Developing a complex intervention to support medication adherence in cancer

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Intellectual Property and Publication Statements

I, Sophie Mary Catherine Green, confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Study One publication (Chapter Two):

Green SMC, French DP, Graham CD, Hall LH, Rousseau N, Foy R, Clark J, Parbutt C, Raine E, Gardner B, Velikova G, Moore SJL, Buxton J, ROSETA investigators, Smith SG. Supporting adjuvant endocrine therapy adherence in women with breast cancer: the development of a complex behavioural intervention using Intervention Mapping guided by the Multiphase Optimisation Strategy. BMC Health Services Research. 2022 Aug 24;22(1):1081.

Contributions of all authors to Study One:

The idea of preparing a conceptual model using Intervention Mapping and the Multiphase Optimisation Strategy (MOST) was conceived by my primary supervisor (SS) prior to me starting the PhD and was included within the grant application. I (SG) adapted Intervention Mapping to fit within the MOST framework, establishing where the frameworks complemented one another and where amendments to Intervention Mapping would be needed. I undertook the six stages of Intervention Mapping. For the needs assessment I conducted two literature reviews and a rapid review, for which I designed the searches, screened studies and extracted data. For the subsequent stages of Intervention Mapping, I considered how theory could inform the causal pathways of the conceptual model and hypothesised interactions between the components. I led the development of two new intervention components (short message service [SMS] messages and information leaflet), with support from my supervisors and co-authors (SS, DF, LH, NR, BG, CP). I adapted an existing side-effect self-management website intervention. Two co-authors (CG and JC) developed the acceptance and commitment therapy (ACT) component, and I supported with the development of the intervention materials. I wrote the original draft of the manuscript and responded to reviewer comments from BMC Health Services Research. All authors approved the final version of the manuscript.

Study Two publication (Chapter Three):

Green SMC, French DP, Hall LH, Bartlett YK, Rousseau N, Raine E, Parbutt C, Gardner B, ROSETA Investigators, Smith SG. Co-development of a text messaging intervention to support adherence to adjuvant endocrine therapy in women with breast cancer: mixed-methods approach. Journal of Medical Internet Research. 2023 May 24;25:e38073.

Contributions of all authors to Study Two:

A version of the series of studies for developing the SMS messages were proposed within the grant application prior to me starting the PhD, as the studies are part of an established approach for developing SMS message content. I (SG) adapted this established approach to be relevant to the current context and to be conducted remotely, with support from my supervisors and co-authors (SS, DF, KB, BG, LH, NR). This included identifying suitable behaviour change techniques, reviewing habit formation literature and adapting the design of each of the studies. I led the University of Leeds ethics application, including creating all associated documents for all four studies. I recruited participants to all studies, with the help of the market research company, Dynata, for the online survey with women with breast cancer. I led the expert workshop with support from co-authors (SS, LH, ER), and I led the patient focus group with support from one co-author (ER). I designed all the online surveys used across the four studies. I led the analysis and interpretation for all studies, with some support in interpretation from my supervisors (SS, DF, LH, NR). I wrote the original draft of the manuscript, which all authors reviewed. I responded to peer review comments from the Journal of Medical Internet Research, and all authors approved the final version of the manuscript.

Study Three publication (Chapter Four):

Green SMC, Hall LH, French DP, Rousseau N, Parbutt C, Walwyn R, Smith SG. Optimisation of an information leaflet to influence medication beliefs in women with breast cancer: a randomised factorial experiment. Annals of Behavioral Medicine. 2023 Jul 26:57(11):988-1000.

Contributions of all authors to Study Three:

I (SG) conceptualised and developed the study and methodology, with support from my supervisors (SS, LH, DF and NR). I developed the conceptual model and intervention

components to be tested in the optimisation experiment with support from my supervisors and co-authors (SS, LH, DF, NR, CP). I led the University of Leeds ethics application for this study. I formatted the survey on Qualtrics and recruited all participants with support from the market research company, Dynata. I analysed the data and undertook a stepped decision-making process to decide on the optimal version of the leaflet, with support from my supervisors and co-authors (SS, LH, DF, NR and RW). I wrote the original draft of the manuscript, which all authors reviewed. I responded to peer review comments from Annals of Behavioral Medicine and all authors approved the final version of the manuscript.

Study Four publication (Chapter Five):

Green SMC, Rousseau N, Hall LHH, French DP, Graham CD, Lloyd KE, Collinson M, Ow PL, Taylor C, Howdon D, Foy R, Walwyn R, Clark J, Parbutt C, Waller J, Buxton J, Moore SJL, Velikova G, Farrin A, Smith SG. Acceptability of four intervention components supporting medication adherence in women with breast cancer: A process evaluation of a fractional factorial pilot trial. Submitted to Prevention Science.

Contributions of all authors to Study Four:

A nested semi-structured interview study was included in the grant application prior to me starting the PhD. I (SG) adapted this proposal by making it a mixed-methods process evaluation, choosing a theoretical framework to base the study on, and choosing to use a rapid approach for the qualitative element, supported by my supervisors (SS, DF, NR, LH). I wrote the process evaluation section of the trial protocol, all associated trial documents and the interview guide, which were included as part of the NHS ethics application for the pilot trial. I wrote the data specifications for all quantitative assessments for the trial database, with some support from a data manager (CT). I conducted all the qualitative interviews, and led the rapid analysis meetings which were attended by three co-authors (SS, CG, LH). I analysed the quantitative and qualitative data, with input from my supervisors (SS, DF, NR, LH). The participant demographic and intervention component withdrawal data were summarised by the Leeds Clinical Trials Research Unit (MC, PLO). I triangulated the data, with a second author (KL) additionally triangulating the data for comparison. I drafted the manuscript for submission to Prevention Science, and all authors reviewed and approved the manuscript prior to submission.

Conference abstracts

Study One was accepted as a poster presentation for the International Behavioural Trials Network Meeting 2022.

Study Two was accepted as an oral presentation at the UK Society of Behavioural Medicine Annual Meeting 2022.

Study Three was accepted as an oral (live research spotlight) presentation at the Society of Behavioral Medicine Annual Meeting 2023.

Study Four was accepted as a poster presentation at the Society of Behavioral Medicine Annual Meeting 2024.

Thesis Structure

I chose to use an alternative style of thesis, including published material, to maximise the output from this PhD. There are four studies, which include published material. An introduction (chapter one) proceeds the four studies. Studies One, Two and Three (chapters two, three and four) have been published in peer-reviewed journals. Study Four has been submitted to a peer-reviewed journal and is under review. A discussion (chapter six) follows the studies to bind the thesis into one piece of work. The four studies have been presented exactly as published or submitted, other than minor formatting changes to ensure consistency of presentation (e.g., table numbers, references, American/British spelling). Each chapter includes its own list of references as per guidance.

Acknowledgements

Firstly, I would like to thank my brilliant supervisors; Professor Sam Smith, Professor David French, Dr Louise Hall and Dr Nikki Rousseau. Thank you for all the guidance and expertise you have provided me over the course of my PhD, and for always creating an encouraging and constructive atmosphere. It has been a privilege to work with such a great team of supervisors, and I hope to have further opportunities to work with each of you throughout my career. I would like to express my extended thanks to my primary supervisor, Sam. I am hugely grateful for the opportunity to have learnt from you. Your generosity with your time has been invaluable in supporting my PhD and my career goals more broadly; I am a much more confident and capable researcher thanks to your support and guidance.

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Thank you to the new friends I've made along the way who have made this an enjoyable experience, in what was a difficult time to begin a PhD. I am very grateful to be able to work in such a friendly and supportive department. Thank you also to my lovely old friends and family who have supported me throughout, and particularly for reminding me there is life outside a PhD!

To my biggest support, Brad; thank you for always celebrating the highs, and picking me up during the lows; there is no one I would rather have gone through this journey with than you.

Finally, this thesis is dedicated to the memory of my wonderful mum, Gill. Your attitude to life continues to inspire me every day. I hope this would have made you proud.

Abstract

Adjuvant endocrine therapy (AET) reduces the risk of breast cancer recurrence and mortality, but up to three-quarters of women do not take AET as prescribed. Most existing interventions aiming to support AET adherence have not been effective. Guided by the Multiphase Optimisation Strategy (MOST), this PhD aimed to develop and assess the acceptability of a complex intervention to support AET adherence.

Study One combined Intervention Mapping with MOST to identify barriers to adherence, and develop a conceptual model. The intervention components included; 1) text messages targeting habit formation; 2) an information leaflet targeting medication beliefs; 3) a guided self-help acceptance and commitment therapy programme targeting psychological distress (via increasing psychological flexibility); and 4) self-management website targeting side-effects. **Study Two** involved a series of studies using mixed-methods to develop text messages promoting habit formation to support AET adherence. A pool of 66 messages, considered acceptable to women with breast cancer and showing fidelity to intended behaviour change techniques, were developed. **Study Three** used a 2^5 factorial experiment to optimise the content of the information leaflet to increase necessity beliefs and reduce concerns. The leaflet comprised five components. Quotes and pictures from breast cancer survivors was the only component to have a main effect on medication beliefs. There were also four significant interaction effects between other components. A stepped decision-making process led the enhanced side-effect information to be screened out of the optimised leaflet. **Study four** was a mixed-methods process evaluation, nested in a pilot trial, which aimed to investigate the acceptability of the four intervention components, guided by the theoretical framework of acceptability. All four components were considered acceptable to women taking AET.

A complex intervention aiming to support AET adherence was developed and considered acceptable to women with breast cancer. This intervention will now be optimised in an optimisation trial.

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Abbreviations

ACT	Acceptance and commitment therapy
ACT-FM	Acceptance and commitment therapy fidelity measure
AET	Adjuvant endocrine therapy
AI	Aromatase inhibitor
AQ	Acceptability questionnaire
ATAC	Arimidex, tamoxifen, alone or in combination
ATLAS	Adjuvant tamoxifen: longer agaist shorter
aTTom	Adjuvant tamoxifen; to offer more?
BCIO	Behaviour change intervention ontology
BCT	Behaviour change technique
BCTTv1	Behaviour change technique taxonomy version 1
BCW	Behaviour change wheel
BMQ	Beliefs about medicines questionnaire
BMQ-AET	Beliefs about medicines questionnaire- adjuvant endocrine therapy
CARIATIDE	Compliance of aromatase inhibitors assessment in daily practice through educational approach
CBT	Cognitive behavioural therapy
CI	Confidence interval
COM-B	Capability, opportunity, motivation, behaviour
COMPAS	Compliance in adjuvant treatment of primary breast cancer
CSA	Component screening approach
CSE	Certificate of secondary education
CSM	Common sense model of self-regulation/ common sense model of illness representations
CTRU	Clinical trials research unit
DNA	Deoxyribonucleic acid
DOSE	Domains of subjective extent of non-adherence
EASE	Effectiveness, affordability, scalability and efficiency

ER/PR+	Oestrogen or progesterone receptor positive
ER+	Oestrogen receptor positive
GP	General practitioner
GUIDED	Guidance for reporting intervention development studies in health research
HCP	Health care practitioner
HCPC	Health and care professional council
HER2	Human epidermal growth factor receptor 2
HRQoL	Health related quality of life
IAPT	Improving access to psychological therapies
IDEAL	Investigation on the duration of extended adjuvant letrozole treatment
IM	Intervention mapping
IMPAACT	Improving patient access and adherence to cancer treatment
INDEX	Identifying and assessing different approaches to developing complex interventions
ISRCTN	International standard randomised controlled trial number
MARS-5	Medication adherence report scale
MEMSCaps	Medication event monitoring system caps
MOST	Multiphase optimisation strategy
MRC	Medical research council
NCF	Necessity-concerns framework
NHS	National healthcare system
NICE	National institute for health and care excellence
NIHR	National institute of health research
O-RCT	Optimisation randomised controlled trial
PACT	Patients anastrozole compliance to therapy
PEV	Posterior expected value
PPI	Patient and public involvement
PR+	Progesterone receptor positive

QALY	Quality adjusted life year
QoL	Quality of life
RAP	Rapid assessment procedure
RCT	Randomised controlled trial
ROSETA	Refining and optimising a behavioural intervention to support endocrine therapy adherence
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SMART	Sequential multiple assignment randomised trial
SMS	Short message service
STRIDE	Symptom-targeted randomised intervention for distress and adherence to adjuvant endocrine therapy
TFA	Theoretical framework of acceptability
TIDieR	Template for intervention description and replication
TNM	Tumour, node, metastasis
TPB	Theory of planned behaviour
UK	United kingdom
US	United states

Chapter 1 : Introduction

1.1 Chapter overview

This chapter provides an introduction to breast cancer, medication adherence and complex intervention development. An overview of treatment pathways for breast cancer is provided, with a detailed discussion of the use of adjuvant endocrine therapy (AET) for early-stage breast cancer. Medication adherence is discussed broadly, before focusing on the barriers to adherence to AET and existing interventions aiming to support adherence. Approaches to complex intervention development are discussed, providing rationale for the methods used in this thesis. The final section outlines the aims and objectives of this thesis.

1.2 Breast cancer

1.2.1 Breast cancer prevalence

Breast cancer is the most common cancer worldwide, and incidence is continuing to rise (1, 2). In 2020, 2.3 million new cases of breast cancer were diagnosed, accounting for one in eight cancer diagnoses worldwide (1, 3). Globally, around 685,000 women die from breast cancer each year, making it the fifth leading cause of cancer mortality (1). In the United Kingdom (UK), there are around 55,900 new cases of breast cancer annually, and around 11,500 annual deaths, making it the most common cancer in the UK, and the second most common cause of cancer death in women in the UK (4).

1.2.2 Development of breast cancer

Healthy cells in the body divide and multiply as part of normal growth and repair. During multiplication, Deoxyribonucleic Acid (DNA), which contains instructions for cell growth and repair, is copied to the new cell. In some instances, replication errors may lead DNA to be damaged in the new cell (5). In cancerous cells, the damaged DNA is not corrected, and the cell can continue to multiply, producing further malignant cells. These cells are cancerous cells, which cluster together to form abnormal growths, known as tumours. Breast cancer is a collection of abnormal cells, growing and dividing in an uncontrolled way to form a tumour in the breast.

The lymphatic system is involved in the spread of cancer beyond the breast (6). Lymph nodes (small bean sized glands) typically contain lymphocytes and antibodies that fight infections and destroy damaged cells (6, 7). Lymph vessels are a network of tubes which carry lymph fluid, containing waste materials, throughout the body. Cancerous cells originating in the breast can enter lymph vessels, and can grow and multiply in lymph nodes, often in axillary lymph nodes in the armpit. When cancerous cells have spread to lymph nodes, there is an increased chance that they could travel around the body through the lymph fluid or blood (7). The cancer cells may reach another part of the body and grow and multiply, forming another tumour.

Breast cancers are commonly referred to as primary/early-stage, locally advanced, and secondary/metastatic (8). Primary breast cancer is when the cancer has not spread beyond the breast or the lymph nodes. Locally advanced is when the cancer has spread only to nearby lymph nodes or the chest wall. Secondary, or metastatic, breast cancer refers to when the cancer has spread outside of the breast or lymph nodes to other organs in the body (6, 7).

1.2.3 Types of breast cancer

Different types of breast cancer can be grouped together, to form biologically and clinically meaningful groups useful for diagnosis and treatment (9). Invasive breast cancer is the most common type of breast cancer, in which the cancer cells have spread into the surrounding breast tissue (10). There are many types of invasive breast cancer. Most (70-80%) breast cancers are invasive carcinoma of no special type (or not otherwise specified), meaning the cancer cells have no specific features (9).

1.2.4 Classifying breast cancer

Cancers are often described with regard to their receptor status, grade and stage, which contribute to determining prognosis and treatment.

1.2.4.1 Receptor status

Receptors are proteins on or in a cell, that hormones or other proteins can attach to (11). Some breast cancers have receptors sensitive to the naturally occurring female hormones, oestrogen and progesterone. In oestrogen receptor-positive (ER+) breast cancer, oestrogen binds to receptors on the cancer cell and stimulates growth. In progesterone receptor-

positive (PR+) breast cancer, progesterone binds to progesterone receptors to stimulate growth. Breast cancers can be ER+, PR+ or both (ER/PR+). Around 80% of breast cancers are ER+ or ER/PR+ (12). Hormone receptor negative breast cancers do not have any hormone receptors, and do not use oestrogen or progesterone to grow.

All invasive breast cancers are tested for the human epidermal growth factor receptor 2 (HER2) gene. High levels of HER2 means there is too much HER2 protein produced, which causes cancerous cells to grow and divide more quickly, typically meaning the cancer is more aggressive (13). Around one in five invasive breast cancers are HER2 positive (14). Breast cancers that are HER2 negative, and oestrogen and progesterone receptor negative are known as triple-negative breast cancers, and account for around 15% of all breast cancers (15, 16).

1.2.4.2 Grade of cancer

Grading refers to abnormality of the cancerous cells compared to normal breast cells, and speed of growth (17). Grade one (low) refers to when the cells look similar to normal breast cells and are growing slowly. Grade two (intermediate) is when the cells look different to normal breast cells. Grade three (high) is when the cells look very different to normal breast cells and are growing rapidly (8, 17). A higher grade typically relates to a poorer prognosis (18).

1.2.4.3 Stage of cancer

Stage of breast cancer refers to the size and spread of the cancer. There are two main staging systems used; the American Joint Committee on Cancer tumour, node, metastasis (TNM) staging system (19), and the numbered staging system (8).

