormonE Therapy following breast cancer (SWEET)

PROTOCOL VERSION NUMBER AND DATE
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PROTOCOL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor.

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

For and on behalf of Sponsor:

Name (print):

Position:

Signature: **Date:**

Chief Investigator:

Name (print):

Position:

Signature: **Date:**

Principal Investigator:
I confirm that I have read and understood Protocol v1.0 dated 11/11/2021. I agree to comply with the study protocol, the principles of Good Clinical Practice and all required regulatory requirements.

Name (print): **Site:**

Position:

Signature: **Date:**

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B. STUDY SUMMARY

Study Title	Improving outcomes for women diagnosed with early breast cancer through adherence to adjuvant endocrine therapy
Short Title	Supporting Women with adhErence to hormonE Therapy following breast cancer (SWEET).
Overview of programme of work for SWEET	This programme of work aims to develop and evaluate an intervention to reduce poor adherence to adjuvant endocrine therapy (AET) and improve cancer-specific health-related quality of life (HRQoL) and, in the longer-term, reduce recurrence, in women with estrogen-receptor (ER) positive invasive breast cancer. The study will be conducted in 6 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 Randomised Controlled Trial (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) Workstream 6 Evaluation of intervention effectiveness in reducing risk of recurrence (months 111-122) **Permission has been granted by the sponsor to apply for HRA/REC approvals separately for the feasibility study (Workstream 2). Therefore, this protocol and IRAS application describe work being undertaken on Workstream 2 only.**
Aim of Workstream 2	The aim of Workstream 2 is to test the feasibility and acceptability of a person-centred, evidence-based and theoretically-informed intervention (HT&Me) to reduce poor AET adherence, and improve cancer-specific HRQoL.
Design & Objectives of Workstream 2	Workstream 2 consists of two components: <u>Sub-study 1: Intervention feasibility study</u> *Objectives:* This sub-study will • identify optimal patient recruitment pathways; • explore feasibility of recruiting women to receive the intervention; • explore feasibility of delivering the intervention; • explore the acceptability and usefulness of the HT&Me intervention to patients; • explore barriers to, and facilitators of, trial implementation, including (i) willingness of staff to recruit women to a RCT; and (ii) willingness of women to be recruited and randomised to a RCT; • test processes for collecting self-reported outcome data. *Design*: single arm feasibility study (with no randomisation). <u>Sub-study 2: Feasibility of using community prescribing data to objectively measure adherence to endocrine therapy</u>

	Objectives: This sub-study will test processes for obtaining prescription encashment data for a small cohort of women with breast cancer initially prescribed adjuvant endocrine therapy some months previously. *Design:* Retrospective cohort study.
Study Participants	Sub-study 1: Eligible participants will be women recently diagnosed with early-stage ER-positive invasive breast cancer and prescribed oral AET (in the past 3 months), who have medium or high risk of recurrence, defined as one of the following: (i) T2 and N0, (ii) T1 and N>0, (iii) T2 and N>0 or (iv) T1 and N0 and grade 3. Sub-study 2: Eligible participants will be women diagnosed with early-stage ER-positive invasive breast cancer and prescribed oral AET in the previous 9-36 months with one of the following: (i) T2 and N0, (ii) T1 and N>0, (iii) T2 and N>0 or (iv) T1 and N0 and grade 3 disease.
Planned Size of Sample (if applicable)	Sub-study 1: 45 women with breast cancer, plus 15-18 health professionals involved in delivering the study at the clinical sites. Sub-study 2: 45 women with breast cancer.
Planned Study Period	The programme of work will run for 80 months from May 2020. Workstream 2 will run from months March 2022-June 2023.

C. FUNDING AND SUPPORT IN KIND

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
National Institute for Health Research (NIHR)	£2,538,229 for the full programme

D. STUDY PROTOCOL: SUPPORTING WOMEN WITH ADHERENCE TO HORMONE THERAPY FOLLOWING BREAST CANCER (SWEET)

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 estrogen 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].

To date no effective intervention to improve AET adherence exists. This programme will address this gap by developing and testing 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.

2. RATIONALE

The proposed programme aligns well with current NHS priorities. 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, recently 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. 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 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 will 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 6 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)
Workstream 6 Evaluation of intervention effectiveness in reducing risk of recurrence (months 111-122)

Permission has been granted by the sponsor to apply for HRA/REC approvals separately for feasibility study (Workstream 2).

Therefore, this protocol and IRAS application applies only to research fieldwork being undertaken in Workstream 2 that is described below.

3. RESEARCH AIMS AND QUESTIONS

The aim of Workstream 2 is to assess the feasibility and acceptability of the SWEET intervention and the future RCT, and identify any changes that are needed prior to the RCT.

Workstream 2 objectives are to:

- identify optimal patient recruitment pathways (sub-study 1);
- explore the acceptability and usefulness of the intervention to patients (sub-study 1);
- explore feasibility of recruiting women to receive the intervention (sub-study 1);
- explore feasibility of delivering the intervention (sub-study 1);
- explore barriers to, and facilitators of, trial implementation, including (i) willingness of staff to recruit women to a RCT; and (ii) willingness of women to be recruited and randomised to a RCT (sub-study 1);
- test processes for collecting self-reported outcome data (sub-study 1);
- assess the feasibility of accessing, and using, community and GP prescribing data to objectively measure adherence to endocrine therapy (sub-study 2);
- identify any necessary refinements to the intervention and plan of evaluation prior to the RCT (sub-study 1 and 2).