The TNM staging system describes three main characteristics; the tumour size (T), spread to the lymph nodes (N) and spread to a different part of the body (M). The cancer is given a T, N and M value to describe each of these characteristics (e.g., T1, N1, M0) (19).

The numbered staging system divides breast cancers into numbered stages based on the same characteristics; the size of the tumour, spread to lymph nodes and spread to other areas of the body (8). Breast cancers can be classified anywhere from stage 0 to stage IV. A higher number indicates a later stage of breast cancer. Stage 0-III cancers can be treated with

curative intent, while stage IV breast cancer indicates that the tumour has spread to at least one other body organ and can be controlled but not cured (8). The TNM staging system can be converted into a numbered stage (20).

1.2.4.4 Incidence and survival by stage

In 2020 in England, at diagnosis, 33.8% of breast cancers were stage I, 37.3% were stage II, 9.2% were stage III, 5.6% were stage IV, and 14.2% were unknown (21). The stage of cancer impacts prognosis, with lower stages typically having a better prognosis. In cancers diagnosed between 2015 and 2019 in England and followed up to 2020, net survival rates five years after diagnosis were 98.2% for stage I, 89.5% for stage II, 73.2% for stage III, and 26.2% for stage IV (22).

1.2.5 Breast cancer treatment

Treatment depends on a variety of factors including the location of the cancer in the breast, the type, size, grade and spread of the tumour, receptor status, a person's menopausal status and general level of health and fitness. An overview of some of the main treatments are provided below.

1.2.5.1 Surgery

The type of surgery a woman will receive will depend on the size and location of the cancer. Some women will undergo breast conserving surgery, in which the tumour is removed with a border of healthy tissue surrounding it. Other women may need to have their whole breast removed (mastectomy) to reduce the risk of the cancer returning (23, 24).

If it is clear prior to surgery that the cancer has spread to the lymph nodes, the lymph nodes will be removed during surgery. Alternatively, a sentinel lymph node biopsy would be undertaken during surgery to check if the cancer cells have spread to the lymph nodes. If cancerous cells have spread to lymph nodes, further treatment to the lymph node area (radiotherapy or surgery) would be scheduled (24).

1.2.5.2 Radiotherapy

Radiotherapy is the use of high energy x-rays to kill cancer cells. For women who have undergone breast conserving surgery, in the UK, whole breast radiotherapy is typically administered over 1-3 weeks to kill any cancer cells that may remain, to reduce the risk of

recurrence (10, 24, 25). Partial breast radiotherapy is used when breast conserving surgery has had clear margins (whereby the outer edges of the tissue removed do not contain cancer cells), and where women are at low risk of local recurrence (24). A meta-analysis involving over 10,000 patients concluded that radiation following breast conserving surgery can reduce breast cancer recurrence by half at 10 years, and mortality by one sixth at 15 years (26). In some cases, women may receive radiotherapy following a mastectomy, particularly if the cancer is large, has spread to axillary lymph nodes, or cancer cells were present close to the edge of the removed breast tissue (24).

1.2.5.3 Chemotherapy

Chemotherapy disrupts the way cancerous and normal cells grow and divide. In primary cancer the aim of chemotherapy is to kill breast cancer cells and prevent recurrence. If the tumour is large, fast-growing, or has spread to surrounding tissue, neoadjuvant chemotherapy can be used before surgery to shrink the tumour and reduce the risk of recurrence (27). If there is a risk that cancer cells have spread beyond the breast, adjuvant chemotherapy can be used after surgery to reduce the risk of recurrence (10). A large meta-analysis involving over 100,000 patients found that adjuvant chemotherapy reduced breast cancer mortality by a third, compared with no chemotherapy (28).

1.2.5.4 Targeted therapies

Targeted therapies target the differences in DNA that a cancer cell has that helps them to grow faster than normal cells and die less easily. There are multiple types of targeted therapies (10). For example, Trastuzumab (also known as Herceptin) attaches to HER2 to stop cancer cells from growing and dividing, and is offered to women with HER2-positive breast cancer (24).

1.2.5.5 Ovarian suppression

Ovarian suppression or ablation can be used as treatment in premenopausal women. Ovarian ablation is the surgical removal of the ovaries to permanently stop oestrogen production from the ovaries. Ovarian suppression is delivered via monthly or three-monthly injections which stop the ovaries from making oestrogen, meaning there is less oestrogen to stimulate cancer growth. Ovarian suppression can be reversible. In premenopausal women, ovarian suppression/ ablation can reduce the risk of recurrence (29, 30).

1.2.5.6 Adjuvant endocrine therapy

AET is typically prescribed for ER+ breast cancer, after breast cancer surgery. It works by reducing the levels of oestrogen in the body, and stopping oestrogen from binding to cancer cells, therefore stopping growth of the cancer. There are two main classes of AET; selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs).

1.2.5.6.1 Selective oestrogen receptor modulators

Tamoxifen is the most frequently prescribed type of SERM, as a 20mg tablet to be taken daily. It works by binding to oestrogen receptors on cancer cells, therefore blocking oestrogen from binding to the cancer cell and stimulating growth.

The development of tamoxifen dates back to 1966, at which time scientists were seeking to develop a new emergency contraceptive pill. The drug, ICI46,474, was effective in rats, but had the opposite, ovulation inducing effect in humans (31-33). This led the drug to be disregarded for the purpose of contraception. However, in the early 1970's there was a renewed interest in ICI46,474 for the purpose of blocking oestrogen for treatment of breast cancer, and it was resultantly developed into the drug now known as tamoxifen (33). In 1970, the first clinical trial was undertaken, evaluating tamoxifen as a breast cancer treatment. The trial indicated responsiveness to the drug, and the incidence of side-effects was lower than other drugs available at the time (34).

In 1972 tamoxifen was approved in the UK for the treatment of advanced breast cancer, and was typically administered for one year. At this time there was concern surrounding side-effects and development of drug resistance if administered for an extended period of time. A number of trials were conducted over the next two decades investigating the effects of different durations of tamoxifen as a treatment for breast cancer, including extending its use to treat primary breast cancer (35).

In 1998, a meta-analysis of 55 trials containing 37,000 patients concluded that tamoxifen, in the treatment of primary breast cancer, was effective in reducing recurrence and mortality in women across all ages (36). With five years of adjuvant tamoxifen, there was a proportional recurrence reduction of 47%, and 26% reduction in mortality[1] (36). Subsequent updated

[1] Reductions in recurrence and mortality are presented as relative risk reductions throughout this thesis unless otherwise stated.

reviews have confirmed these findings, suggesting that five years of adjuvant tamoxifen significantly reduces recurrence and mortality rates across 15 years compared to both no tamoxifen, and one to two years of tamoxifen (37, 38). In 2011, a large review including data from 10,645 women with ER+ breast cancer, suggested that five years of adjuvant tamoxifen reduces recurrence rates by 39% on average in the first 10 years, and reduces mortality rates by a third over the first 15 years (38).

1.2.5.6.2 Tamoxifen side-effects

A list of side-effects of tamoxifen are summarised in Table 1.1. The most commonly reported side-effects reflect menopausal symptoms including hot flushes, night sweats, vaginal dryness and sleep difficulties (39). The two most serious side-effects as a result of tamoxifen use are thromboembolic disorders and an increased risk of endometrial cancer. Thromboembolic events include deep vein thrombosis, strokes and pulmonary embolisms which are slightly increased in women taking tamoxifen. However, the risk is low in women under 54 years old (40). There is some evidence to suggest that taking tamoxifen can increase risk of developing endometrial cancer, when tamoxifen is taken for more than two years (41, 42). A meta-analysis combining data from over 21,000 patients with early-stage breast cancer across 20 trials found that tamoxifen increased endometrial cancer incidence. The risk was very small for women under 54 years, but there was an absolute increase of incidence of 2.6% in women aged 55-69 (38). Recent evidence also suggests endometrial cancer risk may only be increased when there were endometrial abnormalities at baseline (43). Overall, the benefits of tamoxifen appear to outweigh the risk of endometrial cancer (42).

Table 1.1. Side-effects of tamoxifen and aromatase inhibitors

Prevalence	Tamoxifen	Anastrozole	Letrozole	Exemestane
Common (10 in 100)	Hot flushes and sweats, fluid build-up, nausea, fatigue, vaginal bleeding and/or discharge, skin rash, depression	Headaches, hot flushes, nausea, skin rash, painful or stiff joints, fatigue, loss of bone strength	Raised cholesterol, hot flushes, increased sweating, joint pain, fatigue	Increased risk of infection, sleeping difficulties, depression, headaches, hot flushes and sweats, abdominal pain, nausea, liver changes, sweating, pain in muscles and joints, tiredness, weakness
Occasional (between 1 and 10 out of every 100)	Leg cramps, hair thinning/loss, light headedness, cataracts, allergic reaction, headaches, diarrhoea, changes in taste, tingling sensation in hands and feet, muscle aches, blood clots, changes to lining of the womb, endometriosis	Allergic reaction, diarrhoea, vaginal dryness or bleeding, hair thinning, liver changes, carpal tunnel syndrome, loss of appetite, raised cholesterol, bone and muscle pain, tingly/numb skin, change in taste	Change in appetite, depression, headaches, dizziness, heart palpitations, high blood pressure, nausea, indigestion, constipation, diarrhoea, abdominal pain, hair loss, rash, dry skin, weak bones, pain or fractures, arthritis, vaginal bleeding, swollen hands, feet, arms and legs, chest pain, weight gain, muscle pain	Bruising, bleeding gums, nose bleeds, loss of appetite, pain in hands, being sick, diarrhoea or constipation, indigestion, hair loss, skin itchiness, bone thinning and fractures, pain and swelling of hands and feet
Rare (1 in 100)	Inflammation of lungs, low levels of platelets,	Liver inflammation, trigger finger,	Urine infection, pain where cancer is, drop	Allergic reaction, feeling sleepy or

Prevalence	Tamoxifen	Anastrozole	Letrozole	Exemestane
	high calcium levels, inflammation of blood vessels, swelling in ovaries	high calcium levels, severe skin reaction	in white blood cells, anxiety, sleep difficulties, memory difficulties, tingling sensation, loss of taste, stroke, eye problems, heart problems, blood clots, shortness of breath, dry mouth, changes to liver function, vaginal discharge and/or dryness, breast pain, general swelling, thirst, high temperature, weight loss, itchy skin, skin rash	drowsy, inflammation of the liver

Sources: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/tamoxifen
https://www.cancerresearchuk.org/about-cancer/treatment/drugs/anastrozole
https://www.cancerresearchuk.org/about-cancer/treatment/drugs/letrozole-femara
https://www.cancerresearchuk.org/about-cancer/treatment/drugs/exemestane-aromasin

1.2.5.6.3 Aromatase inhibitors

Despite being a more recent inclusion in clinical practice, the development of AIs dates back to the 1980's. In postmenopausal women, oestrogen is no longer produced by the ovaries. Instead, the production of oestrogen comes from an enzyme called aromatase converting androgens (male sex hormones) into oestrogen. Given the evidence that oestrogen contributes to tumour growth in ER+ breast cancer, stopping aromatase from working, and thus stopping production of oestrogen seemed logical. Early laboratory work supported this hypothesis, in that AI injections blocked aromatase activity as expected (44). These AI

injections showed promising results in treating postmenopausal women with metastatic breast cancer; reductions in oestrogen for at least one week were shown, with limited side-effects, and tumours shrank in more than a third of patients (45). Anastrozole (Arimidex) was found to lead to increased time to disease progression compared with tamoxifen alone and had fewer thromboembolic events in postmenopausal women with hormone receptor-positive advanced breast cancer (46).

With these promising results in advanced disease, interest grew in the use of AIs in the treatment of primary breast cancer for postmenopausal women. As tamoxifen was considered the 'gold-standard' adjuvant treatment for women with ER+ breast cancer, with numerous studies confirming its efficacy in reduction of risk of recurrence and mortality (37, 38), AIs had to be either at least as effective, or provide an improved side-effect profile for postmenopausal women. AIs were not initially considered for treatment in premenopausal women, as the ovaries still produce oestrogen, and therefore the mechanism of AIs would be ineffective.

The first trial comparing AIs to tamoxifen in postmenopausal women with early-stage breast cancer was the 'Arimidex, Tamoxifen, Alone or in Combination' (ATAC) trial (47). The ATAC trial randomised over 9,000 postmenopausal women with a 33 month follow-up period, comparing (1) tamoxifen alone for five years; (2) anastrozole alone for five years and (3) tamoxifen for two to three years followed by anastrozole up to five years. This trial was a breakthrough in terms of proving the efficacy of AIs; finding that there was a significantly lower risk of breast cancer recurrence when taking anastrozole only, compared to tamoxifen alone in postmenopausal women with hormone receptor-positive breast cancer (47). There was also a lower incidence of endometrial cancer and thromboembolic events with anastrozole compared with tamoxifen (47). Support for AIs continued in subsequent clinical trials, finding that disease free survival was improved when taking AIs compared to tamoxifen in postmenopausal women (48).

There are now three main AIs used in the treatment of ER+ breast cancer; anastrozole, letrozole and exemestane. Each are taken daily as an oral tablet. These drugs can be split into two classes based on their mechanism of action; steroidal and non-steroidal (49). Steroidal AIs (exemestane) bind to the aromatase enzyme, and are converted into another agent which stops the action of the aromatase enzyme completely; these are known as suicide inhibitors.

Non-steroidal AIs (anastrozole and letrozole) work by preventing androgens from binding to aromatase, stopping the conversion of androgens to oestrogen (49).

The efficacy of AIs is now well established and evidenced in meta-analyses. An initial meta-analysis of two randomised controlled trials (RCTs) found that when using either AI's initially, or after two to three years of tamoxifen, breast cancer recurrence was lower compared with tamoxifen alone in postmenopausal women (50). In 2015, the Early Breast Cancer Trialists' Collaborative Group extended the evidence base to demonstrate reduced mortality (51). They found that for postmenopausal women, five years of AIs reduced breast cancer mortality rates by 15% more than with five years of tamoxifen alone, and estimated that breast cancer mortality rate was reduced by 40% proportionately compared with no endocrine treatment (51). Trials comparing the different types of AI with one another (i.e., anastrozole vs letrozole, or exemestane vs. anastrozole) have found no significant differences in the efficacy between the drugs (52, 53), but some individuals may be able to tolerate each medication differently (54, 55). More recently, the potential to use AIs in premenopausal women has been explored. In combination with ovarian suppression (see section 1.2.5.5), which stops the ovaries from producing oestrogen in pre-menopausal women, AIs can reduce breast cancer recurrence in premenopausal women (56).

For both tamoxifen and AIs the absolute reduction in recurrence and mortality (the actual chance of an event occurring to an individual) varies between individuals. The Predict breast cancer tool is often used in a consultation with a clinician to understand prognosis and benefits from treatment (57). For example, for a 55 year old post-menopausal woman with a 20mm, grade 2, ER+ tumour, five years of AET would provide an absolute increase in 10-year survival of 2.9% (58).

1.2.5.6.4 Aromatase inhibitor side-effects

Table 1.1 displays side-effects of AIs. Due to their effects on oestrogen, AIs share a similar side-effect profile to tamoxifen. For example, hot flushes and night sweats are commonly reported across all types of AET (59). One reason aromatase inhibitors have been implemented in routine clinical practice is due to the lower prevalence of life-threatening adverse events in postmenopausal women, compared with tamoxifen (60). In the ATAC trial, there were fewer thromboembolic events and endometrial cancers in women receiving

anastrozole compared with women receiving tamoxifen (47, 60). However, as AIs reduce the overall level of oestrogen in the body, they lead to a loss in bone density, which can increase the risk of fractures. In the ATAC trial, significantly more fractures and osteoporosis were reported in women receiving anastrozole compared with tamoxifen (47, 60). Arthralgia (joint stiffness and pain) is also more prevalent in women taking AIs, compared with tamoxifen (61, 62). Overall, compared to tamoxifen in postmenopausal women, AIs have a favourable safety profile, with fewer reports of life-threatening adverse events (59).

1.2.5.6.5 Recurrence of breast cancer

Even after treatment there is a risk that breast cancer can return (whereby the same breast cancer returns). Recurrence can be local, in which the cancer is in the breast or surrounding area, locally advanced, or secondary/ metastatic. The risk of recurrence varies considerably between individuals, dependent on the characteristics of the cancer and treatment received (63, 64). In a meta-analysis including data from over 62,000 women with ER+ breast cancer, the risk of distant recurrence (a cancer that has spread to other parts of the body) ranged between 10% and 41% after five years of AET. The variation in risk correlated with the original tumour size, lymph node status and grade of cancer (63). The risk of recurrence is highest in the first few years after a breast cancer diagnosis, but remains elevated for at least 20 years (63).

1.2.5.6.6 Optimal duration of AET

As breast cancer recurrences continue after the initial five years of AET, the optimal duration of AET has been a focus of research over the past two decades (65).

For premenopausal women taking tamoxifen, extending the duration by a further five years could be beneficial. The ‘Adjuvant Tamoxifen; To Offer More?’ (aTTom) trial randomised 6,953 women to either stop tamoxifen after five years, or continue to 10 years, and found extended tamoxifen reduced recurrence and mortality after years seven and 10 respectively in women with ER+ breast cancer (66). The ‘Adjuvant Tamoxifen: Longer Against Shorter’ (ATLAS) trial also compared five and 10 years of tamoxifen in 6,846 women, and similarly to the aTTom trial, found that 10 years of tamoxifen reduced recurrence and mortality more than five years of tamoxifen in women with ER+ breast cancer (40).

With regard to the benefits of extending AI's beyond five years, evidence has been mixed. In the MA.17 trial involving over 5,000 patients, five years of extended letrozole (vs placebo) following five years of adjuvant tamoxifen was found to reduce recurrence by 42% at the early 2.5 year follow-up. The strong effects led the trial to be un-blinded with all participants being offered extended letrozole (67). The longer term follow-up of MA.17 confirmed increased disease-free survival with extended letrozole, but lost power due to the un-blinding (68). The NSABP B-42 trial, which randomised 3,966 patients to receive either five years extended letrozole or placebo (after an initial five years of AI), found that five years of extended letrozole did not significantly improve disease free survival compared with a placebo (69).

More recent evidence has suggested that seven to eight years of adjuvant therapy, with at least five years of an AI could be optimal in terms of balancing efficacy and side-effects (70, 71). In a trial randomising 3,484 postmenopausal women with ER+ breast cancer, extending anastrozole for an additional five years (10 year total treatment) had no benefit compared with extending AI treatment by two years (seven year total treatment) but was associated with greater risk of bone fractures (71). Similarly, the DATA trial randomly assigned postmenopausal women to either three or six years of anastrozole after an initial two to three years of tamoxifen. They found no statistically significant benefit of six years of anastrozole over three years of anastrozole, but did report increased joint and muscle pain in the six year group (72). The 'Investigation on the Duration of Extended Adjuvant Letrozole treatment' (IDEAL) trial randomised 1,824 postmenopausal women to either 2.5 or five years of extended letrozole treatment after the initial five years of AI. There was no benefit of five years of letrozole over 2.5 years of letrozole following an initial five year period of AET (73).

Until recently, evidence for the benefits of extended AI treatment was restricted to reductions in recurrence, with no evidence regarding survival (74). This was likely due to the limited follow-up periods. The recent GIM4 study randomised 2,056 postmenopausal women with early-stage breast cancer who had been taking tamoxifen for two to three years, to receive either the standard two to three years of letrozole, or extended five years of letrozole (total treatment period seven to eight years) and had a median follow-up period of 11.7 years. Extended five years of letrozole (following two to three years of tamoxifen) led to a significant increase in disease free survival, compared with two to three years of letrozole (70). Current evidence suggests that an optimal duration of AIs might be between seven to eight years.

However, relatively few trials have compared durations of AI, and extended AI treatment may only be beneficial in those at higher risk of recurrence (73, 74). Further trials are needed to confirm that 10 years of extended AI therapy does not provide additional benefits (74).

1.2.5.6.7 Current clinical guidelines for AET to treat ER+ breast cancer

In the UK, the National Institute for Health and Care Excellence (NICE) suggest for premenopausal women with early or locally advanced ER+ breast cancer, tamoxifen should be offered as the initial AET. For postmenopausal women, an AI should be offered initially in those at medium or high risk of disease recurrence. For those at lower risk of disease recurrence, or those who are unable to take AIs due to side-effects or contraindications, tamoxifen can be offered (24).

For postmenopausal women who have been taking tamoxifen for two to five years, extended endocrine therapy using an AI should be offered for those at medium to high risk (e.g., spread to lymph nodes, larger or higher grade tumours) of recurrence, and considered for those at lower risk (e.g., smaller or lower grade tumours, which have not spread to lymph nodes). For premenopausal women taking tamoxifen, extending the duration beyond five years should be considered (24). All considerations of extended therapy should involve a discussion of the benefits and the risks (24).

1.2.6 Section summary: breast cancer

Breast cancer is a heterogeneous disease, with multiple types and classifications which impact prognosis and treatment pathways. Most breast cancers are ER+, and are treated using AET, which reduces breast cancer and mortality but can cause side-effects.

1.3 Medication adherence

Pharmacological interventions are one of the most common approaches to treat and manage chronic illnesses (75). However, across a range of chronic illnesses an estimated 50% of patients do not take their medication as prescribed (76).

1.3.1 Non-adherence

Medication non-adherence is the extent to which a person's medication-taking behaviour corresponds with agreed recommendations from a health care provider (77). Adherence to medication can be split into three components; (1) initiation; the time taken to start the medication from first prescription; (2) implementation; whether the medication-taking corresponds with what was prescribed; and (3) discontinuation; when a patient ceases to take the medication (78).

Other terms are often used to describe medication adherence, however they have different connotations. Medication compliance refers to acting in accordance with a dosing regimen (79). Compliance, however, assumes the patient is a passive subject, whereas 'adherence' acknowledges the active role that a patient plays in medication-taking (79). Non-persistence refers to when a patient stops taking a medication early (78, 80). For example, in women prescribed AET for five years, non-persistence would occur when a patient has stopped taking AET before five years.

1.3.2 Impact of non-adherence to medications

Adherence to a medication is commonly defined as a patient taking 80% or more of the prescribed dose (81-83). For an individual, non-adherence can reduce medication effectiveness. In a review of 63 studies assessing medication adherence across a range of medical conditions, higher adherence was associated with better treatment outcomes (84). Reduced adherence has been associated with increased morbidity and mortality, and reduced quality of life across a range of chronic illnesses (84, 85). However, associations do not suggest causality, and as such it is possible that quality of life could determine non-adherence, as well as non-adherence reducing quality of life. On a societal and economic level, medication non-adherence is costly, with estimations of annual costs of €80-125 billion in the European Union, and US100 to US$290 billion in the US (United States) (86-88). These cost estimates consider

factors such as increased risk of hospitalisations, waste of medications that are not taken, and loss of productivity or absenteeism at work (87).

However, while adherence is important in many cases, non-adherence to a medication can also be an informed, reasoned choice (89). Adherence to medication is not universally the 'right' choice for a variety of reasons (89). For example, many medications may cause unpleasant side-effects that reduce quality of life. Some may feel enduring unpleasant side-effects is not worth the potential benefits that the medication could provide.

1.3.3 Factors associated with non-adherence

Adherence to a medication is a complex behaviour, and a variety of factors may influence adherence. Medication non-adherence can be considered intentional (e.g., making a decision to not take a medication) or unintentional (e.g., forgetting or lacking the resources to be able to access prescriptions) (75, 79). Factors impacting both intentional and unintentional medication adherence can broadly be separated into five categories; (1) social and economic factors, (2) disease related factors, (3) therapy related factors, (4) patient related factors and (5) health care system related factors (76, 77).

Social and economic factors include factors such as education level, ethnicity and financial status. Increased education, White ethnicity and better financial status often have positive associations with medication adherence, but this varies widely dependent on the condition and specific medication (77). There has been mixed evidence for disease related factors, with some studies finding more chronic diseases being associated with increased adherence, while others have found more chronic disease to be associated with reduced adherence (77). Therapy-related factors of adherence concern aspects related to the medication regimen. Regimen complexity has been associated with medication non-adherence (90). Patient-related factors include demographics such as age and gender. In the context of cancer medications, evidence suggests younger (< 45 years), and older (> 75 years) people are generally less adherent (75, 77, 91, 92). Increased cost of medication and length of waiting times, and poorer communication between a patient and physician, are health care system related factors that could contribute to reduced adherence to medication (75, 77).

Medication adherence varies between people, conditions and treatments, and within people themselves over time (75, 77, 79). Therefore, it is important to consider medication adherence specific to the condition and treatment of interest.

1.3.4 Non-adherence to AET

As described in section 1.2.5.6, AET is prescribed to women with ER+ breast cancer to reduce recurrence and mortality. Initiation (starting AET), implementation (taking AET as prescribed), and discontinuation (non-persistence with AET) are all important behaviours (78). In the US, it is estimated that around 9-17% of women with early-stage breast cancer prescribed AET never initiate it (93-95). There is limited UK data with regard to initiation of AET (96). Of those who do begin taking AET, up to three-quarters of women do not take AET as prescribed (97-102). In a UK based interview study assessing non-adherence, intentional and unintentional non-adherence were reported by 17% and 83% of women respectively (103). In a US study, using a self-reported questionnaire, intentional non-adherence was reported by 34% of women, while unintentional non-adherence was reported by 59% (104). While unintentional adherence was more prevalent in both of these studies, the higher prevalence may in part reflect the fact that women may feel more able to admit to unintentional non-adherence than intentional non-adherence (103, 104).

Adherence to AET decreases across the initial five years that it is prescribed for (99, 105, 106). One large database study, including over 11,500 women prescribed AET, reported rates of adherence of 58% at year one, 51% at year two, 49% at year three, 47% at year four and 36% at year five (107). Multiple studies have indicated that the largest drop in adherence is in the first year of prescription, and therefore this could be an important time period to provide additional support to women prescribed AET (107-109).

Non-persistence to AET is defined as when a person stops taking AET completely, and it is estimated that around 50% of women do not take AET for the full five year duration (97, 99, 100, 105). One large database study found 59% of women persisted for the first year of AET being prescribed, and only 24% persisted for the full five years (106). However, persistence estimates vary between studies. A recent review highlighted that non-persistence estimates vary between self-report and database methods, with 7% and 25% of women reporting non-persistence in each method respectively (105).

Similar to medications more broadly, non-adherence to AET may be the appropriate choice for some women (as described in section 1.3.2). Intentional non-adherence to AET has been associated with unpleasant side-effects such as hot flushes and joint pain (110), with some women reporting that taking AET is not worth the reduced quality of life (111). As such, while adherence to AET reduces recurrence and mortality, it may not be right for all women.

1.3.5 Impact of non-adherence to AET

Non-adherence and non-persistence to AET are associated with an increased risk of breast cancer recurrence and an increased risk of breast cancer mortality (100, 112-115). In a study of over 8,000 women taking tamoxifen or AIs, early discontinuation and non-adherence of AET were associated with a 26% and 49% increase in all-cause mortality respectively, when using a cut-off of 80% to define adherence (112). When an adherence cut-off of 90% was used, there was no significant adverse effect on survival, suggesting increasing adherence from < 80 to > 90% could improve outcomes.

Non-adherence and non-persistence to AET have also been associated with reduced quality-adjusted life years (QALYs) (116, 117). A QALY is a unit of measurement assessing the number of years someone lives in perfect health, taking into account quality of life (QoL) and length of life (118). One QALY is equal to one year in perfect health. A large cohort study including women prescribed tamoxifen found that low adherence to tamoxifen reduced QALYs by 1.12 compared to those with high adherence to tamoxifen (116).

In terms of the economic impact of non-adherence to AET in the UK, low adherence (< 80%) has been estimated to have increased costs of £5,970 per patient compared with high adherence over the expected lifetime, due to factors such as increased in-patient stays and dispensing costs of other medications (116). NICE guidelines consider the value of one QALY to be between £20,000 to £30,000 (119). Assuming a midpoint of this estimate of £25,000, the value of changing a patient from low adherence (below 80%) to high adherence (above 80%) has been estimated to be worth £33,897 using simulation data (116). While AIs have been established as a cost-effective alternative to tamoxifen in postmenopausal women (120, 121), no studies have extensively evaluated the value of low vs high adherence in AIs.

1.3.6 Assessment of non-adherence

One of the major issues with non-adherence research broadly, including in the context of adherence to AET, is the difficulty in assessing adherence. There is currently no 'gold-standard' assessment of non-adherence. Non-adherence rates of AET vary considerably between studies (97-102), which is likely at least in part due to the variation in assessments. Broadly, assessments of non-adherence can be categorised into objective assessments (e.g., biological markers, dispensing records), and self-report measures (e.g., Medication Adherence Report Scale (122)).

Biological assessments involve using biomarkers, such as blood plasma or urine drug levels to determine adherence. Biological assessments are often considered the most objective measure of adherence (75), and have been used to assess AET discontinuation (123, 124). However, urine assays can only indicate whether AET has been discontinued, and cannot assess whether the medication had been taken day-to-day (124, 125). Moreover, biological assessments tend to require more intensive resources (e.g., time and money).

Medication event monitoring systems caps (MEMSCaps) are an alternative assessment for adherence which are also considered objective. These are electronic devices that automatically register when a patient opens the medication bottle. MEMSCaps have the benefit of providing information about the frequency and time of day that the medication bottle was opened (75). However, MEMSCaps are expensive, and rely on the assumption that opening the bottle is equal to ingesting the medication (126). The presence of a MEMSCap can act as an intervention in itself as a reminder to take the medication, and therefore may lead to overestimates of adherence (127). This is particularly important to consider in interventional trials, as effects may not be seen in clinical practice if the MEMSCap was not provided.

In the UK National Healthcare System (NHS), it is becoming increasingly possible to obtain electronic health data. For example, in the context of AET adherence, prescription and refill data may be accessible. This is a promising opportunity as it is more objective than MEMSCaps methods, and requires no input from the patient. However, data only reports on the date a prescription was dispensed or collected, and does not provide information about whether the medication was ingested (75).

Self-report measures are an alternative to objective assessments of adherence. Self-report measures are beneficial in that they are relatively easy to administer to large populations, are generally inexpensive, can be analysed easily and can provide an overview of adherence, including intentional and unintentional reasons for non-adherence (128). There is variability in self-reported measures of adherence, ranging from single items to multiple items assessing intentional and unintentional barriers to adherence (126, 129). Promisingly, self-reported assessments of non-adherence have correlated with objective assessments in numerous instances (130-133).

Regardless of the specific measure used, self-report assessments of adherence have limitations. There is large variation in phrasing and recall time between measures, which makes it difficult to compare studies using different assessments (128). Some assessment measures produce ceiling effects, whereby a large proportion of participants score the maximum score, reducing the utility of the measure. Self-report also risks social desirability bias and consequently may overestimate adherence behaviours (128). Social desirability may be a particular issue in interventional clinical trials, whereby participants may overestimate their adherence if they received an intervention that they thought was designed to improve their adherence (128). Normalising non-adherence at the start of the measure and administering the questionnaire via a computer survey rather than face to face can reduce social desirability bias (128).

As there is no current 'gold-standard' assessment of adherence, focus is now turning to the potential to combine multiple measures of adherence (75, 128). For example, a self-report measure could be used in combination with prescription refill data to provide both a subjective and objective overview of adherence in an individual. Combining adherence measures could reduce the limitations faced by using one single approach (75, 128).

1.3.7 Barriers to adherence to AET

A number of systematic reviews have been conducted to synthesise the existing evidence of the barriers to taking AET. Barriers can be split into sociodemographic and clinical factors which tend to be unmodifiable, and modifiable barriers which include intentional and unintentional barriers to adherence.

1.3.7.1 Sociodemographic and clinical factors associated with AET adherence

Lower adherence is commonly observed in younger women (below 40 years old), and older women (above 70 years old) (91, 98, 102, 134, 135). Women from ethnic minority groups are more likely to report both intentional and unintentional non-adherence than White British women, even when controlling for other demographic variables such as age and socio-economic status (96, 136-138). In terms of clinical associations, a systematic review consisting of 61 studies, found that there were no consistent associations between tumour size, previous chemotherapy and lymph node status and adherence, but that a higher number of hospitalisations was associated with lower adherence (91).

1.3.7.2 Modifiable barriers to AET adherence

Unintentional non-adherence primarily relates to forgetting to take a medication; including forgetting to take a tablet, forgetting to order or collect a prescription, or forgetting to take AET when away from home. Forgetfulness has been associated with decreased adherence across a range of studies (102, 104, 139). Forgetfulness may be exacerbated by cognitive difficulties that are commonly reported in women with breast cancer following active hospital-based treatment (140, 141).

A number of intentional, modifiable barriers to AET adherence have also been reported. The balance between beliefs about the necessity of AET and concerns about AET is one of the most consistently cited barriers to non-adherence (142). Women often report low personal perceived need for AET and high concerns, particularly surrounding side-effects (91, 98, 102, 110, 111, 142-146). The low personal perceived need and high concerns surrounding AET may be in part due to the lack of knowledge that women report about how AET works and its potential side-effects (143). Women prescribed AET have frequently reported wanting more accurate information about the medication (111, 145).

Increased psychological distress has been associated with lower AET adherence (142, 147). The period in which women are prescribed AET can be a challenging period, during which they are discharged from active hospital-based treatment, and transition from being a patient to a ‘survivor’. Women face a variety of challenges in this period that may contribute to psychological distress; including feeling abandoned due to the reduced level of professional

support, fears and uncertainty surrounding recurrence, feelings of survivor guilt, processing their traumatic experience(s), and returning to 'normal' (111, 147-150).

The presence, severity and number of side-effects experienced have all been associated with adherence (142). Many studies have reported that the presence of side-effects reduces adherence and quality of life in women taking AET (98, 134, 142-144, 151-154). Arthralgia and cognitive changes have been most commonly associated with adherence (142). The difficulty in managing side-effects and the lack of information available about management strategies is a common concern of women prescribed AET (111, 148). However, inconsistencies in the relationship between side-effects and adherence have been reported, with some studies finding no relationship between side-effects and adherence (91, 142). It is possible that the experience of side-effects in combination with other barriers to adherence, such as psychological distress and beliefs about the medication, may lead to their association with non-adherence (142).

Facilitators to AET adherence include increased social support, including from other breast cancer survivors and health care professionals (91, 98, 134, 136, 143, 151, 155), self-efficacy (and associated belief in one's ability to take the medication) (91, 143, 151, 153), and better patient-physician communication (91, 134, 142, 151, 155).

Adherence to AET is a complex issue with multiple barriers and facilitators. As such, any intervention developed aiming to improve adherence to AET should include a detailed consideration of the number of barriers to AET adherence, and will likely require a multicomponent intervention to sufficiently address adherence.