4. METHODS

A. SWEET INTERVENTION

The SWEET intervention is described in Appendix 1. In brief, it includes five elements:

(i) An animation focussing on necessity of taking AET, common concerns that women have about AET and practicalities of taking AET; this will be provided to women prior to the consultation in step (ii);

(ii) A consultation with a "HT navigator" (SWEET study nurse), tailored to an individual woman's initial experiences of AET, necessity beliefs and concerns either delivered by delegated SWEET study nurse(s) at site, or through Breast Cancer Now as per site agreement

(iii) A web-app, containing information, tools to support adherence, and signposting to support;

(iv) A follow-up consultation with the SWEET study nurse (either face to face, by telephone or video-call) to address any emerging concerns and problems;

(v) Regular, brief, motivational messages delivered by email or text, promoting adherence and encouraging use of the web-app in the event of any questions or problems.

B. METHODOLOGY AND STUDY DESIGN

We will use mixed-methods to explore acceptability and feasibility issues, including:

(i) Can we identify and recruit potentially eligible patients?

(ii) Is it feasible to deliver the initial intervention consultation within 8 weeks of recruitment?

(iii) Are the baseline and follow-up questionnaires acceptable?

(iv) Do women find the intervention acceptable and useful?

(v) What is the timeliness and quality of primary care prescription encashment data and/or GP prescribing data, and is it possible to use to compute an objective measure of adherence to AET?

Sub-study 1 is a single arm, non-randomised feasibility study to explore the acceptability and feasibility of delivering the SWEET intervention. Recruited women will receive the intervention and will be followed for 7-8 weeks, at which point they will complete a follow-up questionnaire and some will undergo interviews. Interviews will also be conducted with a sample of participating health professionals (n=8-15).

Sub-study 2 is a retrospective cohort study which will test the processes for obtaining prescription encashment data for a small cohort of women with breast cancer initially prescribed AET at hospital/by consultant recommendation (thereby testing, on a small scale, the processes that will require to be followed in the subsequent RCT). The prescribing history for each individual recruited woman will be obtained through linkage of the sub-study 2 cohort to the National Cancer Registration Database (NCRD) and the NHS Business Services Authority (BSA) Primary Care Prescribing Database (PCPD) [55]. This will provide information on timeliness and completeness. Should there be any issues accessing the prescribing dataset (due to changes with PHE) we will access GP prescribing data.

C. STUDY SITES

Substudies 1 and 2 will draw participants from a minimum of three NHS clinical sites (this may increase to five if required to support recruitment). These are expected to include Newcastle-upon-Tyne Hospitals NHS Foundation Trust (NuTH), Oxford University Hospitals NHS Foundation Trust (OUHFT), and Imperial College Hospital Trust (ICHT), London.

D. ELIGIBILITY

Sub-study 1: The target population for the feasibility study (and subsequent RCT) will comprise women with greatest potential to benefit clinically from AET, that is, women with early-stage ER-positive breast cancer who have medium or high risk of recurrence [49]. Risk of recurrence will be defined following Pan et al [56].

Inclusion criteria:
The following patients will be eligible:

- Aged 18+
- Female
- Diagnosis of ER positive invasive breast cancer
- Medium or high risk of recurrence, defined as **one of the following**
    - T2 and N0
    - T2 and N>0
    - T1 and N>0
    - T1 and N0 and grade 3.
- Within **3 months of first oral AET prescription** (tamoxifen or aromatase inhibitor);
- Completed surgery
- Completed chemotherapy (if applicable)
- Can access to the internet and have an email address; and

- Are willing to use a support package with a web-based component.

Women on anti-HER2 therapies or ovarian suppression drugs will be eligible provided they fulfil the above criteria, as will women who have had neo-adjuvant ET and women who have had a previous primary breast cancer (as long as they did not have AET to treat that first cancer).

Exclusion Criteria:
The following patients with early-stage ER+ve invasive breast cancer will be ineligible:

- Male
- Have been prescribed adjuvant CDK4/6i (abemaciclib);
- Have cognitive impairment sufficient to preclude participation, as judged by the clinical team;
- Are unable to read and understand English;
- Had previous AET (for another breast cancer);
- Have not had surgery for breast cancer.

Eliciting and addressing women's AET beliefs and concerns, in light of their initial treatment experience, is the bedrock of the intervention, so it is important that women are at a point when they should have initiated AET by the time of their first consultation with the SWEET study nurse. However, they should not be too far beyond the start of treatment at the time of recruitment. Thus, the focus is on recruiting women within 3 months of when they would have been due to start taking AET.

The evidence-base for the SWEET intervention (including the primary research by the SWEET team) comprises research among women with breast cancer. The intervention has been co-developed in partnership with women with breast cancer. Its suitability for men is not known, therefore, men will be excluded.

Sub-study 2: The target population for this sub-study will be women diagnosed with ER-positive invasive breast cancer who have medium or high risk of recurrence [49]. Risk of recurrence will be defined following Pan et al [56].

Inclusion Criteria:
The following patients will be eligible:

- Aged 18+;
- Female
- Diagnosis of ER positive invasive breast cancer
- Medium or high risk of recurrence, defined as **one of the following**
    - T2 and N0
    - T2 and N>0
    - T1 and N>0
    - T1 and N0 and grade 3.
- Were first prescribed oral AET (tamoxifen or aromatase inhibitor) **within the past 9-36 months***
- Have completed surgery;
- Have completed chemotherapy (if applicable);

Women on anti-HER2 therapies, or ovarian suppression drugs, will be eligible provided they fulfil the criteria above, as will women who have had neo-adjuvant ET, and women who have had a previous primary breast cancer (as long as they did not have AET to treat that first cancer).

***** This timeframe has been chosen as there is a delay of several months in prescription encashment data being available through the NHS BSA, and for that in turn, to be available through NCRD.

Exclusion Criteria:
The following patients with early-stage ER+ve invasive breast cancer will be ineligible:

- Male
- Have been prescribed adjuvant CDK4/6i (abemaciclib);
- Have cognitive impairment sufficient to preclude participation, as judged by the clinical team;
- Are unable to read and understand English;
- Had previous AET (for another breast cancer);
- Have not had surgery for breast cancer.

E. SAMPLE SIZE

Sub-study 1: The average feasibility study size is 36 [57] but there is little guidance on an appropriate size for our study. We propose to recruit a minimum of 45 eligible women over a period of up to three months (anticipating at least one woman per week per site is achievable, and assuming a minimum of 3 sites recruiting).

We will also conduct interviews with approximately 8-15 health professionals involved in supporting the study at the clinical sites.

Sub-study 2: Based on the logic for sub-study 1, we propose to recruit 45 women to sub-study 2.

F. RECRUITMENT & PROCEDURES

Sub-study 1: Assessment of acceptability & feasibility

Flowchart 1 (Document: *Sub-study 1 Recruitment Pathway* summarises the flow of women through the study.

Identification of eligible women: Two methods will be used to identify potentially eligible women. The second option allows for the identification (and recruitment) of women who received adjuvant chemotherapy (duration approx. 5 months) before starting AET, within the tight timeline for the feasibility study. It is important to test the acceptability of the intervention to this group of women (as well as those who do not have chemotherapy).

Identification Option 1: Potentially eligible women will be identified at an appropriate MDT after their breast cancer surgery. A member of hospital staff will review women's medical records to assess eligibility.

Identification Option 2: Potentially eligible women who underwent adjuvant chemotherapy will be identified from hospital records (e.g. clinician files, medical records or online record systems,

hospital pharmacy records). A member of hospital staff will review women's medical records to assess eligibility.

Recruitment: Two options for recruitment will be used.

Women identified via Identification Option 1: In most instances, we anticipate that eligible women will be approached and provided with the Participant Information Sheet (PIS) at a clinic appointment (Document: *Sub-study 1 Participant Information Sheet*). The initial contact will be made by a research nurse or another member of the hospital team. If not already available, telephone numbers will be obtained for women who are potentially interested in taking part.

At least 24 hours after the receipt of the PIS, a research nurse (or another member of the hospital team) will telephone the woman, answer any questions and, if she wishes to take part, take informed consent (Document: *Sub-study 1 Verbal ICF*). It should be noted that if a woman is happy to be consented immediately, and the study team are satisfied the woman has fully comprehended what is being asked of her, then consent can be taken immediately without a 24 hour wait period. It is acceptable for the patient to complete the baseline questionnaires immediately after informed consent.

Alternatively, women may be sent the PIS in the post ahead of a scheduled clinic appointment. As women approached via this route will have had adequate time to consider their participation, they may be consented at the appointment (Document: *Sub-study 1 ICF*).

The woman will be asked to provide her email address and a phone number. If the woman does not wish to take part, the reason for declining will be recorded on a screening log (Document: *Sub-study 1 Decliners Log*). These reasons will be monitored to identify any issues or common trends that could inform the future design for an RCT.

The woman's appointment with the SWEET study nurse will be confirmed by telephone, email or post by the SWEET Study Nurse. If a site is using the Breast Cancer Now (BCN) support model, the patient details will be shared with the BCN-employed SWEET Study Nurse(s) who will arrange this appointment with the patient. Under both models, the baseline questionnaire and link to the animation will be sent by email or post by the research nurse, dependent on patient preference (see below) (Document: *Sub-study 1 Baseline Questionnaire Pack*).

For consented women, the site will inform participants' GPs that they are in the study and receiving an intervention to encourage and support hormone therapy adherence (Document – *Sub-study 1 GP letter*).

Women identified via Identification Option 2: A research nurse, or another member of the hospital team, will send a letter of invitation to each woman, signed by her consultant, and enclosing the PIS, ICF and baseline questionnaires (Document: *Sub-study 1 Letter of Invitation*). After a few days, a research nurse or other member of the hospital team will telephone the woman, answer any questions and, if the woman wishes to take part, complete the consent process and prompt the woman to complete the baseline questionnaire as soon as able. The woman will be asked to provide her email address and a phone number in order for her appointment to be arranged. If the woman does not wish to take part, the reason for declining will be recorded, using a standard proforma (Document: *Decliners Log*).

Screening logs: For both methods of identification and recruitment, a research nurse (or another member of the hospital team) will complete screening logs documenting each potentially eligible

patient including whether the relevant clinical data could be found to determine her eligibility (e.g. T, N , grade, anti-HER2 therapy, receipt of chemotherapy), whether she was eligible and, if so, whether she was approached and consented (and, if not, reasons why will be recorded).

Allocating SWEET study nurse appointment & baseline data collection. Once recruited, each woman will be assigned an appointment slot with a SWEET study nurse, this appointment will be confirmed by email or post by the SWEET study nurse. For sites utilising the BCN support model, this will be a BCN nurse. The recruiting site will provide the patient with the baseline questionnaires, a freepost envelope if the woman prefers to complete the questionnaire on paper, and a link to the animation, which she will be asked to view before the SWEET study nurse appointment. Women will be offered the opportunity to reschedule the appointment if the timing does not suit them. Up to two reminders to complete the questionnaire prior to the consultation will be sent if needed (by email in the first instance after 7 days, and by telephone call after 14 days)) .

The baseline questionnaire will include questions on: socio-demographics; lifestyle (e.g. smoking, alcohol consumption, physical activity); AET necessity beliefs (i.e. beliefs about the necessity of taking AET to remain healthy) and AET concerns beliefs (i.e. concerns about the negative effects of taking AET)[58]: whether they have initiated, or intend to initiate, AET; AET adherence (assessed using MARS-5)[69]; and cancer-specific HRQoL (assessed using the FACT-G)[60]; and utility (as measured using the EQ-5D-5L) [61] and an additional health service resource use questionnaire, based on a modified version of the UK Cancer Costs Questionnaire [62]). Baseline and follow-up questionnaires (Document: *Sub-study 1 Baseline Questionnaire Pack* and *Sub-study 1 Follow-up Questionnaire Pack*) were developed with input from the SWEET Patient Advisory Group (PAG)

Relevant medical details for each woman as included on the baseline case report form will be abstracted from medical records by the research nurse or another member of the hospital team. It will be made clear on the PIS and consent form that participation in the study involves agreeing to the individual's medical records being accessed to abstract relevant details.