1.3.8 Existing interventions targeting non-adherence

A large Cochrane review of 182 RCTs of interventions aiming to increase medication adherence across a range of medical conditions, found that very few interventions were effective, and those that were effective had small effect sizes (83). Most included RCTs had moderate or high risk of bias, and many of the interventions were not cost-effective. The investigators called for the need for novel and innovative approaches to address non-adherence across conditions (83).

Aligned to the fact that improving AET adherence could reduce breast cancer recurrence and mortality, and reduce costs associated with non-adherence, a number of interventions have

been developed specifically aiming to support adherence to AET. Four reviews have provided an overview of existing interventions to support AET adherence (156-159).

The earliest review, conducted in 2016, identified five behavioural interventions supporting adherence to AET (156). Four out of five interventions were focused on adherence to AIs, and three out of five related to trials of the same intervention in different contexts (160-162). The intervention used in three of the five trials was the 'Patients Anastrozole Compliance to Therapy' (PACT) intervention (160). PACT consists of nine leaflets and personal letters sent to participants, providing information regarding breast cancer, treatment, side-effects, strategies for enhancing adherence, and information about diet or physical activity. Three studies included in the review tested the PACT intervention in different settings. The 'Compliance in adjuvant treatment of primary breast cancer' (COMPAS) trial evaluated the efficacy of two different interventions; personalised motivational reminder letters, and nurse led calls providing motivational interviewing (163). The final study included in this review was the 'Improving Patient Access and Adherence to Cancer Treatment' (IMPAACT) trial. IMPAACT evaluated the efficacy of a culturally tailored patient navigation intervention in which participants received written information and an interview with a patient navigator to attempt to improve adherence to AET (164). No interventions included in this review had a significant effect on medication adherence in primary analyses.

The second review included seven studies; four from the aforementioned review, and three new studies (157). The first of these new studies involved comparison of two interventions; an app in which participants recorded their symptoms and adherence, compared with an app plus a reminder system to use the app (165). The second new intervention was a patient information leaflet combined with 15 minute phone call sessions including information on the mechanisms of AET, the benefits, and its side-effects (166). The final new trial in this review was a further evaluation of the PACT intervention materials previously described (167). Across all seven studies included in this review there was no significant effect on adherence (157).

The third review expanded on previous reviews by including both interventions and papers that examined strategies and approaches for improving adherence to AET (158). The review included 16 studies with a variety of study designs including RCTs, retrospective and prospective studies, cross-sectional and observational studies. Similar to previous reviews, it was reported that the most common strategy used to improve AET adherence was written

information given to patients, with none reporting significant findings in primary analyses (158).

The most recent meta-analysis[2] provided an updated overview, including 25 unique studies representing 367,873 women (159). This meta-analysis was the first to demonstrate a small statistically significant effect overall of the interventions on adherence to AET. They found a range of intervention types could be effective, with varied efficacy, including medication reminders, communication, and psychological/coping strategies (159). Educational approaches for side-effect self-management were mostly ineffective, and policy changes lowering medication costs (predominantly in the US) were consistently effective (159).

Across these reviews and meta-analyses, several limitations of existing interventions have been highlighted (159). Many interventions tend to have a narrow focus and do not target multiple barriers to AET adherence identified in the literature (159). A large proportion of intervention strategies used tend to consist solely of educational materials (156, 158, 167). Educational materials may be important to provide women with accurate information, but used in isolation they do not appear to be sufficient for behaviour change.

Furthermore, a large proportion of interventions aiming to support AET adherence have not been grounded in theory, and have not being guided by any intervention development framework (156, 157, 159). Clearly describing the theoretical basis of the intervention in a coherent model provides clarity about how the intervention is expected to have an effect (75). Using theory to guide the development of an intervention can improve understanding as to why an intervention does or does not work.

The most recent meta-analysis highlighted that effect sizes for interventions aiming to support adherence to AET have not increased over time (before vs after 2017), suggesting slow progress to supporting adherence in women with breast cancer (159). This slow progress could be because we have a limited understanding as to what parts of an intervention are having what effect upon adherence, and whether different parts of an intervention are interacting. Greater understanding of which parts of an intervention are impacting adherence could advance our understanding of how best to support adherence to AET (159).

[2] Note: This meta-analysis was published in August 2023, and therefore was not included in Studies one to three (chapters two to four) of this thesis, which were published prior to August 2023.

1.3.9 Theoretical frameworks of non-adherence

A range of health behaviour models and psychological theories have been used to predict medication adherence. Some of these models have informed the development of a minority of interventions to support AET adherence (156, 157). The most common models applied to non-adherence to AET include the health belief model, the theory of planned behaviour (TPB) and the common-sense model of self-regulation (CSM) (168-172). A brief overview of these models, their applications and limitations are presented below.

The health belief model proposes that increased perceptions of illness severity, susceptibility, and benefits of a health behaviour will increase one's motivation to undertake a health behaviour, while perception of strong barriers will reduce the likelihood of performing the behaviour (168, 169). The model also accounts for internal (e.g., bodily sensations) and external (e.g., reminders about doctors' appointments) factors that could influence engagement in the behaviour (168, 169). The IMPAACT intervention, consisting of written information and patient navigation phone calls to improve AET adherence, was based on the health belief model. This intervention showed no significant difference on adherence when compared with usual care (164). Evaluations of the health belief model have concluded that the constructs are not good predictors of behaviour, and there is weak evidence for use of this model in developing successful medication adherence interventions (173, 174).

The TPB suggests that attitudes towards a behaviour, subjective norms and perceived behavioural control influence one's intentions to perform a behaviour, which in turn predicts one's actual behaviour (e.g., medication adherence) (170). Attitudes include one's beliefs about the behaviour, subjective norms relates to perceptions of what other people in a similar situation think of the behaviour and whether others would approve, and perceived behavioural control refers to one's perception of control over performing the behaviour. In a large cross-sectional study investigating adherence to tamoxifen, intention, subjective norms and attitudes towards adherence were associated with intentional and unintentional non-adherence (175).

Laboonté and colleagues developed a community based pharmacy programme aiming to improve AET adherence, guided by the TPB (176). They identified four broad determinants of the intention to take AET; lack of knowledge about AET, negative attitude towards AET, insufficient perceived social support from health professionals, and poor perceived

behavioural control in terms of difficulty coping with side-effects and establishing a routine to take AET (176). This intervention is currently being tested in a pilot study.

The TPB has received substantial criticism regarding its usefulness in predicting health behaviour change (177). The TPB has consistently been found to predict intention to perform a behaviour, rather than the actual behaviour. In a meta-analysis of 27 studies investigating the use of the TPB applied to adherence behaviours across chronic conditions, the TPB accounted for 33% variance in intentions, and only 9% of variance in treatment adherence (178). More broadly, the TPB has been criticised for not accounting for emotional influences on behaviour, for suggesting that all influences on behaviour are mediated through the TPB, and for not being able to predict long-term behaviour change (177). These criticisms question the applicability and usefulness of the TPB alone to predict adherence behaviours (177, 178).

The CSM proposes that one's engagement in a health-related behaviour (e.g., taking medication) is dependent on how well the behaviour fits with their personal representation of their illness (171, 172). It suggests that cognitive and emotional representations impact how people understand and behave in response to a health threat. Cognitive representations of an illness include (1) identity; illness or symptom experiences; (2) beliefs about the cause of the illness; (3) perceived timeline of the illness; (4) the extent to which a person feels the illness can be cured or controlled; and (5) the perceived consequences of the illness (172). Emotional representations include factors like fear or worry that can be evoked by an illness. The model suggests that engagement in coping behaviours is driven by these cognitive and emotional representations. However, a large meta-analysis suggested that the relationship between illness representations and adherence to self-management behaviours (e.g., medication-taking) is weak (179).

An extended version of the CSM, acknowledging the role of specific beliefs about a medication may be more helpful in explaining medication adherence (180-182). Medication beliefs can be split into two broad categories; beliefs specific to the medication (e.g., concerns about side-effects) and beliefs about the use of medication in general (e.g., concerns about becoming dependant on a medication) (180). Medication beliefs can be explained by the necessity-concerns framework (NCF), which suggests that the balance between one's beliefs about the personal perceived need of a medication compared with their concerns about that medication can influence medication adherence (180). Specific medication beliefs have been

associated with adherence to AET in a range of quantitative and qualitative studies (91, 98, 102, 110, 142-144, 151, 153, 155). These specific medication beliefs may mediate the relationship between illness perceptions and medication adherence (181, 183, 184). Evidence is more mixed regarding the association between general medication beliefs and adherence to AET, with the suggestion that specific medication beliefs are more strongly related to adherence than general medication beliefs (110, 145, 146, 185).

1.3.9.1 Combining theories to guide intervention development

It is well established that medication adherence is a complex and multi-faceted behaviour, with a number of determinants that could influence adherence to any medication. As such, generalised theoretical models may not be able to sufficiently explain adherence behaviours due to their complexity and specificity to the clinical population (178). Combining models may provide greater value in explaining non-adherence and may provide a more helpful basis for intervention development.

In the context of adherence to AET, Moon and colleagues have combined the TPB and CSM to develop an intervention to support medication adherence to tamoxifen (186). Here, a substantial amount of formative work identified key barriers and facilitators of adherence to AET, including medication beliefs, concerns about side-effects, illness perceptions, psychological distress, social support and side-effects (91, 111, 136, 175). The CSM was used to identify the importance of modifying illness and treatment beliefs, suggesting that information to counter common myths and providing information on symptoms and concerns could be beneficial (186). Constructs from the TPB were also considered, such as providing information about how tamoxifen works and its effectiveness to promote more positive attitudes toward the medication (186). In a small, single-arm pilot study, the intervention was considered to be acceptable to women with breast cancer and showed small, promising, improvements in adherence, medication beliefs, personal control, coherence, symptom experience, distress and self-efficacy for managing side-effects (187).

Jacobs and colleagues also combined a number of theoretical perspectives in the development of the 'Symptom-targeted randomised intervention for distress and adherence to adjuvant endocrine therapy' (STRIDE) intervention (188). The development of this intervention was broadly informed by the health information technology acceptance model;

which combines the health belief model and the technology acceptance model. Broadly, this model proposes five antecedents to behaviour; health status, health belief and concerns, subjective norms, health information technology reliability, and health information technology self-efficacy (189). Further relevant theories were considered and incorporated for different aspects of the intervention. For example, the intervention was broadly based on cognitive behavioural therapy (CBT) to optimise AET adherence, reduce distress and manage symptoms, but aspects from mindfulness theory (190) and symptom perception theory (191) were also incorporated into the intervention modules throughout. The resulting intervention was considered acceptable to women taking AET in a pilot study, showed positive trends on improvement in symptom distress, quality of life, coping skills, anxiety symptoms and self-efficacy, but showed no effect on AET adherence (192).

Combining multiple theories in the development of an intervention could be a promising approach to developing a theory-informed complex intervention to support adherence to AET. This fits with wider suggestions to not rely on a singular theory when developing an intervention to target medication adherence, as single theories generally cannot fully explain the behaviour (193).

1.3.10 Section summary: medication adherence

In line with interventions to support medication adherence in general, there are a lack of effective strategies to sufficiently support adherence to AET in women with breast cancer. The extent of non-adherence to AET is broad, and a number of barriers and facilitators to AET adherence have been reported. Existing interventions have been largely unsuccessful and have limitations. Any intervention developed to address AET adherence should target multiple barriers associated with non-adherence, and should consider multiple theoretical perspectives in its development.

1.4 The development, optimisation and evaluation of complex behavioural interventions

In sections 1.2 and 1.3, I have provided a rationale for the development of an intervention to support adherence to AET in women with breast cancer. In this final section, I will introduce possible approaches to the development and evaluation of such an intervention, providing a rationale for the approaches taken to intervention development and optimisation in this thesis.

1.4.1 Complex interventions

Complex interventions are multicomponent interventions often used to address a wide variety of health issues, including weight loss (194), smoking cessation (195, 196) and medication adherence (195, 196). An intervention can be considered complex based on a number of factors; the number of components (any part of an intervention that can be separated out for study (197)), the number and range of behaviours targeted, expertise required to deliver the intervention, or number of levels targeted (e.g., patients, healthcare systems) (198). Complex interventions can also be considered as events in systems, in which the interaction between the intervention and the context can influence how and why an intervention is having an effect (198, 199).

1.4.2 Guidance for developing and evaluating complex interventions

UK Medical Research Council (MRC) guidance for developing and evaluating complex interventions describes four phases of complex intervention research; (1) development (2) feasibility, (3) evaluation and (4) implementation (198). The development of an intervention involves creating a new intervention, or adapting an existing intervention (200). The feasibility phase involves undertaking studies to address key uncertainties about interventions or a more definitive evaluation. It is recommended that predefined progression criteria are used to guide the decision on whether to proceed to the next phase of research (198, 201). The evaluation phase typically involves using a trial to answer a specific research question. A parallel group RCT is often used to assess the effectiveness of an intervention compared to a suitable comparator, such as usual care. MRC guidance acknowledges that alternative experimental designs may be appropriate to answer different research questions of importance, including how an intervention works, how it interacts with its context, and

whether it is cost-effective (198). The implementation phase involves considering how an intervention could be delivered in routine clinical practice, including factors such as who will deliver the intervention, staff time and overall delivery costs. Importantly, MRC guidance emphasises that implementation should be considered early in the intervention development process, to enable interventions to be developed that are deliverable in real-world settings (198).

Across these four phases of research, MRC guidance highlights six core elements that should be considered throughout each phase (198). These are (1) context; a consideration of how context might influence the effectiveness of the intervention; (2) programme theory; detailing the mechanisms of action of how an intervention is expected to have its effect and influence of wider contextual factors; (3) inclusion of stakeholder's perspectives; (4) identifying and answering the key uncertainties; (5) intervention refinement; and (6) economic considerations.

MRC guidance also acknowledges the importance of process evaluations in developing and evaluating complex interventions (202). A process evaluation is a study (or studies), often nested in a trial, to maximise learnings about trial procedures and the intervention(s) being tested. They can provide explanation of why an intervention is working or not working, how it can be improved, and contribute to understanding the mechanisms of impact (198). MRC process evaluation guidance highlights three key functions of process evaluations of complex interventions; (1) understanding contextual factors that may influence theory, implementation and outcomes; (2) implementation, which considers the quantity and quality of what was delivered; and (3) mechanisms, which involves investigation of how the intervention is working, through what mediators, and if there are any unexpected pathways and consequences (202).

The exact function of a process evaluation depends on the phase of research (202). For example, at the pilot/ feasibility phase there may be a focus on whether the intervention was acceptable to those receiving and delivering it (acceptability) and whether it can be delivered and is received as planned (fidelity). Acceptability of an intervention to the target population is important to consider, as it can impact adherence to the intervention and can inform adaptations to be made prior to the next phase, while acceptability to intervention deliverers it can impact fidelity of intervention delivery (203). In the evaluation phase, the focus of a

process evaluation may lie more in understanding the context and mechanisms of effect (198, 202).

1.4.3 Parallel group randomised controlled trials

In a parallel group RCT, participants are randomised to an intervention or control arm. Randomisation increases the likelihood that the outcome would be equally distributed between groups with no intervention, which can increase confidence that any difference in outcome is explained by the effect of the intervention (204). The effectiveness of an intervention is compared with a suitable comparator to determine whether the intervention as a whole (often made up of multiple intervention components) is better in improving the outcome than the comparator. A parallel group RCT is a suitable design to answer definitive research questions regarding the effectiveness of an intervention package as a whole.

However, a parallel group RCT has limitations within complex intervention research (205). Using a parallel group RCT, complex interventions are evaluated as an overall package, meaning the effects of individual intervention components on an outcome cannot be estimated (206). This means it contributes limited information as to what components are driving any observed effect. A parallel group RCT is also unable to provide any information about the interactions between intervention components (206). It is possible that some components may work better together, whereas others may be less effective when combined (207). Understanding the main and interaction effects of intervention components that make up intervention packages would enable investigators to identify key parts of an intervention that are having positive or negative effects on the outcome of interest. This would allow ineffective or redundant components to be removed from an intervention, therefore not unnecessarily using valuable resources (208).

Difficulty in implementing complex behavioural interventions which have been evaluated in trials is a recurring issue (209, 210). It is often the case that if an intervention shows a statistically and clinically significant effect in evaluation in a parallel group RCT, further work may then attempt to implement the intervention. Further work would likely involve scaling the intervention up to a wider population and attempting to implement it in routine care (211, 212). Ad hoc adaptations may be made to accommodate resource constraints (213), but the effects these changes are having on the proven effectiveness would be unknown (211, 212).

Using the typical parallel group RCT approach, complex interventions may be evaluated that are not then implementable in the desired setting.

Parallel group RCTs are resource intensive, but provide limited information beyond the effectiveness of an intervention package as a whole. This raises the question as to whether relying on RCTs as the main approach to evaluate complex behavioural interventions is the most beneficial use of resources (208). Many existing interventions supporting adherence to AET described in section 1.3.8 have been evaluated using an RCT to establish the effectiveness of the intervention as a whole. This approach has left us with limited understanding of effective strategies to support adherence to AET thus far, and therefore an alternative approach may be warranted.

1.4.4 The Multiphase Optimisation Strategy

The Multiphase Optimisation Strategy (MOST) is a framework that can be used to accelerate our understanding of behavioural interventions (214). MOST is an engineering inspired framework used to develop, optimise and evaluate multicomponent complex interventions (206, 214). It provides guidance on how to develop optimised interventions that balance effectiveness (E, effect in a desired direction) against affordability (A, extent to which an intervention is within budget), scalability (S, extent to which an intervention can be delivered in real-world settings) and efficiency (E, extent to which an intervention produces good outcomes without wasting resources) (211). This is known as optimising to promote intervention EASE (208).