Delivery of intervention and follow-up: Recruited women will have a consultation with the SWEET study nurse that will last approximately 30 minutes. We intend for these appointments to take place within eight weeks of recruitment and will measure the extent to which this is achieved. The appointment may take place face-to-face or by telephone/videoconferencing, depending on COVID-19 restrictions in place at the time and current practice for follow-up appointments at the relevant site and logistical considerations. Any consultation by SWEET study nurses via the BCN model will always be performed remotely. If a woman does not attend the appointment, she will be sent a second appointment with the option to reschedule again if the date or time does not suit.

Prior to the appointment, the woman will be set-up with an account on the HT&Me web-app using her email address. The woman will be provided with a dummy password which can be changed later if she wishes.

The appointment will be tailored by the SWEET study nurse to the women's beliefs, concerns and AET behaviours using elicitation. The SWEET study nurse will also introduce the woman to the web-app, confirm web-app log-in information and a contact number in event of problems (helpline), and provide the contact number for the local site breast cancer nurses. A sample of consultations will be audio-recorded (approximately one-third, but more may be recorded if necessary) for the purpose of assessing fidelity. It will be made clear on the PIS and consent form that the consultation may be audio-recorded.

The timeline of events following the initial SWEET study nurse appointment will then be as follows:

- **Following the appointment:** The woman will be sent a letter (by email or post), reiterating her web-app log-in details and enclosing a "how to" guide for the web-app and the helpline number.

- **At approximately 10-14 days:** The woman will receive the first motivational email/text message. This will prompt her to complete the *My Personal Support* section of the web-app. The central research team will check whether the woman has accessed the web-app using the web-app analytics data. If she has not, a member of the team will follow-up by phone to encourage and support her to do so.

- **At approximately 3 weeks:** The woman will receive a second motivational message. The content of these may vary across women to enable the central research team to test acceptability of different messages. The SWEET study nurse will call her to schedule a convenient time for the follow-up consultation.

- **At approximately 4 weeks:** The follow-up consultation with the SWEET study nurse will take place face-to-face or by telephone or video-call. A sample of consultations will be audio-recorded for the purpose of assessing fidelity (approximately one third but more may be recorded if necessary). If a woman does not attend the SWEET study nurse appointment, she will be sent a second appointment with the option to reschedule if the date or time does not suit.

- **At approximately 7-8 weeks:** The woman will be sent (by email or paper) the follow-up questionnaires. This will assess self-reported adherence and mediator variables to provide an indication of questionnaire acceptability, likely response rate and data completeness (although the timing of administration will be different in the main trial). It will include intervention assessment questions, including ratings of satisfaction with the intervention overall and specific elements such as initial consultation, follow-up consultation, app/website/workbook, email/text message. Women will be asked to describe best bits, where there is room for improvement and, in an open text section, to provide any other comments on the intervention [63]. Participants will also be asked whether they would like ongoing access to the web-app after they have completed their involvement in the feasibility study. To test processes for collecting health economic data, the pack will also include the EQ-5D-5L and a resource use questionnaire. If needed, up to two reminders to complete the questionnaire will be sent (by email, telephone call or post) at approximate 10-day intervals.

- **At approximately 8-9 weeks:** Semi-structured interviews will be conducted, by a member of the research team (from Newcastle University, Oxford Brookes University or UCL), with a sample of participants (approx. 20-30). These will gauge experiences of recruitment, the intervention (including mode of delivery) and the baseline and follow-up questionnaire, as well as eliciting views on the behaviour change techniques incorporated within the intervention. These interviews will also shed light on why different elements of the website are used/not used.

  Interviewees will be sampled for maximum variation based on socio-demographic characteristics and their intervention assessment questionnaire responses. Recruitment will continue until reasonable data saturation, which will be defined as no new issues arising in last three interviews; our experience suggests around 20-30 interviews will be required. A

member of the research team will contact sampled women by telephone to schedule the interview.

Interviews will be face-to-face, by telephone or by video-conferencing according to interviewee preference and relevant COVID-19 guidance in place at the time of the study, and guided by a topic guide (Document: *Sub-study 1 Patient Topic Guide*). They will last approximately 60-90 minutes, or as long as the participant wants. They will be audio-recorded (this will be made clear on the PIS and consent form), transcribed, anonymised, and content analysis [64] conducted to identify key issues relating to recruitment and the intervention.

- **Throughout:** App/website analytics will also be examined to determine whether women use the web-app and, if so, how often and which elements; it will be made clear on the PIS and consent form that analytic data will be recorded and reviewed.

Factors influencing feasibility: Following each SWEET nurse intervention consultation, the SWEET study nurse will record the date and length of the consultation and, using a checklist informed by TIDieR [65] and intervention BCTs, what was covered. For those interviews which have been audio-recorded, the research team will review the audio-recording of the consultation against the checklist to assess the extent to which the SWEET study nurses can maintain intervention fidelity and quality. The distribution of time between recruitment and the first consultation will be examined as a measure of the feasibility of scheduling these appointments. In the event that a consultation is not delivered to a recruited woman (or the consultation is delivered more than eight weeks post-recruitment), reasons will be documented by the SWEET study nurse.

After three months of patient recruitment at the site, semi-structured interviews with approximately 15-18 key site staff (including, but not limited to, SWEET study nurses, breast cancer consultants, breast cancer nurses and patient navigators) will explore how recruitment and intervention delivery fitted into routine care and any changes that would be required for trial recruitment or intervention delivery to larger numbers of women. Interviews will be face-to-face, by video-conferencing software or telephone, depending on interviewee preference. The SWEET study nurses will also be invited to reflect on experiences of the training package.