1.4.4.1 Stages of MOST

Figure 1.1 depicts the three phases of MOST; preparation, optimisation and evaluation.

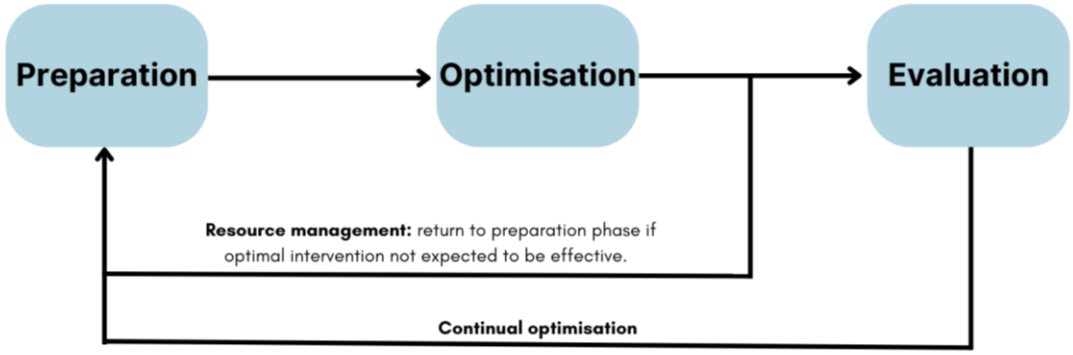

Figure 1.1. Multiphase optimisation strategy
Adapted from Collins et al., (214).

1.4.4.1.1 Preparation phase.

The purpose of the preparation phase is to develop a conceptual model, candidate intervention components, and to operationalise an optimisation objective (208, 215). The development of a conceptual model is fundamental in the preparation phase of MOST (216). A conceptual model is similar to a logic model in that it visually demonstrates the mechanisms of an intervention, and is informed by theory and empirical literature (215). A conceptual model, however, specifically hypothesises the causal pathway for each candidate intervention component (215) (Figure 1.2). To aid decision-making in the optimisation phase, ideally each intervention component should target one specific mediator in the conceptual model, as demonstrated in Figure 1.2 (215). Importantly, the components must be independent, so that one component does not depend on the presence of another. Specifying the model in this way is important for the optimisation phase of MOST.

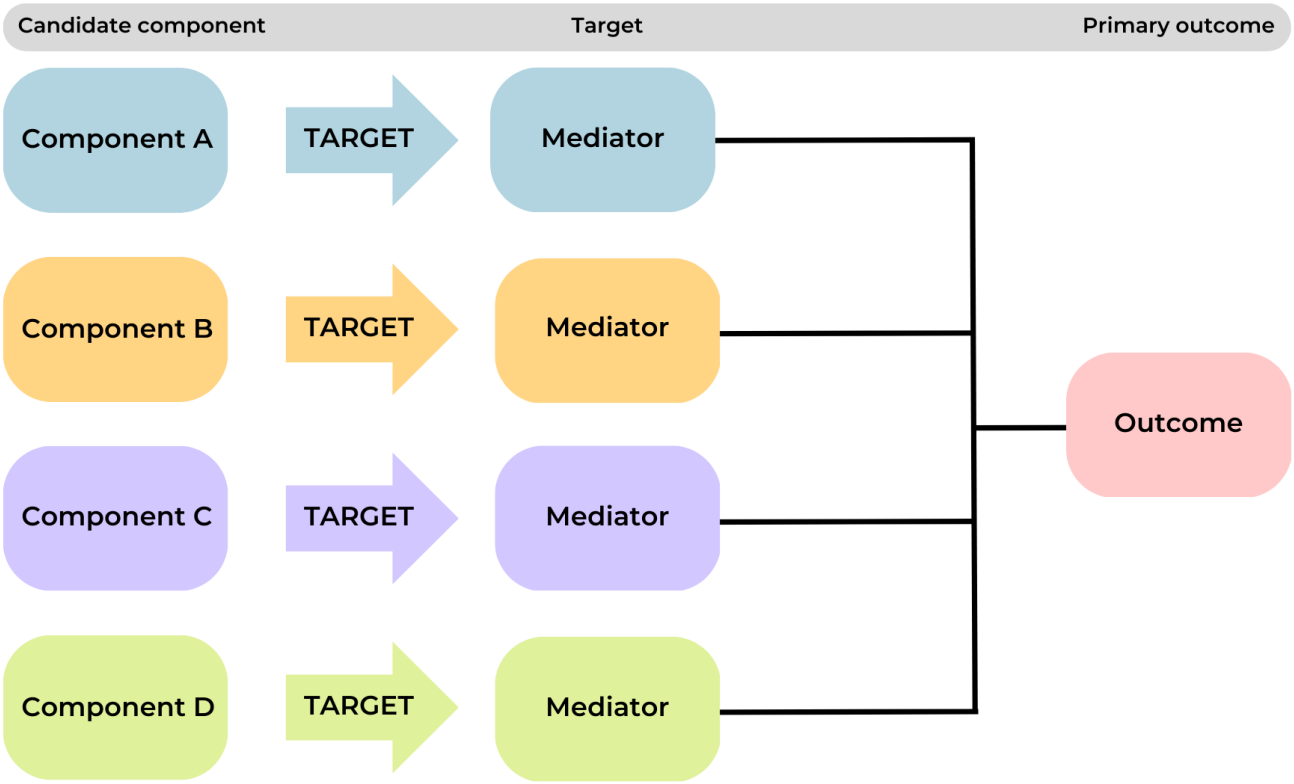

Figure 1.2. Example conceptual model

Once the conceptual model is established, candidate components should be developed or identified in the preparation phase. While the intervention development process may be somewhat similar to a typical intervention development process, there are some key considerations to enable optimisation in the MOST framework. A consideration of the granularity (size) of components is important (215), dependent on the research question and resources available. More granular intervention components (e.g., individual text messages) would likely lead to smaller expected effect sizes, and therefore a larger sample size may be required to remain sufficiently powered (215). Less granular components (e.g., groups of text messages) may require a smaller sample size to detect the expected effect size, but would provide less information on the individual components. How individual intervention components fit together as a package must also be considered in the development phase. This is important to ensure participants do not receive a disjointed intervention package, or large duplication of information across components.

Developing interventions that are affordable and scalable is a core aim of the MOST framework. Implementation considerations begin in the preparation phase by specifying an

optimisation objective (215, 216). An optimisation objective pre-specifies constraints on resources, with the aim to achieve intervention EASE (215). For example, investigators may want to develop the most effective intervention package for under £300 per person. The optimisation objective is not restricted to cost, however. It can contain any constraint relevant to the intervention being developed, such as time required to participate in or deliver the intervention. If there are no resource constraints, then the 'all active components' objective can be used. This aims to build an optimal intervention package including only components that are having a positive impact on the outcome, irrespective of potential constraints (208).

Once the conceptual model and intervention components have been developed and an optimisation objective has been considered, pilot testing of the candidate components and optimisation trial processes is recommended in the preparation phase (215). Here, a pilot study is defined as a subset of a feasibility study in which a future study or trial is conducted on a smaller scale (217). A pilot study in this context can be helpful to assess whether each level of each component is feasible and acceptable, and to assess randomisation processes, adherence and dropout rates in all conditions, and availability of outcome data.

The work involved in the preparation phase of MOST is fundamental in providing the foundations for the optimisation of a complex intervention. Despite its importance, there is a relatively small body of research describing work in this preparation phase. A recent systematic review consisting of 58 articles, found that there was wide variability in reporting of this formative work, with specification of the optimisation objective and MOST terminology particularly lacking (216). Sufficient reporting of this preparatory work is important for transparency in intervention development.

1.4.4.1.2 Optimisation phase

The optimisation phase of MOST involves conducting an optimisation randomised controlled trial (O-RCT) to establish which candidate component levels will make up the optimised intervention, based on the optimisation objective (214). Empirical information obtained in an O-RCT is used to make decisions on the optimised intervention package (212).

The MOST framework does not dictate which experimental design should be used in the optimisation phase. The resource management principle, a core aspect of the MOST framework, states that a design should be selected based on efficiency in the use of resources

to answer the specific scientific question (206, 208, 218). Factorial and fractional factorial designs are commonly used in the MOST framework when optimising a fixed intervention. A fixed intervention is one in which all participants randomised to receive an intervention component receive an identical version of that component at the same time-point in their participation in the trial (219).

A 2^k factorial design is a sufficiently powered, highly efficient experimental design that can estimate the main effects and interaction effects of intervention components (220, 221). With four intervention components, a 2x2x2x2, or 2^4 factorial design would be used (Table 1.2), with five components a 2^5 design would be used, and so on. When a candidate component is included in an optimisation experiment, it is referred to as a factor. Factors are independent variables that are manipulated (220, 221). In the 2^4 design, each factor would have two levels, which determines the presence or absence of a component (e.g., on vs. off) (221). The 2^4 design would result in 16 experimental conditions corresponding to all possible combinations of the four factors and their levels (Table 1.2) (220, 221). In analyses, main effects and interaction effects are estimated for each intervention component. In the case of the 2^4 example, an estimate would be calculated for four main effects, six two-way interactions, four three-way interactions and one four-way interaction.

Table 1.2. Experimental conditions for a 2^4 factorial design

Experimental condition	Factor A	Factor B	Factor C	Factor D
1	On	On	On	On
2	On	On	On	Off
3	On	On	Off	On
4	On	On	Off	Off
5	On	Off	On	On
6	On	Off	On	Off
7	On	Off	Off	On
8	On	Off	Off	Off
9	Off	On	On	On
10	Off	On	On	Off
11	Off	On	Off	On
12	Off	On	Off	Off
13	Off	Off	On	On
14	Off	Off	On	Off
15	Off	Off	Off	On
16	Off	Off	Off	Off

One of the major benefits to the factorial design is its efficiency, which can be best explained with comparison to using a parallel group RCT (Table 1.3). Using the aforementioned example including four intervention components, a variety of experimental designs could be used to evaluate these components. Four individual parallel group RCTs could be used, in which each of the intervention components would be compared against a control. Alternatively, a five-arm RCT could be used in which each intervention component would form an arm of the trial, with a fifth arm as a control. As displayed in Table 1.3, these designs would require 792 and 495 participants respectively, and the interactions between the intervention components could not be estimated.

Table 1.3. Sample sizes needed to evaluate four intervention components using different experimental designs

Design	Required sample size	Experimental conditions	Interaction estimation
4 individual RCTs	792	8	Cannot be estimated
5-arm RCT	495	5	Cannot be estimated
Complete factorial	208	16	All estimated
Fractional factorial	200	8	Some estimated

Assumptions: Cohens d = 0.4, power > 0.8, alpha = 0.05.
Calculated using 'MOST' R package (222).
Key: RCT = Randomised controlled trial.

Using a complete factorial experiment, a much smaller sample size (n = 208) can be used under the same assumptions of effect size and alpha, while retaining 80% power. The smaller sample size is possible because direct comparisons are not made between experimental conditions. The main effect of a factor is calculated by comparing the means of conditions where the factors is set to its higher level with conditions in which the factors is set to its lower level. For example, to calculate the main effect of factor A in Table 1.2, the mean of conditions one to four would be compared with the mean of conditions five to eight. Rather than there being one control condition, as is the case in a parallel group RCT, each factor has its own control group (i.e., the mean of the conditions whereby that factor is set to its lower level) (221). Thus, the factorial design achieves its efficiency as all participants are involved in every estimate (220). As a result, sufficient power can be achieved, even with a small number of participants in each condition; it is the overall number of participants that must be sufficiently large.

A fractional factorial design can reduce the number of experimental conditions required, relative to a full factorial design. This can be beneficial, as in some instances resources may not allow for 16 (2^4 factorial design), 32 (2^5 factorial design) or even 64 (2^6 factorial design) experimental conditions (223). A fractional factorial design combines (or aliases, as referred to by statisticians) scientifically important effects with effects that are not scientifically important and expected to be negligible. Following the principle of effect hierarchy, typically interaction effects specified in the conceptual model, and lower order effects (e.g., main effects, two-way interactions) are considered more important than higher-order (e.g., three- and four-way interactions) and therefore would not be combined together (223). Combining effects means that not all interaction effects can be estimated, and any combined effects must be interpreted together (223). An example fractional factorial design, called a 2^{4-1} design is displayed in Table 1.4. In a pilot trial, it is acknowledged that effect estimates will be underpowered, and therefore a fractional factorial design may be beneficial to reduce the number of experimental conditions, as combining effects is less problematic.

Table 1.4. Example 2^{4-1} fractional factorial design

Condition	Factor A	Factor B	Factor C	Factor D
1	Yes	Yes	Yes	Yes
2	Yes	Yes	No	No
3	Yes	No	Yes	No
4	Yes	No	No	Yes
5	No	Yes	Yes	No
6	No	Yes	No	Yes
7	No	No	Yes	Yes
8	No	No	No	No

Following an O-RCT, empirical information obtained from the trial is used to make decisions on the optimal combination of conditions (212, 224). The component screening approach (CSA), which is current best practice, involves a stepped approach to screen in and screen out intervention components dependent on their main and interaction effects (212). Following the principle of effect hierarchy, the first step is to screen in any components with a significant main effect. Next, any significant interaction effects are examined in turn to determine whether to screen in the components associated with the effects. Once a screened-in and screened-out list is established, the components are set to their corresponding levels; anything on the screened-in list is set to ‘on’ or its higher level, while anything on the

screened-out list is set to 'off' or its lower level (212). The optimisation objective, specified *a priori*, is applied to determine the combination of intervention components providing the best expected outcome, in the constraints of the optimisation objective. The resulting combination of intervention components set to their higher levels makes up the optimised intervention (212).

Once this optimisation phase is complete, investigators will either progress to the evaluation phase, or revisit the preparation phase with the view to conducting further optimisation (212). If the optimised intervention looks to be effective, investigators would most likely proceed to the evaluation phase to confirm its effectiveness. However, if the results of the optimisation trial suggest that no, or very few components are having an effect on the outcome, more benefit may be obtained by returning to the preparation phase to adapt the conceptual model and potentially develop new candidate components, in line with the resource management principle (212) (Figure 1.1).

1.4.4.1.3 Evaluation phase

In the evaluation phase, the optimised intervention package is evaluated by comparing it to a suitable control, typically using a parallel group RCT (214). One of the key principles of MOST is the continual optimisation principle, which refers to the idea that investigators should be continuously moving towards a better intervention (211). Interventions can be continually optimised based on new knowledge and insights gained. If after conducting a definitive RCT of the optimised intervention package, the results indicate that the intervention package is not effective, then investigators should return to the preparation phase (Figure 1.1). Returning to the preparation phase at this point is not returning to square one; a vast amount of knowledge is gained during an optimisation trial that would not have been gained if only a parallel group RCT had been conducted (212).

As discussed in section 1.3, adherence to AET is complex, with multiple barriers to adherence. Existing interventions have been evaluated using parallel group RCTs, and as such there is a lack of information about what specific intervention components might be effective in supporting adherence to AET. Using the MOST framework to address the problem of adherence to AET has the potential to lead to the development of an intervention balancing

effectiveness with affordability, scalability and efficiency, and to provide an increased understanding of the mechanisms underlying specific intervention components.

1.4.5 Combining MRC and MOST frameworks

The MOST framework fits in, and expands on existing MRC guidance; it is not the case of choosing one or the other. Both frameworks share overlapping principles; each provides a multi-phase approach to guide intervention development, both acknowledge the importance of formative research, both consider implementation from an early-stage, and both highlight the importance of mechanisms of action underlying complex interventions (197). The MOST framework complements the MRC framework, providing a systematic, logical and empirically based approach to intervention optimisation, to answer research questions beyond the effectiveness of an intervention package. Figure 1.3 demonstrates how each phase of the MOST framework fits in MRC guidance.

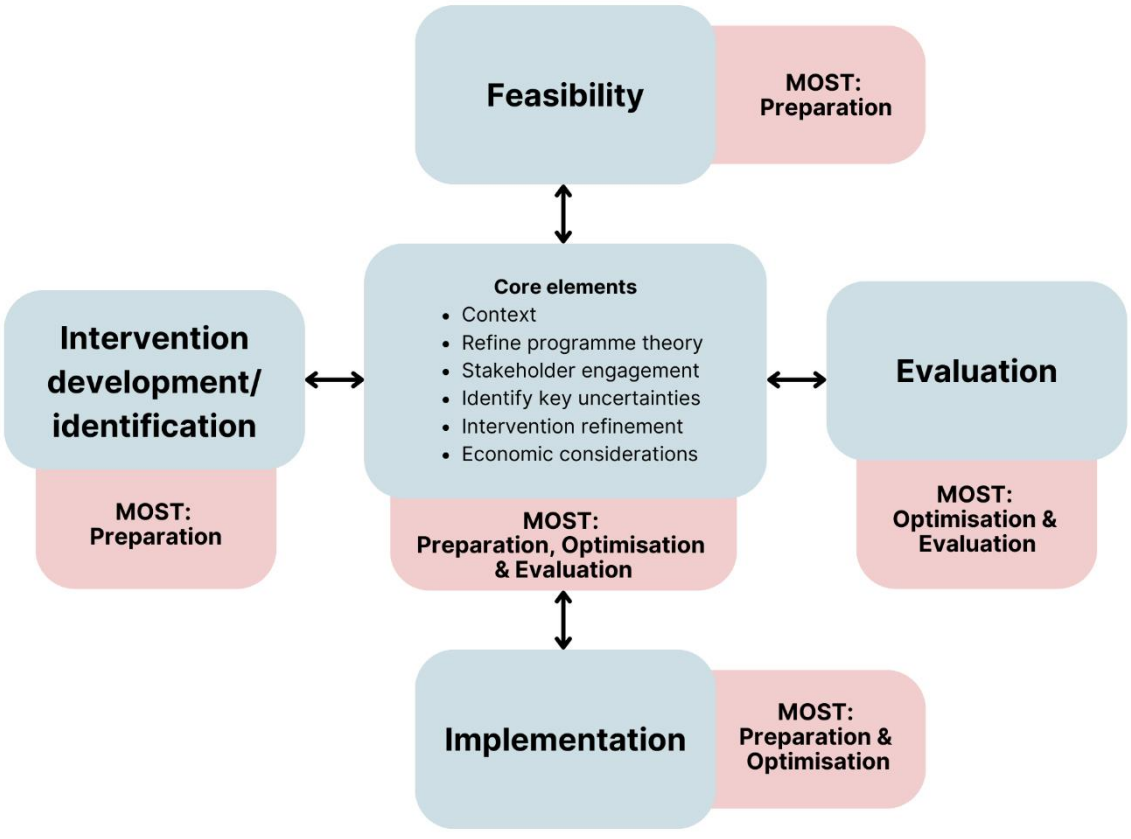

Figure 1.3. MRC and MOST frameworks
Note: Blue boxes relate to MRC framework. Red boxes relate to MOST framework.

1.4.5.1 Preparation phase and MRC guidance

The preparation phase of MOST spans the intervention development, feasibility and implementation phases of MRC guidance. As previously described, the preparation phase of MOST recommends conducting a pilot optimisation trial, which falls in the feasibility phase of MRC guidance. The specification of the optimisation objective in the preparation phase of MOST involves considering implementation restraints such as cost and time, hence fulfilling the MRC guidance recommendation for implementation considerations to begin early in the development process (198).

1.4.5.2 Optimisation phase and MRC guidance

The optimisation phase of MOST spans the evaluation and implementation phases of MRC guidance. MRC guidance acknowledges that research questions solely focusing on effectiveness are not always the most important (198). The MOST framework seeks to address wider questions in the evaluation of complex interventions, such as what is the most cost-effective combination of intervention components, and therefore moves beyond just examining effectiveness.

In terms of implementation, MRC guidance advocates for "deliberate effort to increase impact and uptake of successfully delivered health interventions" (198). The key objective of the MOST framework is to balance intervention effectiveness with efficiency, scalability and affordability, to develop interventions that are readily implementable within constraints relevant to the context (208).

1.4.5.3 Evaluation phase and MRC guidance

In the MOST framework, evaluation would typically involve evaluating an optimised intervention package for effectiveness using a parallel group RCT. While this research question aligns with MRC guidance, the addition of the prior optimisation phase in the MOST framework means that the intervention package being evaluated will have been optimised for effectiveness (only components having a positive effect on the outcome will be included) and efficiency (redundant components removed), meaning it may be more likely to be effective in a definitive RCT.

1.4.5.4 Core elements of MRC guidance

The MOST framework additionally aligns with many of the core elements outlined in the MRC framework. Specifically, O-RCTs are able to aid refinement of programme theory (by testing hypothesised causal pathways (225)), refinement of an intervention (by removing redundant or ineffective components) and can specifically consider economic considerations via the optimisation objective. Moreover, stakeholder engagement can, and should, be incorporated through every phase of MOST.

1.4.6 Intervention design frameworks

So far, this section has focused on broad frameworks of behavioural intervention development that cover the process of "iterating and tailoring based on empirical evidence" (197). A limitation of the MOST and MRC frameworks are that they do not provide detail regarding how exactly to develop intervention components for a complex intervention (226). Intervention design frameworks are an additional resource that can be used to determine the specific content, format and delivery of intervention components, and could be incorporated into the preparation phase of MOST (197). For the purpose of this thesis, I considered further frameworks to guide the specific development of intervention components. Different frameworks focus on key intervention development activities (e.g., incorporation of theory, evidence and patient input) to varying extents (226). I focused on frameworks in particular that incorporated the views of the target population to ensure key barriers to AET adherence were targeted, and frameworks that acknowledge the importance of embedding theory into intervention development, which has been a limitation of previous interventions developed to support AET adherence (159, 226).

1.4.6.1 Behaviour change wheel

The behaviour change wheel (BCW) synthesises 19 behaviour change frameworks (227, 228). It is rooted in the capability, opportunity, and motivation model of behaviour change (COM-B), which suggests that behaviour is influenced by one's capability, opportunity and motivation to perform the behaviour. Broadly, using the BCW to develop an intervention is a three step process; (1) identifying and defining the behaviour and identifying what needs to change; (2) identifying the intervention functions and policies that will drive the change; (3) identifying behaviour change techniques (smallest parts of an intervention that have the

potential to change behaviour (229)) and appropriate modes of delivery for the intervention (227). The BCW has a strong focus on theory and evidence to inform intervention development, but lacks guidance regarding stakeholder input (226).

1.4.6.2 Person-based approach

The person-based approach aims to guide the development of interventions grounded in the psychosocial needs of potential users (230). There are two key processes; (1) in-depth qualitative research with a range of stakeholders at every phase of research; and (2) identifying guiding principles, which involves stating key intervention design objectives and the ways in which the intervention will achieve each objective (230). Once an intervention is developed, iterative cycles of qualitative interviews and intervention adaptations are conducted to improve the intervention. The person-based approach focuses on incorporating user input, but can be used in combination with other frameworks that focus on incorporating evidence and theory into intervention design (230).

1.4.6.3 Intervention mapping

Intervention mapping (IM) is a six-stage process spanning from a needs assessment through to evaluation of an intervention (231, 232). The six stages involve (1) needs assessment of the problem; (2) identifying intervention targets; (3) selecting theory-based intervention methods; (4) develop intervention materials; (5) plan for implementation of intervention; (6) develop evaluation plan (231, 232). Stages can be moved between iteratively, and stakeholder engagement is encouraged throughout. IM has previously been used to develop interventions to support adherence to AET (176, 186).

1.4.7 Combining IM with the MOST framework

For the purpose of this thesis, I combined the IM framework with MOST, as it provided a systematic and logical structure to the development of the intervention components in the preparation phase of MOST, with sufficient flexibility to combine the two approaches. While all aforementioned frameworks could have been adapted to fit within the preparation phase of MOST, IM was the most comprehensive framework, including stages from conception through to planning the full evaluation, with emphasis on incorporating stakeholder views, theory and evidence in the development process, which was a strength compared to other

frameworks considered (226). IM acknowledges the importance of implementation from the beginning of intervention development, and includes a specific stage devoted to implementation considerations (stage 5). This stage aligns well with the process of developing an optimisation objective as part of the MOST framework.

1.4.8 Section summary: complex intervention development

This section has defined complex interventions and outlined the approach to intervention evaluation typically used when evaluating interventions to support adherence to AET. A broad overview and justification of the MOST framework that will be used in this thesis has been provided.

1.5 Aims and objectives

In this thesis I aimed to develop a complex behavioural intervention to support adherence to AET in women with breast cancer. I had four objectives:

1) Develop a conceptual model for a complex behavioural intervention guided by intervention mapping and the multiphase optimisation strategy;
2) Conduct a series of studies to co-design a short message service (SMS) intervention encouraging habitual behaviours around medication-taking;
3) Develop and optimise an information leaflet supporting medication beliefs in women taking AET;
4) Undertake a process evaluation to evaluate the acceptability of the intervention components developed in this thesis.

1.6 Thesis overview

An overview of the thesis structure is summarised in Figure 1.4. **Chapter one** has presented an introduction to this thesis; discussing breast cancer and its treatment, non-adherence to AET and approaches to developing, optimising and evaluating complex interventions. **Chapter two** (Study One) presents work undertaken in the preparation phase of MOST. Specifically, chapter two outlines the development of a conceptual model for an intervention aiming to support adherence to AET in women with breast cancer. This chapter demonstrates how IM can be used in the preparation phase of MOST. Broadly, this chapter includes reviews to understand the barriers to AET adherence, existing and ongoing interventions to support

adherence, identification of four intervention targets and consideration of multiple theories to guide intervention development. Four intervention components were proposed in the conceptual model; two intervention components were newly developed (detailed in chapters three and four) and two were adapted from existing interventions. **Chapter three** (Study Two) presents the development process of an SMS intervention to target forgetfulness, which was a barrier to adherence identified in Chapter two (Study One). A series of quantitative and qualitative studies were used to develop a bank of brief text messages to support habit formation around medication-taking. **Chapter four** (Study Three) aimed to optimise an information leaflet to support medication beliefs in women with breast cancer. In chapter two, medication beliefs were identified as a key determinant of non-adherence to AET, and an information leaflet was developed to address medication beliefs. As an information leaflet is made up of multiple components in itself, the study in chapter four aimed to optimise this information leaflet. A randomised factorial experiment, involving 1,604 women, was used to optimise an information leaflet to support medication beliefs in women with breast cancer.

The four intervention components developed in chapters two, three and four were included in a pilot optimisation trial as part of a wider programme of work, which is not included in this thesis. Only the process evaluation of this pilot trial forms part of this thesis (Figure 1.4). **Chapter five** (Study Four) details the mixed-methods process evaluation of this pilot optimisation trial. In the process evaluation, I aimed to assess the acceptability of the four intervention components. **Chapter six** discusses the findings of all chapters and the overall conclusions.

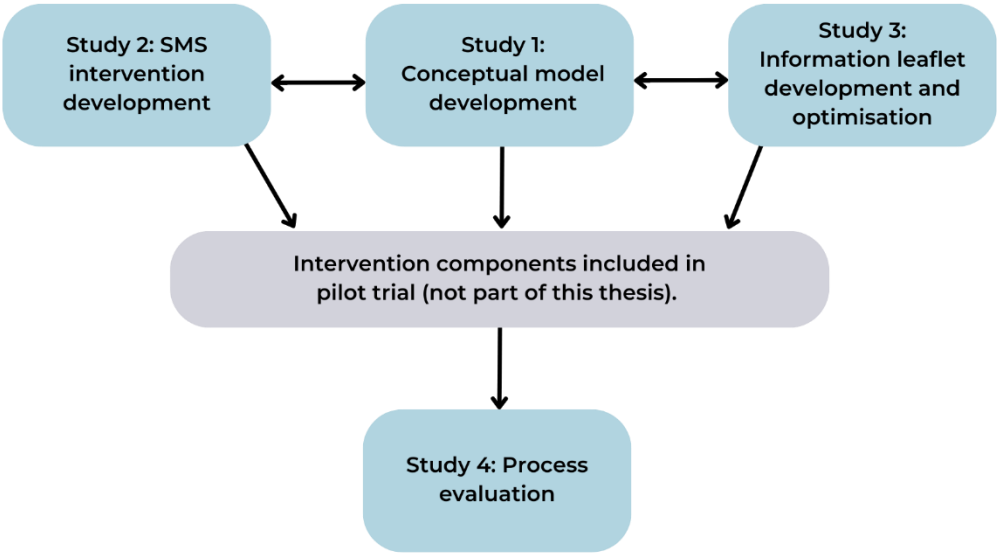

Figure 1.4. Thesis structure

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Chapter 2 : Supporting adjuvant endocrine therapy adherence in women with breast cancer: the development of a complex behavioural intervention using Intervention Mapping guided by the Multiphase Optimisation Strategy

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2.2 Abstract

Background: Adjuvant endocrine therapy (AET) reduces the risk of breast cancer recurrence and mortality. However, up to three-quarters of women with breast cancer do not take AET as prescribed. Existing interventions to support adherence to AET have largely been unsuccessful, and have not focused on the most salient barriers to adherence. This paper describes the process of developing four theory-based intervention components to support adherence to AET. Our aim is to provide an exemplar of intervention development using Intervention Mapping (IM) with guidance from the Multiphase Optimisation Strategy (MOST).

Methods: Iterative development followed the six-stage IM framework with stakeholder involvement. Stage 1 involved a literature review of barriers to adherence and existing interventions, which informed the intervention objectives outlined in Stage 2. Stage 3 identified relevant theoretical considerations and practical strategies for supporting adherence. Stage 4 used information from Stages 1-3 to develop the intervention components. Stages 1-4 informed a conceptual model for the intervention package. Stages 5 and 6 detailed implementation considerations and evaluation plans for the intervention package, respectively.

Results: The final intervention package comprised four individual intervention components: Short Message Service to encourage habitual behaviours surrounding medication-taking; an information leaflet to target unhelpful beliefs about AET; remotely delivered Acceptance and Commitment Therapy-based guided self-help to reduce psychological distress; and a website to support self-management of AET side-effects. Considerations for implementation within the NHS, including cost, timing and mode of delivery were outlined, with explanation as to how using MOST can aid this. We detail our plans for the final stage of IM which involve feasibility testing. This involved planning an external exploratory pilot trial using a 2^{4-1} fractional factorial design, and a process evaluation to assess acceptability and fidelity of intervention components.

Conclusions: We have described a systematic and logical approach for developing a theoretically informed intervention package to support medication adherence in women with breast cancer using AET. Further research to optimise the intervention package, guided by MOST, has the potential to lead to more effective, efficient and scalable interventions.

2.3 Background

Breast cancer is the most common cause of cancer death in women (1). Around 75% of breast cancers are oestrogen receptor-positive (ER+) (2). Adjuvant endocrine therapy (AET), including tamoxifen and aromatase inhibitors (AIs; anastrozole, letrozole, exemestane) are prescribed to women with ER+ breast cancer to reduce the risk of cancer recurrence and mortality (3, 4). AET is prescribed for 5-10 years (5), with 7-8 years potentially the optimal duration (6-9). However, up to three-quarters of patients do not take AET as prescribed (10-13). Non-adherence and non-persistence (not continuing to take the medication for the prescribed duration) are linked to an increased risk of recurrence, lower survival and reduced quality-adjusted life years (14-16). Improving adherence to AET could reduce healthcare costs associated with cancer recurrence (15).

Modifiable barriers to AET adherence have been identified (17-20). Most existing interventions do not target multiple factors associated with adherence, and predominantly consist of solely educational interventions, such as leaflets (21-23). Such interventions have either been ineffective or yield small effect sizes (21-23). This is characteristic of interventions aiming to support adherence across a wide range of chronic conditions, highlighting the need for improved interventions to support adherence more generally (24). Considerations of theory in interventions aiming to support AET adherence are often lacking, with little transparency of the intervention development process. The UK Medical Research Council Framework (MRC) for developing and evaluating complex interventions, and INDEX guidance (Identifying and assessing different approaches to developing complex interventions) suggest interventions should be developed based on theory in a systematic manner to aid replication and implementation (25-27). Developing interventions grounded in theory can improve our understanding of why an intervention is successful or unsuccessful. Intervention mapping (IM) is a systematic approach that can be used to develop theory and evidence-based health interventions that can fulfil MRC and INDEX guidance (28). It consists of six stages that cover designing, implementing and evaluating an intervention, and it promotes relevant stakeholder engagement throughout development (28). IM has previously been used to develop interventions targeting adherence (29-31) and women with breast cancer (32, 33).

The AET adherence trials published to date are mostly evaluated using parallel groups randomised controlled trials (RCTs). RCTs can definitively evaluate whether an intervention package as a whole has a statistically significant effect compared with a comparator. However, RCTs alone are unable to explain which components of a complex intervention affect the outcome, whether there are interactions between intervention components, and whether the benefits of an intervention component are justified based on resource demands. The Multiphase Optimisation Strategy (MOST) addresses these limitations (34) by optimising interventions based on the performance of individual intervention components relative to resource constraints. MOST consists of three phases: (1) preparation, in which intervention components are developed; (2) optimisation, in which efficient experimental designs, which estimate main effects and interactions between intervention components, are used to build an optimal intervention package; and (3) evaluation, in which the optimised intervention package is evaluated, typically using a parallel groups RCT.

There are important factors to consider when developing interventions within the MOST framework. These include ensuring each intervention component targets a specific mediating variable, that there is minimal overlap between the content of the intervention components, and that thought is given to the challenges of delivering all intervention components within a single package (35). Combining the IM and MOST frameworks enables these considerations of MOST to be acknowledged systematically throughout every stage of development within IM. This paper describes the development of an intervention package to support AET adherence in women with early-stage breast cancer, aiming to provide an exemplar of how to incorporate IM into the MOST framework.

2.4 Methods

We progressed through six stages of IM in line with published guidance (Table 2.1) (28). We followed the guidance for reporting intervention development studies in health research (GUIDED) (36).

Table 2.1. Adapted intervention mapping framework

Stage	What was done?
Stage 1- Needs assessment	• Literature review of the problem of non-adherence, barriers to adherence, and existing interventions to support adherence to AET • Population of interest described • Overall goal for the intervention established and stated
Stage 2- Intervention objectives	• Selection of behavioural determinants to be targeted, based on needs assessment and context of intervention • Intervention component objectives stated • Conceptual model created, detailing causal change pathways and hypothesised interactions between components
Stage 3- Intervention design	• Theories relevant to each determinant identified were considered • Existing interventions explored, informed by the needs assessment and practical applications considered
Stage 4- Intervention development	• Intervention components finalised based on Stage 3 • Intervention development work completed; intervention materials created and drafted • Stakeholder input from clinicians, patients and research team used to refine intervention materials
Stage 5- Implementation planning	• Implementation in the development phase discussed, and MOST optimisation objective outlined
Stage 6- Evaluation plan	• Hypothesised interactions between intervention components outlined and explained • Evaluation plan considered

Key: MOST = Multiphase Optimisation Strategy. AET = Adjuvant endocrine therapy.