Eligible staff will be provided with an Information Sheet (Document: *Sub-study 1 HCP Information Sheet*) and, after at least 24 hours have passed, contacted to ask whether they would be willing to be interviewed (if staff member is happy to be consented immediately then consent can be taken without 24 hour wait period). Interviews will take place face-to-face, by telephone or videoconference, depending on interviewee preference and COVID-19 restrictions in place at the time. At the outset of the interview, informed consent will be sought (Documents: *Sub-study 1 HCP Verbal ICF*; *Sub-study 1 HCP ICF*). The interview will be guided by a topic guide (Document: *Sub-study 1 HCP Topic Guide*) and will be audio-recorded (this will be made clear on the information sheet and consent form), transcribed, anonymised, and subject to content analysis [85] to identify potential barriers to delivering the intervention and the RCT. Interviews with SWEET study nurses will last approximately 60 minutes; those with other health care professionals are likely to last 30-40 minutes. Interviews will be conducted by a member of the research team from Newcastle University, Oxford Brookes University or UCL.

Optimising the intervention: The assessments of feasibility and acceptability are likely to identify potential changes that, if implemented, could improve the intervention, the manual and training package and planned trial procedures, including assessment of outcomes. Those changes which are

feasible (i.e. possible within the specification of the intervention and context) and congruent with the evidence-base will be implemented, thus optimising the intervention and future RCT.

Participant remuneration: Women who take part in interviews will be offered a £30 voucher as a thank you for their time and to cover any expenses associated with the interview.

Sub-study 2: Testing processes for obtaining prescription encashment data for individual women

The primary outcome for the main RCT will be poor adherence to AET. This will be determined for each woman using, as recommended as best practice [66], a combination of an objective measure (prescription encashment records) and a subjective measure (self-report using the MARS-5) [59]. Although considered a good measure of adherence, encashment slightly overestimates adherence as people may collect medication but not use it. Self-report is highly specific for non-adherence [67] and its use will reduce misclassification in adherence measured using encashment data. Therefore, combining encashment data and self-report at the level of the individual woman will allow us to more correctly classify women.

The purpose of sub-study 2 is to test the process for obtaining prescription encashment data for individual recruited women (thereby testing, in miniature, the processes required in the RCT).

Identification of eligible women: Potentially-eligible women will be identified from hospital records (e.g. clinician's files, hospital systems, medical records, hospital pharmacy records), based on a first prescription for oral AET (Tamoxifen or aromatase inhibitor) in the relevant time window. A member of hospital staff will review women's medical records to assess eligibility.

Recruitment: Different options for recruitment will be available depending on what works best of the individual site.

Option 1: A research nurse, or another member of the hospital team, will send a letter of invitation to each woman signed by her consultant (Document: *Sub-study 2 Letter of Invitation*) and with a PIS enclosed (Document: *Sub-study 2 Participant Information Sheet*). After approximately a week, a research nurse, or another member of the hospital team, will telephone the woman, answer any questions and, if she wishes to take part, take informed consent (Document: *Sub-study 2 Verbal ICF*).

Option 2: Eligible women who are due to attend a clinic appointment, will be sent (by a research nurse or another member of the hospital team) a letter of invitation signed by her consultant, enclosing a PIS. The woman will be approached about the study at the clinic appointment, any questions she has will be answered, and, if she is willing to take part, informed consent will be obtained (Document: *Sub-study 2 ICF*).

Option 3: Eligible women will be approached and provided with the PIS at a clinic appointment by a research nurse or another member of the hospital team. If not already available, telephone numbers will be obtained for women who are potentially interested in taking part. After approximately a week, a research nurse or another member of the hospital team will telephone the woman, answer any questions and, if she wishes to take part, take informed consent.

Abstraction of clinical details: Relevant clinical details for each woman such as date of diagnosis, stage (T, N, M), grade, date of surgeries, whether they had radiotherapy, whether they had neo-adjuvant AET, date of first AET prescription, and NHS number which is required for linkage, will be abstracted from medical records by the research nurse or another member of the hospital team. It will be made clear on the PIS and consent form that participation in the study involves the

participant agreeing to their medical records being accessed to abstract relevant details and then shared with NHS Digital for the purposes of linkage.

Obtaining prescription encashment data: We will provide a file containing details required for matching (including name, date of birth, NHS number) and the other abstracted clinical details to NHS Digital, which is data controller for the NCRD data, and which can access the PCPD. They will extract records of endocrine therapy and other prescriptions encashed for each woman (e.g. bisphosphonates) during the time from date of breast cancer diagnosis to the date of data extraction and return this information to the research team. NHS Digital will remove personal identifying details and return the pseudonymised linked dataset to the research team for analysis.

The research team will scrutinise this to assess timeliness and likely completeness of AET prescriptions. They will also examine the data on the other prescriptions to determine whether this can be used as part of the health economic assessment of resource use.

If it is not possible to obtain data from NHS Digital, we will seek to obtain GP prescribing data for participants. The focus will be on prescriptions relating to the breast cancer.

G. PARTICIPANT WITHDRAWAL

Participants in either sub-study 1 or sub-study 2 may withdraw from the study at any time with no obligation to provide a reason or explanation. In the event of withdrawal, the participant's personal identifying data will be destroyed but any other data collected (e.g. interview transcript, completed questionnaires, prescribing data) will be retained, as will any screening information that was used to inform their eligibility for the study. Consent forms will be retained but will be marked as a withdrawn participant.

H. END OF STUDY

For sub-study 1, for an individual participant, completion of the follow-up questionnaire or participation in the interview (whichever is the later) will constitute the end of their participation in the study. Overall, the end of the study will be defined as the point when questionnaires and interviews have been completed, all data analysed, and any changes required before the RCT have been made.

For sub-study 2, for an individual participant, providing consent for their hospital records to be linked to the national cancer registry and BSA will constitute the end of their participation in the study. Overall, the end of the study will be defined as the point when the linked data has been obtained and scrutinised for timeliness and completeness.

5. ETHICAL AND REGULATORY CONSIDERATIONS

A. CONSENT

Participation in sub-studies 1 and 2 will be contingent on informed consent being obtained. Prior to expressing their interest in participating, all potential participants will be provided with the appropriate participant information sheet detailing the study objectives and what taking part will involve.

All potential participants will have the opportunity to ask questions using contact details provided and will be given at least 24 hours between being provided with the information about the study and

being asked to provide consent (if participant is happy to be consented immediately, and the study team feel they fully understand what is being asked of them, then consent can be taken without a 24 hour wait period). Immediately prior to being asked to provide informed consent, participants will be given further opportunity to ask any questions.

Participants will be informed that participation is voluntary and that they can withdraw from the study at any point, without affecting their medical care or legal rights. It will be made clear that any information arising from the study will be anonymised so they will not be identifiable in any publications or report. Participants will be asked to indicate their understanding that this anonymous information may be used in future related research, or may be shared with other researchers working in collaboration with the research team, including students.

Written consent will be obtained from those being consented in person. For those from whom consent is obtained by phone or video conference interviews, the verbal consent form will be used, in adherence with Sponsor SOPs.

The timing of consent for substudies 1 and 2 is described under section 4F.

B. ASSESSMENT AND MANAGEMENT OF RISK

Sub-study 1: It is possible that participation in sub-study 1, particularly the qualitative interviews, may have emotional consequences for women with breast cancer and may involve them considering and discussing potentially upsetting issues related to their own experiences.

The project leads (Professor Sharp & Professor Watson) and the researchers are experienced in interviewing individuals who have had cancer and/or other potentially vulnerable patient groups. If an interviewee does not wish to answer any question during the interview, this will be respected. If the interviewee becomes upset, the researcher will ask them if they wish to stop the interview, either temporarily or permanently. Moreover, if an interviewee becomes very distressed, the researcher will ask whether they would like them to contact someone (e.g. a family member, friend, GP, or clinician) on their behalf. A similar process will be followed in the event that a participant becomes distressed during either the initial SWEET study nurse appointment or the follow-up call.

The participant information sheets will contain information about who (patient) participants might contact if they feel they want to discuss any issues arising from taking part in the study. For example, this will suggest that they contact the research team, their GP, their clinical team in the hospital, and will direct interviewees to information and helplines such as those offered by Breast Cancer Now and Mind.

Sub-study 2: No data will be collected directly from participants themselves – they will simply be asked for consent for access to their medical records and for linkage to national datasets.
The participant information sheet will contain information about who they might contact if they feel they want to discuss any issues arising from agreeing to take part in the study. For example, this will suggest that they contact the research team, their GP, their clinical team in the hospital, and direct interviewees to information and helplines such as those offered by Breast Cancer Now and Mind.

C. RESEARCH ETHICS COMMITTEE REPORTING

Ethical approval will be obtained from a UK Health Department's Research Ethics Service NHS Research Ethics Committee (REC) for the study protocol, informed consent forms, participant information sheets and other study materials.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained. The chief investigator will organise the production of research reports as required and notify the REC of the end of the study. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

D. REGULATORY REVIEW AND COMPLIANCE

Before any site can enrol patients into sub-study 1 or sub-study 2, the Chief Investigator or a designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor, will submit information to the appropriate body for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites) so they can put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

E. AMENDMENTS

If a substantial amendment to the REC application or the supporting documents is required, approval will be sought from the sponsor before submitting a notice of amendment to the REC for consideration. The sponsor will categorise the amendment as substantial or non-substantial. The Health Research Authority will be informed.

Substantial and non-substantial amendments will be communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Some amendments that may be considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

The Chief Investigator will be responsible for the decision to amend the protocol and any supporting documents. The amendment history will be logged in the site-files. The protocol and all supporting documents will be version tracked, so that the most recent versions can be identified easily.

F. PEER REVIEW

The project has been funded by the National Institute for Health Research (NIHR). The funding application for this project was independently peer reviewed by several independent experts and by The NIHR Programme Grants for Applied Research funding panel. It has also been reviewed by independent breast cancer experts on the National Cancer Research Institute (NCRI) Breast Cancer Group, and experts in cancer survivorship research on the NCRI Psychosocial Oncology & Survivorship Group.

G. STAKEHOLDER AND PATIENT AND PUBLIC INVOLVEMENT

In developing the larger NIHR programme grant proposal we recruited two patient representatives to the team (team members Rose & Turner), who 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.

When the programme began, we established a Patient Advisory Group (PAG) which includes a diverse group of 11 women with a range of experiences of AET. User co-applicants co-chair the PAG group and also sit on the study Programme Management Committee (PMC). The PAG meet regularly and have been closely involved in co-designing the intervention web-app and in developing the scripts for the initial and follow-up consultations. They have also reviewed the patient-facing documents for the feasibility study and provided input to the choice of questionnaires for assessing outcomes and mediators. For the later stages of the programme (i.e. after these substudies), those PAG members who wish to be involved in analysis of study data will be given relevant training by team members. 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.

PAG members receive payment for their time in line with NIHR INVOLVE recommendations and receive reimbursement for travel and any carer expenses.

We also established a wider PPI group called a Community of Interest (CoI)**.** The CoI includes 30 women with breast cancer who have been prescribed 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 extensively 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 (Breast Cancer Now, 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 Breast Cancer Now, who are partners in the programme.

H. DATA PROTECTION AND PATIENT CONFIDENTIALITY

Data controllers and regulatory compliance: The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) is Sponsor for the study and will act as data controller. All investigators, researchers and study site staff will comply with the requirements of the Data Protection Act 2018, with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles and General Data Protection Regulation (GDPR).

Recruitment of patient participants (sub-study 1 & 2): The local clinical team will act as 'gate keepers' and eligible patients will be initially informed of the study via their healthcare professionals. The research team (including where BCN are involved) will not have access to contact details for any patient participants, until they themselves give their permission, provide their details directly, or indicate to the relevant member of the clinical team that they are happy for their details to be passed onto the researcher.