2.4.1 Stage 1: Needs assessment

The needs assessment involved three sub-stages: (1) a literature review to understand the extent of non-adherence in women prescribed AET; (2) a literature review to understand the barriers to AET adherence, predominantly focusing on existing reviews identified through backward citation searching (11, 18, 20, 37-45); and (3) a rapid review and search of trial registries to identify published interventions and ongoing trials addressing AET adherence. The terms "hormone therapy" "breast cancer", "adherence", "intervention" and their variations were used. One author (SG) screened the texts and extracted data. The needs assessment informed the primary aims of the intervention package.

2.4.2 Stage 2: Intervention objectives

Modifiable determinants of AET adherence to be targeted in the intervention package were selected based on the results of Stage 1. For each determinant chosen, specific objectives for an intervention component to target were defined. Stage 2 considered how IM could be incorporated into MOST. An important aspect of the preparation phase of MOST is the conceptual model (35), similar to the logic model produced in IM. A conceptual model details how each intervention component is expected to change the outcome. It is recommended that each intervention component targets one specific mediating variable to aid decision-making within the optimisation phase (46). The intervention components should be reasonably independent to ensure one component does not depend on the presence of another. This means that the delivery of a component, and what the participant receives, should not be affected by the levels of the other components they may receive (35). Conceptual model development was iterative; draft illustrations of the model were created, discussed within the research team, and with Patient and Public Involvement (PPI) members.

2.4.3 Stage 3: Intervention design

For each determinant of AET adherence that we identified and selected in Stages 1 and 2, existing interventions and associated literature were explored to identify suitable theories, evidence-based behaviour change methods and practical strategies that could address them. We identified psychological theories specific to the determinants, and considered how these theories could inform the development of the intervention components. The research team,

in collaboration with PPI members, used this evidence to discuss which strategies were most likely to be effective and implementable within the UK healthcare system.

2.4.4 Stage 4: Intervention development

Four intervention components were developed; two new components and two adapted from existing interventions. Clinician, researcher and patient views were considered throughout. To aid future replication, the intervention components were coded onto the behaviour change techniques taxonomy (BCTTv1) by one author (SG) who had completed BCTTv1 training (47). Component coding was discussed between members of the research team (SG, SS, CG, LH). Disagreements were discussed and resolved. To evaluate readability, a Flesch-Kincaid reading age and grade level was calculated for each component (48). We aimed for a reading grade level of 7 to 8 which are described as 'fairly easy' and 'standard' levels respectively (48).

2.4.5 Stage 5: Implementation planning

Implementation factors such as cost, time and delivery method were considered. An optimisation objective by which the intervention will be optimised was specified, as recommended by the MOST framework. The optimisation objective operationalises the primary outcome, and key considerations that the optimised intervention should fit within, such as effectiveness, cost and time (49).

2.4.6 Stage 6: Evaluation plan

The research team selected the evaluation design, and prepared a protocol for a pilot trial (ISRCTN: 10487576). We specified expected interactions between intervention components, based on theoretical assumptions identified in Stage 3. The *a priori* specification of hypothesised interactions is important, as components forming the interactions will be prioritised when deciding the optimised intervention package (50).

2.4.7 Patient and public involvement

Our PPI panel of five members met remotely with two researchers (SG, ER) every 2-3 months throughout the development phase. The panel comprised five women with a diagnosis of breast cancer and experience of taking AET, recruited by advertising through a charity supporting people affected by cancer. Members were compensated for their time.

2.5 Results

2.5.1 Stage 1: Needs assessment (findings from literature reviews)

2.5.1.1 Extent of non-adherence

Adherence to AET is suboptimal, with up to 73% not taking it as prescribed (11, 41). A large number of women discontinue AET within the first year (51). Adherence diminishes over time, with up to 50% of women being non-adherent within 5 years (10, 13). Unintentional non-adherence (e.g., forgetting to take medication) may be more prevalent than intentional non-adherence (e.g., deciding to miss a tablet) (52-54).

2.5.1.2 Factors associated with adherence and non-adherence

Barriers to and facilitators of AET adherence were identified (Table 2.2).

2.5.1.2.1 Side-effects

Literature has suggested that the frequency, severity and inability to manage side-effects are common barriers to AET adherence and persistence (11, 18, 20, 39, 42-45, 62). However, some reviews have questioned this relationship, citing inconsistent evidence (37, 42). Qualitative studies highlight reasons for non-adherence including the impact of side-effects on quality of life (17), side-effects outweighing the benefits (17, 58), a lack of understandable information about the range and intensity of side-effects (58, 61), and women feeling unsupported in managing side-effects (17, 55, 58). There is a clear demand for information about side-effects and their management (63).

2.5.1.2.2 Medication beliefs and illness perceptions

Necessity beliefs and concerns about AET, and the cost-benefit balance between these are associated with reduced adherence (11, 18-20, 37, 39-41, 43, 45). For example, adherent women tend to report strong necessity beliefs, such as “Tamoxifen is keeping me alive”, AET helps them to feel in control, and that AET will enable them to stay alive for their family (17, 61). In contrast, less adherent women report more concerns, such as AET benefits not being worth the reduced quality of life, and worry about the chance of cancer elsewhere (17). Representations of breast cancer, such as believing the likelihood of recurrence is low, are also associated with lower adherence (56, 57).

Table 2.2. Summary of barriers to AET adherence

Factor associated with adherence	Explanation	Evidence
Experience of side-effects[a]	Barrier: Increased frequency and intensity of side-effects	(11, 18, 20, 39, 42-45, 55-58)
Medication beliefs[a]	Facilitator: more beliefs about the necessity of AET	(11, 18-20, 37, 39-41, 43, 45).
	Barrier: more concerns about AET	
Illness perceptions[a]	Facilitators: beliefs that certain lifestyle behaviours can cause a recurrence	(56, 57, 59)
	Barriers: low risk perception of recurrence, high tamoxifen consequences, belief that psychological factors cause a recurrence	
Knowledge/ information available[a]	Barriers: Lack of knowledge of side-effects and the mechanisms of AET	(39).
Psychological distress[a]	Barriers: Increased distress (including depression and anxiety)	(20, 60).
Forgetfulness[a]	Barriers: forgetting to take medication, memory difficulties	(18, 41, 61)
Social support	Facilitators: Increased social support	(11, 37, 39, 40, 42, 43, 57).
Self-efficacy	Facilitators: Increased self-efficacy	(37, 39, 43, 45)
Patient-physician communication	Facilitators: Better patient-physician relationship	(20, 37, 40, 42, 43)

Key: AET = Adjuvant endocrine therapy.
[a]Indicates factor included within the conceptual model for the intervention in Stage 2.

2.5.1.2.3 Knowledge of medication

Lower knowledge about AET is associated with reduced adherence (39). Women consistently report receiving insufficient information about AET (17, 55). Approximately one fifth of breast cancer survivors in a Dutch survey did not know how AET worked, but wanted further information, and a third did not know how large the risk reduction effect was (53).

2.5.1.2.4 Psychological distress

Immediately following active treatment, approximately half of women with breast cancer report higher levels of psychological distress than observed in the general population (20, 64, 65). Psychological distress in breast cancer can include rumination and worry about breast cancer recurrence, difficulties in returning to 'normal', and distress from AET side-effects (17, 58, 63). Higher levels of distress are associated with lower adherence (20, 60), although some inconsistencies with this relationship have been observed (42, 66).

2.5.1.2.5 Forgetfulness

Women with breast cancer commonly report memory problems following chemotherapy, which can increase forgetfulness and consequently unintentional non-adherence (18, 37, 41, 61, 67-69).

2.5.1.2.6 Additional barriers to AET adherence

Social support, patient-physician communication and self-efficacy have also been identified as barriers to AET adherence (11, 20, 37, 39, 40, 42, 43, 57, 70). Women often feel abandoned when ending active treatment and being discharged from care (71). Higher social support from family, friends and other breast cancer survivors are associated with improved adherence and persistence (11, 37, 39, 40, 42, 43, 57, 70). Self-efficacy in the patient-physician interaction (confidence in the ability to get medical information from a physician (39, 43, 72)), and perceived self-efficacy in relation to learning about and taking AET (37, 39, 43) are associated with higher adherence (37, 39, 43). Patient-reported positive relationships with physicians are associated with higher adherence (20, 37, 40, 42, 43), specifically, the quality and person-centeredness of the relationship, frequency of communication, and sufficiency of information received about AET (43).

2.5.1.3 Existing interventions supporting adherence

We identified 16 published trials evaluating interventions targeting adherence to AET (Table 2.3) and 15 ongoing trials (Appendix A.1). Within the 16 published trials, there was little high-quality evidence that these interventions were effective. Of the 16 published interventions, six reported statistically significant improvement in adherence. Two of those with significant findings were pilot trials and therefore were not designed to examine efficacy, two found significant findings in post-hoc analyses, and for one, a significant effect was not maintained

at follow-up. Six published trials evaluated interventions composed only of educational materials which were not effective in supporting adherence (73-78). The theoretical basis and development process were inadequately described for most published interventions.

Table 2.3. Existing interventions supporting adherence to AET in women with breast cancer

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
Ell et al., (2009) (73)	Written information plus structured 'patient navigation' phone interviews consisting of education, addressing barriers to adherence, problem solving, self-management support and emotional support.	Written information and telephone	All	2-arm RCT- enhanced usual care (information) vs written information plus patient navigation	No significant difference; 67% vs 69% (p = 0.80).	Health Belief model and socio-cultural explanatory theory
Yu et al., (2012) (74)	PACT materials used. Patient education (welcome pack and quarterly newsletters) with information about breast cancer and adherence. Follow-up reminder calls.	Written information and telephone	Anastrozole or letrozole	Prospective, multicentre controlled observational study	No significant difference; 95.9% vs 95.8% one-year persistence rate (p = 0.95).	None reported
Ziller et al., (2013) (75)	COMPAS study. Letter group: 8 personalised motivational reminder letters were sent over two years with information on topics side-effects and treatment. A breast cancer information leaflet containing information on topics such as nutrition and sport.	Written information/ telephone	AI	3-arm RCT- usual care vs letters vs telephone calls	No significant difference in adherence in primary analysis. In post-hoc analysis when pooling the intervention arms, adherence increased significantly in the	Learning theory

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
	Reminder phone calls: 8 telephone calls over two years which used motivational interviewing to address any questions, challenges to adherence, provide information and reminders.				intervention arms vs control (p = 0.039).	
Hadji et al., (2013) (76)	PACT Program: educational materials sent to participants (9 mailed letters and brochures), monthly reminders on persistence to endocrine therapy, gift items sent e.g., 7 day tablet box, pocket mirror. Educational materials included information on relevant issues such as side-effects, efficacy, nutrition, communication.	Written information	Anastrozole	RCT- usual care vs written information	No significant difference in compliance at 12 months (p = 0.81).	None mentioned
Neven et al., (2014) (77)	CARIATIDE program. PACT materials used- welcome pack and 9 letters and brochures mailed out, containing information on side-effects, exercise, diet, communication.	Written information	AI	Randomised, parallel group observational study; usual care vs intervention	No significant difference in compliance between arms at 12 months (p = 0.4524). In Finland/Sweden, compliance was	None mentioned

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
					significantly higher in the intervention arm (p = 0.0246).	
Graetz et al., (2018) (79)	App: Web based app in which participants asked to record symptoms and report adherence in the past 7 days. Alerts sent to care team for any concerns. App+ reminder: Web based app in which participants asked to record symptoms and report adherence in the past 7 days. Alerts sent to care team for any concerns. Weekly reminders sent to use the app via text or email.	App and text or email	AI	Pilot RCT- app use only vs app use plus reminders to use app	Proportion of patients adherent in the experimental group (100%) was greater than control group (72.7%); p < 0.05.	None mentioned
Heisig et al., (2015) (80)	Enhanced information leaflet and 15-minute phone calls sessions including information on the mechanisms of AET, benefits and side-effects.	Written information and telephone	Any	Interventional single cohort study	Greater adherence observed at 3-month follow-up.	None mentioned

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
Markopoulas et al., (2015) (78)	PACT materials. Educational materials sent to participants 9 times in one year, consisting of information on side-effects, communication, sport, nutrition, benefits, tips on how to take AET.	Written information	Anastrozole or letrozole	RCT- standard care vs intervention	No significant difference in compliance or persistence between the groups at 12 months.	None mentioned
Castaldi et al., (2017) (81)	Patient navigation program. Initial visit include assessment of barriers to adherence. Navigator provides reminder calls prior to follow-up appointments, meets patients at outpatient appointments and on day of surgery, and a financial consultation where required.	Patient navigation	Tamoxifen and AI	Non randomised, historical care vs navigated care	68.6% adherence in standard care vs 100% in patient navigation ($p <$ 0.0001).	None mentioned
Hershman et al., (2020) (82)	SMS messages sent twice weekly over 36 months. Content included overcoming barriers to medication adherence, cues to action, statements related to medication efficacy and reinforcements of the recommendation to take the medication. 40 messages repeated over intervention.	Text messaging	AI	RCT; text messages vs no text messages	No significant difference between text messages (55.5%) and no text messages (55.4%) at 36 months.	None mentioned

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
Moon et al., (2019) (33, 83)	Self-directed paper booklet designed in line with CBT and behaviour change theory. Included sections to modify beliefs about recurrence and the medication, to help manage side-effects and to increase perceived behavioural control.	Written information	Tamoxifen	Pilot trial; no control group	Primary outcomes were feasibility and retention. Change from 100% to 91% who were non adherent after intervention. D = 0.31 for improvement of unintentionally non adherent women.	Common sense model and theory of planned behaviour
Bhandari et al., (2019) (84)	Prescriptions given in a 30-day bubble pack with labelled day of the week; dispensed as 1- or 3-month supply.	Medication packaging	Tamoxifen and AI's	Single-arm prospective investigational pilot study	Suggestion of improved adherence with bubble packaging (no control arm)	None mentioned
Tan et al., (2020) (85)	Weekly SMS reminders sent on a Monday morning reading "Mdm <NAME> please be reminded to take your anti-cancer medicine as instructed by your doctor. Take one tablet once every day."	Text messaging	All	Open level, multi centre prospective RCT	Higher percentage of adherence in SMS (72.4%) vs standard care (59.5%) at 6 months (p = 0.034), but not at one year (p = 0.617). No	None mentioned

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
					difference in serum hormone levels.	
Krok-Schoen et al., (2019) (86)	Daily text message reminders focusing on initiation, continuation and adherence to prescribed dose; 14 messages repeated. Dynamic intervention in which participants complete weekly surveys on an app. Participants received feedback based on survey responses; either encouraging messages or problem solving. Physicians notified and patient has option to leave voice message and share with physician.	Text messaging and app	Tamoxifen or AI	Pilot trial; no control group	Significant improvement for self-reported medication adherence (p = 0.015), significant decreases in oestradiol, oestrogen and oestrone hormone levels ($p < 0.001$).	None mentioned
Labonte et al., (2020) (32)	Community based pharmacy intervention; motivational interviewing given by pharmacists in brief individual consultations. Discussions focused on mode of action of AET, side-effect coping and benefits of the medication.	In person (pharmacist)	All	Intervention mapping development	N/A- development paper	Theory of planned behaviour, motivational interviewing

Authors	Description of intervention	Intervention modality	AET type	Design	Key results (adherence related outcomes)	Theory that informed the intervention
Getachew et al., (2018) (87)	Breast care nurses were trained as navigators to improve patient adherence in rural Ethiopia	Breast nurse navigators	Tamoxifen	RCT	N/A- protocol abstract only	None mentioned

Key: RCT = Randomised controlled trial; PACT = Patients anastrozole compliance to therapy; COMPAS = Compliance in adjuvant treatment of primary breast cancer study; CARIATIDE = Compliance of aromatase inhibitors assessment in daily practice through educational approach. AET = Adjuvant endocrine therapy; SMS = Short messaging service; CBT = Cognitive behavioural therapy; AI = Aromatase inhibitor.

2.5.1.4 Intervention goals

The needs assessment established the overall goal of the programme; to develop a multicomponent intervention to improve AET adherence in women with early-stage breast cancer. This will be determined using primary outcome data within the optimisation phase. All barriers to AET adherence identified in Stage 1 were considered in Stage 2.

2.5.2 Stage 2: Intervention objectives

Based on findings from Stage 1, and following discussion within the research team and agreement from patient representatives, four main intervention targets were selected; living with side-effects, medication and illness beliefs, forgetfulness and psychological distress. These cover a range of intentional and unintentional barriers to adherence. Table 2.4 summarises identified determinants and the specific intervention component objectives. Illness perceptions and knowledge can affect medication beliefs through providing an understanding of how the medication works, which can enhance beliefs about its necessity (88, 89). We therefore targeted knowledge in combination with medication beliefs.

Three determinants were not chosen as mediating variables within the conceptual model: social support; self-efficacy; and patient-physician communication. These factors are likely to be addressed by the intervention components already chosen. For example, support from a psychological therapist as part of one of the proposed components has the potential to reduce feelings of abandonment, thus targeting one aspect of social support. In a similar vein, providing information about AET as part of another component is likely to address barriers associated with patient-physician communication in which women report not receiving sufficient information about AET (43).