Identifiable data, consents, screening logs and decliners log: Any identifiable data will be stored securely on an NHS network. We will utilise the REDCap software hosted by the Newcastle upon Tyne Hospital NHS Foundation Trust, which is HSCN compliant. This database will also include clinical details extracted from women's medical records for the purpose of the study. Those at clinical sites (e.g. Research nurses) will only be able to access the details of women recruited through their site. A small number of designated members of the research team will be able to access identifiable and contact information on all women recruited as required for specific purposes (e.g. delivering the intervention, sending questionnaires, arranging interviews, sending summary of findings). Any other members of the research team who required access to the database will only be able to see anonymised information.

Screening logs & the decliners log will be held in site files with copies (excluding identifiable details) held at Newcastle University.

Paper records of consent, which contain names or study IDs, will be kept at site for five years following the end of the study in order to allow for audit of the research process if required. No other personal data such as contact details will be kept longer than is necessary and any identifying information will be anonymised in the data for analysis.

Questionnaires (sub-study 1): Questionnaires will be identified by study ID numbers only. The patient will either enter the data directly onto the patient facing database (REDCAP) or if they use paper copies, these will be stored at site and entered onto REDCAP for the central research team to access for the purpose or analysis

Interviews and consultations (sub-study 1): Paper copies of the details of the SWEET study nurse consultations (including date delivered and checklist of items covered) will be entered by site to REDCAP (in the case of BCN involvement, these details will be provided to site for input). The audio-recordings of the interviews and SWEET nurse consultations will be stored on a secure part of the Newcastle University network (SWEET OneDrive), with access restricted to designated members of the research team. Transcription of the interviews will be undertaken by a member of the research team or an external company, Type it Write (TiW). TiW will be asked to sign a Non-Disclosure Agreement. Sending interview recordings to TiW and receipt of transcripts will follow a defined protocol (Document: *Sub-study 1 Transcription Protocol*). Files to be transcribed will be saved in a password-protected, encrypted zip folder and immediately uploaded to TiW using their file upload service. The password will be provided to the service separately by email.

Recordings will be retained until the end of sub-study 1 to allow researchers to return to the data as needed. Following this they will be permanently deleted.

Interview transcripts (sub-study 1) will be anonymised (e.g. removing places, names) and stored on a secure part of the Newcastle University network (SWEET OneDrive). Each transcript will be saved with the individual's unique study ID number.

Digital analytic data (sub-study 1) will be stored in the cloud, using UK-based servers only (Azure Cloud). Any personal identifiable information recorded will be pseudonymised and stored separately

from the information relating to the woman's use of the application. The pseudonymised personal data will be deleted once the analysis has been completed.

Pseudonymised prescription data (sub-study 2) returned to the study team by NHS Digital (or from participants' GPs) will be stored on a secure location on the Newcastle University network. Access will be restricted to specified members of the research team who require access for the purposes of the study.

Site files will be held by the Principal Investigator for each clinical site in a lockable office. This folder will contain essential documents as well as recruitment and screening logs for the study site (who has been approached/written to about the study) and consent forms.

Archiving: After each study has ended, anonymised data will be archived in line with Sponsor policy once the final report and publication are complete. Research data will remain available for 5 years following any publication, after which retention will be reviewed.

Data sharing: The consent procedures include informing participants about the sharing of data and make clear that only their fully anonymised information will be used in future relevant research or shared with other researchers outside of the immediate research team.

I. ACCESS TO THE FINAL STUDY DATASET

Sub-study 1: The final data set will be accessible by the research team; anonymized data may be made available to other researchers, including students, for secondary analysis. The consent procedures include consent for the sharing of data. It will be explained to participants verbally and in writing, that anonymised data may be shared in future for relevant research by other researchers working in collaboration with the research team.

Sub-study 2: The final pseudonymised dataset will be accessible only to members of the research team.

J. DISSEMINATION AND OUTPUTS

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 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, as is possible in light of Covid-19, (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. 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 in sub-study 1 will be given the option of receiving a lay summary of the findings once the sub-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.

Appendix 1: Overview of the HT&Me intervention

NOTE: The timing of delivery of the elements of the intervention described below are as they will be in the full RCT. The timing for the feasibility study (sub-study 1) will be compressed, as described earlier, so that the specific elements can be tested for feasibility and acceptability.

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 feasibility study has gone through extensive pre-testing with the SWEET PAG, and through two optimisation studies (IRAS 293238). 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 [68]. 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)) [69]. The NCF and Leventhal's Common Sense model [70] 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 <u>preventing</u> 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.

(i) Animation

This is a short video (approximately 5 minutes) which addresses necessity for AET and common AET concerns and supports self-efficacy, motivation, goal-setting and developing an adherence habit. This will be provided to women with the details of the initial SWEET study nurse appointment.

This video was developed with input from the SWEET PAG and Clinical Reference Group.

The animation can be viewed here: https://vimeo.com/552494938/dd06c374b2

(ii) Initial consultation with SWEET study nurse

The intervention also involves a 30 minute consultation (either face-to-face or by video conferencing software) with a (allied) health professional such as research/breast care nurse. This appointment will ideally take place within the treating hospital, or by videoconference, within 8 weeks of recruiting women to the study. The health professional will be trained in the delivery of the intervention, to ensure fidelity.

This consultation will be tailored around each woman's beliefs about the need to take AET and her concerns about AET. This will elicit key perceptual and practical barriers to adherence and focus on addressing these. The discussion will employ motivational interviewing and cognitive behavioural therapy techniques. If they have not already accessed it, where possible, women will view the animation at the consultation.

The outline and "script" (which will be tailored by the SWEET study nurse as appropriate for the woman) for the initial consultation is included below; this may be further refined with additional PPI and stakeholder input.

(iii) HT&Me web-app

The HT&Me web-app was based on our existing prototype. It contains: evidence-based information on AET effectiveness; the animation; a facility to set reminders to collect prescriptions and/or take medication; a facility to monitor symptoms/side-effects; hints, tips and tools to overcome practical barriers to taking AET and facilitators to support this (e.g. facility to set reminders, anchoring); hints, tips and tools to manage and cope with any side-effects (e.g. support to reframe negative thoughts, advice on how to ask for help from a health professional on sensitive side-effects); advice on speaking to others and accessing support; and links to the Breast Cancer Now (BCN) "Ask our Nurses" email support service and online peer support forum. It also contains a section on coping with the emotional impact of breast cancer.

For tailoring, the web-app includes a section called *My Personal Support* which includes three screening questions (taken from the BMQ). These are used to 'profile' and provide appropriate adherence messages and/or direct the woman to relevant elements of the web-app (although all content will be available to each woman at all times). These "profiling" questions will be available to

women at any time, if they want to find response to questions or be directed to sections of the web-app that are particularly pertinent to any concerns that they have at that time.

The web-app has been developed in partnership with our Patient Advisory Group and multi-disciplinary Clinical Reference Group. It is currently undergoing extensive user testing and refinement with 40+ women with breast cancer.

The current version of the web-app can be found here: https://sweet.ncldata.dev
To access the web-app, users will be allocated an access code provided by the research team.

(iv) Follow-up consultation with SWEET study nurse

Women will have one 15-20 minute tailored telephone/video-call consultation with the SWEET study nurse three months after the initial consultation. Any side-effects or other problems with adherence are likely to have started to emerge by this point. This appointment will communicate the continuing importance of treatment and address any emerging AET-related concerns or issues. The appointment will be tailored around the woman's current necessity and concerns beliefs about AET.

The outline and "script" (which will be tailored by the SWEET study nurse as appropriate for the woman) for this consultation is included below. This may be further refined with additional PPI and stakeholder input.

(v) *Motivational mes*sages

In addition, at regular intervals during follow-up extending throughout the period of prescribed medication, 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 *My Personal Support* section of the web-app to access tailored information and support.

Women will have the option to opt out of receiving the motivational messages after the receipt of the second message (month 4), although they will continue to receive the messages on the *My Personal Support* section of the web-app.

In the full RCT the motivational messages will be timed as follows:

- Week 2 – Message encouraging recipient to complete My Personal Support
- Month 2 – Motivational message 1
- Month 4 – Motivational message 2
- Month 5 – Message encouraging recipient to complete My Personal Support
- Month 7 - Motivational message 3
- Month 8 – Motivational message 4
- Month 9 – Motivational message 5
- Month 10 - Motivational message 6
- Month 11 – Message encouraging recipient to complete My Personal Support
- Month 13- Motivational message 7
- Month 14 - Motivational message 8
- Month 15 - Motivational message 9

- Month 16 - Motivational message 10
- Month 17 – Message encouraging recipient to complete *My Personal Support* section.

Message content is being developed with the SWEET PAG. Examples of draft message content are provided below:

- Did you know that making a plan can really help you to take your hormone therapy every day? Visit the HT&Me web-app to find our more and make a plan.
- Knowing how hormone therapy works can really help you to understand why it's important to take it. You can find out more about hormone therapy and answers to your questions in the HT&Me web-app.
- Did you know that if you have hormone therapy side-effects, there are lots of things you can do to manage these? Find out more about this in the HT&Me web-app.
- Did you know that having a healthy lifestyle works really well with hormone therapy to prevent breast cancer coming back? You can visit the HT&Me web-app to find out more and set some realistic healthy lifestyle goals.

Initial consultation with SWEET study nurse: Nurse's Guide

This is intended as a guide for the study nurse(s). The appointment and content will be tailored to the individual patient.

1. Introduction

The purpose of this appointment is to chat with you about the hormone therapy you have recently been prescribed, to make sure you understand why it has been prescribed and it is important for you to take, to see how you have been getting on with taking it, and to answer any questions or concerns that you may have.

2. HT history

Check when first prescribed HT. Check if has started taking it, and if so when; If not, when will they start?

3. Animation

Did you receive the link to short video to watch about HT? [If no, explain will provide the link later]. Did you get the chance to watch it? How did you find it?

4. Necessity, Beliefs and Concerns

Check understanding of why prescribed hormone therapy (if necessary, explain why). And how do you feel about taking HT? How important is it to you? (if necessary, explain importance)

Do you understand how HT works? (if not provide brief explanation and refer to video)

How is it going so far with taking HT? Any questions? Any concerns? How do you find remembering to take it?

5. Introduce SWEET web-app

- Introduce main sections
- Create a medication plan / set reminder etc
- Demo using diary (only if they have side effects?)
- Introduce *My Personalised Support* function

6. End

I will be back in touch with you in around three months' time to see how you are getting on. In the mean time you will receive some messages from us to remind you about using the webapp if it could be helpful for you.

Follow-up consultation with SWEET study nurse: Nurse Guide

This is intended as a guide for the study nurse(s). The appointment and content will be tailored to the individual patient.

1. **Introduction**
   It's a couple of months now since we met and the purpose of this appointment is to check in with you and see how you are getting on with your hormone therapy.

2. **HT experiences**
   How have you been finding taking your hormone therapy?

   Have you settled into a routine of taking a tablet every day?

   Are you finding it easy to take daily? Have you missed any days do you think? Was this intentional or did you forget?

   Have you had any problems or concerns? (If so, establish what and what they have done about this and offer appropriate advice and support)

   How are you feeling about continuing to take it? Do you have any worries about this?

   Have you used the HT&Me website?

   Is there anything else I can help you with?

3. **End**
   If they have raised problems and concerns can offer a further appointment. Otherwise remind them of website, Breast Cancer Now details and to contact their clinical team or GP if any problems arise in the future that they are not able to manage themselves or via website / helplines.

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