Table 2.4. Summary of intervention components to target determinants

Determinant	Intervention component objective	Strategy	Intervention component	Description of intervention component	BCTs targeted	Theoretical basis
Management of side-effects	Increase ability to self-manage side-effects Reduce impact of side-effects	Inform patients of self-management strategies for common side-effects	Self-management website	A website for self-management of side-effects. Strategies to manage side-effects with a summary of the strength of evidence for that side-effect in a patient-friendly manner. Side-effects included are arthralgia, fatigue, vulvovaginal symptoms, gastrointestinal symptoms, hot flushes and sleep difficulties.	1.2, 3.1, 3.3, 4.1, 5.1, 5.3, 5.6, 6.2, 6.3, 9.1, 11.1, 12.2, 12.5, 12.6	-
Medication and illness beliefs	Increase beliefs about the necessity of using AET beliefs Reduce concerns about AET	Provide information on how AET works and the benefits of AET. Provide information on the prevalence of side-effects, answer common concerns about AET.	Information Leaflet	A written information leaflet with five different elements: (1) An explanation of how AET works, including medical diagrams (2) Information and infographics about the benefits of AET (3) Information about the prevalence of side-effects from AET	1.2, 4.1, 4.3, 5.1, 5.2, 5.6, 6.2, 6.3, 9.1, 9.2, 11.2, 13.2	Necessity-Concerns Framework, Common Sense Model of Illness Representations

Determinant	Intervention component objective	Strategy	Intervention component	Description of intervention component	BCTs targeted	Theoretical basis
	Support formation of accurate illness perceptions	Provide information on the mechanism of AET and the benefits of AET to enhance coherence, personal and treatment control		(4) Answers to common concerns about AET (5) Quotes from breast cancer survivors about their experiences taking AET, and a statement highlighting that the leaflet was co-designed		
Knowledge	Learn about AET, including how it works, the benefits and side-effects of it	Provide information about AET, it's mechanism of action, benefits and side-effect information	Information Leaflet	As above	As above	As above
Forgetfulness	Learn strategies to remember to take AET	Support the habit formation of daily medication-taking and associated activities such as ordering and collecting prescriptions	SMS messages	SMS messages providing practical strategies to support taking medication regularly each day. Messages are sent in the following frequency: • 2 weeks of daily messages • 8 weeks of twice weekly messages • 6 weeks of weekly messages	1.2, 1.4*, 2.3*, 7.1*, 7.3, 8.3*, 11.3, 12.1)*, 12.5)*	Habit Theory

Determinant	Intervention component objective	Strategy	Intervention component	Description of intervention component	BCTs targeted	Theoretical basis
Psychological distress	Reduce psychological distress	Increase psychological flexibility	ACT	A guided-self-help intervention based on ACT principles involving four skills: (1) Mindfulness: broad awareness of the here-and-now. (2) Unhooking: engaging and disengaging from thoughts as suits your purpose, and letting go of struggles with yourself. (3) Follow your values: ongoing engagement with your values; consistently choosing to move in meaningful directions. (4) Living beyond labels: Taking a perspective beyond labels and responding to yourself in ways that help you grown and learn The modules contain home practice tasks and are supported by individual sessions with a	1.1, 1.2, 1.5, 1.6[a], 1.7, 2.3, 2.4, 3.1[b], 4.1, 4.4, 5.2, 5.4, 5.6, 6.1, 6.2, 8.1, 8.2, 8.7, 9.1, 9.2, 10.9, 11.3, 11.4, 13.4, 15.2, 15.3	ACT (based on relational frame theory)

Determinant	Intervention component objective	Strategy	Intervention component	Description of intervention component	BCTs targeted	Theoretical basis
				psychologist in the following format: (1) 15 minute introduction (2) 3x 25 minute sessions following modules 1, 2 and 3 (3) 15 minute closing session following module 4		

Key: BCT = Behaviour change technique; AET = Adjuvant endocrine therapy; SMS = Short messaging service; ACT = Acceptance and commitment therapy.
*Refers to the BCTs selected for messages to be based on during a one-day workshop with behaviour change experts.
[a] Note: goals may be conceptualised differently in ACT (i.e., based on values) to how they are conceptualised in this taxonomy
[b] Note: The definition of this BCT states "advise on, arrange or provide social support OR non-contingent praise or reward for performance of the behaviour. It includes encouragement and counselling". The coding of this BCT reflects the encouragement provided as part of the support sessions. It does not reflect 'non-contingent praise or reward for performance of the behaviour', which is not consistent with an ACT approach.
1.1 Goal setting (behaviour); 1.2 Problem solving; 1.4 Action Planning; 1.5 Review behaviour goals; 1.6 Discrepancy between current behaviour and goal; 1.7 Review outcome goal(s); 2.3 Self-monitoring of behaviour; 2.4 Self-monitoring of outcome(s) of behaviour; 3.1 Social support (unspecified); 3.3 Social support (emotional); 4.1 Instruction on how to perform a behaviour; 4.3 Re-attribution; 4.4 Behavioural experiments; 5.1 Information about health consequences; 5.2 Salience of consequences; 5.3 Information about social and environmental consequences; 5.4 Monitoring of emotional consequences; 5.6 Information about emotional consequences; 6.1 Demonstration of the behaviour; 6.2 Social comparison; 6.3 Information about others' approval; 7.1 Prompts/cues; 7.3 Reduce prompts/cues; 8.1 Behavioural practice/ rehearsal; 8.2 Behaviour substitution; 8.3 Habit formation; 8.7; Graded tasks; 9.1 Credible source; 9.2 Pros and cons; 10.9 Self-reward; 11.1 Pharmacological support; 11.2 Reduce negative emotions; 11.3 Conserving mental resources; 11.4 Paradoxical instructions; 12.1 Restructuring the physical environment; 12.2 Restructuring the social environment; 12.5 Adding objects to the environment (12.5); 12.6 Body changes; 13.2 Framing/ reframing; 13.4 Valued self-identity; 15.2 Mental rehearsal of successful performance; 15.3 Focus on past success.

The selection of determinants based on the needs assessment, informed the conceptual model. A conceptual model, as recommended by the MRC framework, can provide a visual representation of the theoretical basis of the intervention and can improve generalisability and replicability of the intervention (26). The development of a conceptual model is a key part of the preparation phase of MOST, in which separate intervention component targets are specified (35). Stages one and two of IM informed the intervention target, pathway and outcome aspects of the model (Figure 2.1). Stages 3 and 4 of IM provide detail on the individual intervention components. For two determinants (forgetfulness and psychological distress), there are additional stages in the conceptual model to demonstrate the pathway to adherence, described in detail in Stage 3.

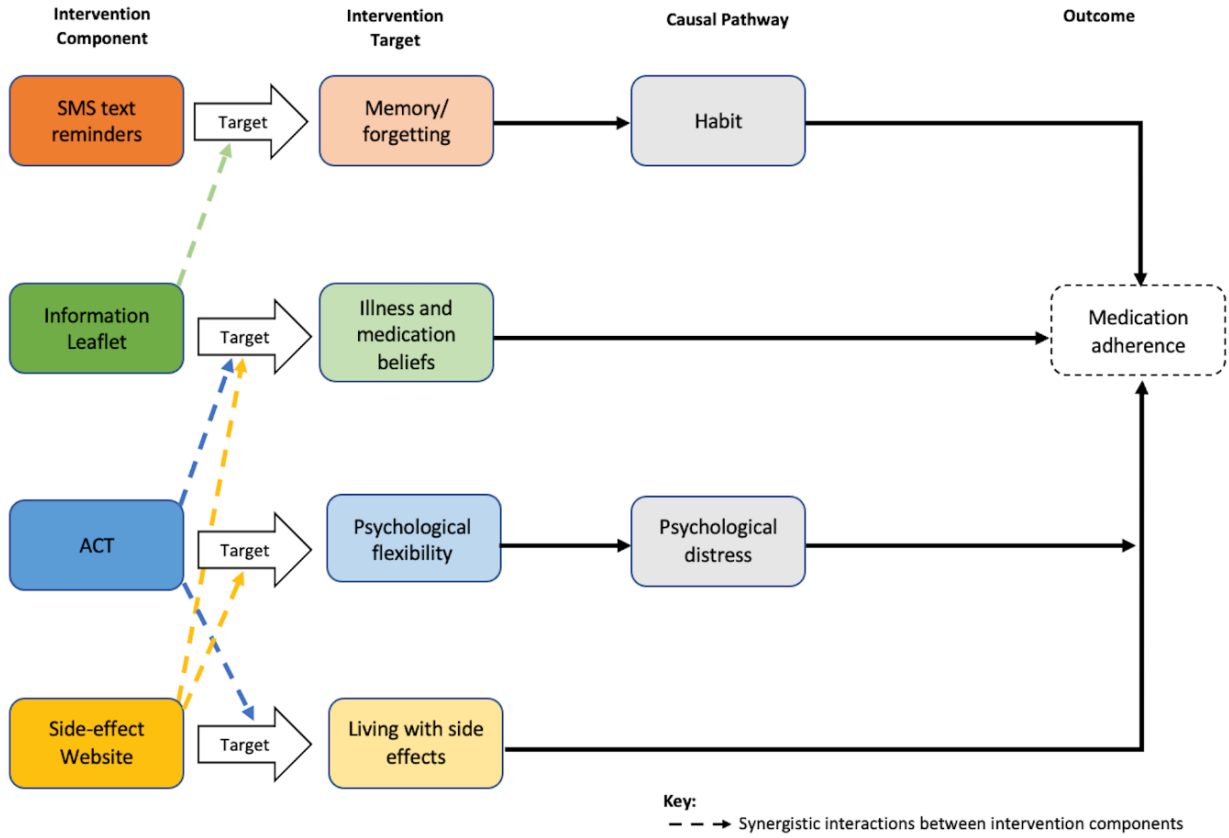

Figure 2.1. Conceptual model

2.5.3 Stage 3: Intervention design

To develop intervention components according to the conceptual model, it is recommended that there is minimal overlap between the content of each intervention component to aid interpretation within the optimisation phase (35, 46). This was considered in Stages 3 and 4. Taking the four main intervention component targets in Stage 2 (memory, illness and medication beliefs, psychological distress, side-effects), Stage 3 focused on identifying theory-based change methods and practical strategies to target these mediators.

2.5.3.1 Forgetfulness

Habit theory was considered to address forgetfulness, as if medication-taking becomes habitual and less reliant on memory, unintentional non-adherence may reduce (90-94). Habit theory stipulates there are multiple conceptual phases in forming a habit; deciding to act, acting on that decision, and doing so repeatedly in a manner conducive to development of behaviour cue associations (91, 94, 95). The formation of cue-behaviour associations, as is essential to habit formation, has the potential to lead to sustained behaviour change. Habit-based interventions have been successful in improving adherence in other long-term conditions (96-98). Based on published guidance, we selected six behaviour change techniques (BCTs) related to habit theory that were feasible to target (94, 99-101) (Table 2.4).

Mobile messaging interventions are increasingly used to promote adherence to medications, and could be cost-effective for promoting habit formation (102-104). Meta-analyses and systematic reviews have highlighted the significant positive effects SMS interventions could have upon medication adherence in long-term conditions, although none included women with breast cancer (102, 105). Individual studies of SMS interventions to promote adherence in women with breast cancer have shown mixed results (82, 85, 86). These interventions did not target habit formation specifically, and often repeated the same messages, which could cause response fatigue (102, 103, 106).

2.5.3.2 Medication and illness beliefs

Information provision can support the formation of medication beliefs (107, 108). The Necessity-Concerns framework suggests patients weigh up the benefits and costs when considering a medication (109). An extended version of the common-sense model of illness representations (CSM) highlights that cognitive and emotional illness representations, in

addition to medication beliefs, influence adherence (110). The CSM has previously been applied to the development of an intervention to support AET adherence (33). Illness representations have been correlated with necessity and concern beliefs in women with AET (59), suggesting they could be targeted together. Providing positively framed and accurate written information about the benefits and risks of AET could increase necessity beliefs and reduce unhelpful concerns and illness representations (88, 89, 108, 111-113).

2.5.3.3 Psychological distress

Within a range of long-term conditions including cancer, Acceptance and Commitment Therapy (ACT) can reduce psychological distress (114, 115) and improve functioning and quality of life (114-120). ACT is a newer type of cognitive behavioural therapy, derived from the philosophy of 'Functional Contextualism' and relational frame theory (121). Consequently, ACT aims to help people engage in activity they find enriching and meaningful, even in objectively difficult situations (for example being diagnosed with cancer), by engendering a quality called psychological flexibility (121). Psychological flexibility involves individuals approaching experiences with openness and awareness to engage more fully with their own overarching goals and values (121). Psychological inflexibility is associated with psychological distress in breast cancer survivors (122).

Preliminary studies show psychological flexibility is positively correlated with treatment uptake and adherence in long-term conditions, and that ACT could be helpful for improving medication adherence (114, 123-126). ACT could improve overall wellbeing and reduce psychological distress by enabling individuals to function effectively alongside common emotional experiences that occur in this population (71).

2.5.3.4 Living with side-effects

Many side-effects women experience while taking AET can be managed without speaking to a healthcare professional (127). Many women taking AET already self-manage their symptoms, and most want more support to do this (128). In previous co-development work, patient representatives and healthcare professionals suggested that a website would allow patients to access side-effect management resources when required (71). Demand for an online resource detailing evidence-based solutions to manage side-effects has also been

reported elsewhere (129). Therefore, a practical strategy to inform women about side-effects and their management was required.

As a result of Stage 3, the practical strategies to target each determinant were confirmed, to be developed in Stage 4.

2.5.4 Stage 4: Intervention development

Four intervention components were developed using distinct formats: SMS messages, an information leaflet, ACT sessions, and a side-effect management website (Appendix A.2). The SMS messages and information leaflet were newly developed, while the ACT sessions and side-effect management website were adapted from existing interventions (71, 130, 131). To develop components according to the conceptual model, the same considerations were applied here as in Stage 3, to minimise duplication of information across components (35). As a result, the four intervention components largely targeted a range of separate BCTs, with some minimal overlap (Appendix A.3, Table 2.4). Readability of the components ranged between 11 and 14 years old (Table 2.5). The 12-item 'Template for Intervention Description and Replication' (TIDieR) checklist describes the intervention components (132) (Appendix A.4).

Table 2.5. Readability of intervention components

Intervention Component	Flesch-Kincaid Grade	Age range
SMS messages	7.6	12-13 years old
Information leaflet	7.1	12-13 years old
ACT participant manuals		
Module 1	6.1	11-12 years old
Module 2	6.9	11-12 years old
Module 3	7.8	12-13 years old
Module 4	8.3	13-14 years old
Website	7.2	12-13 years old

Key: SMS = Short messaging service; ACT = Acceptance and commitment therapy.

2.5.4.1 SMS development

SMS messages were co-developed using an established method for producing acceptable messages with high fidelity to the intended BCT (133). This method has previously produced SMS messages that maintained acceptability and fidelity to intended BCTs when sent within a feasibility trial (134), and were successful in changing hypothesised mediating variables

(135). For our intervention component, behaviour change experts created messages based on BCTs during a one-day workshop, and rated the BCTs on relevance to adherence and the fidelity of individual messages to the BCT they intended to target, on a 10-point scale. Messages scoring below an *a priori* threshold of 5.5 were removed. The remaining messages were revised following a focus group with PPI members, and rated on acceptability by breast cancer survivors in an online survey on a 5-point Likert scale. Messages scoring below an *a priori* threshold of 3 were removed. An additional group of behaviour change experts rated message fidelity to the BCT on a 10-point scale, and messages scoring below an *a priori* threshold of 5.5 were removed (136).

The SMS intervention component will begin with 2 weeks of daily messages, as habit formation occurs most rapidly within the first 2 weeks (95, 137). The messages will reduce to twice weekly for 8 weeks to ensure they do not become intrusive. One of the main reasons for non-adherence in an SMS trial was cited as forgetting at weekends due to a change of routine (85, 138). Messages sent twice weekly could support medication-taking in the change of routine at weekends (139). The SMS messages will then reduce to weekly reminders for 6 weeks, as medication-taking should become sufficiently habitual to persist despite a reduction in support. Frequent messages over a long period could lead to response fatigue; weekly messages are less susceptible to this effect (102, 103, 106). It is important to reduce the frequency so that habit formation is not dependent on reminders, but is due to creating cues for medication-taking (99). To target all phases of habit formation concurrently, a combination of BCTs will be targeted throughout (94).

2.5.4.2 Information leaflet development

The development of the information leaflet was an iterative process. It contains five elements (Table 2.4). PPI members were involved throughout, including planning the content, critiquing drafts, and confirming the content of the final version. Content was informed by information from reputable sources (e.g., NHS website, MacMillan and Cancer research UK). A professional design company was commissioned to create the leaflet. Design decisions, including font size, colour contrasts and layout were informed by the Medicines and Healthcare products Regulatory Agency best practice for information design (140). The leaflet underwent further refinement via patient feedback within PPI meetings, and clinical input from a consultant pharmacist.

2.5.4.3 Acceptance and commitment therapy development

The ACT component was developed from an existing guided self-help intervention for improving quality of life and distress in people with muscle disorders (130, 131). The programme, which includes common ACT techniques (141), was adapted to be relevant to women with breast cancer taking AET. It was adapted by two clinical psychologists (CG and JC) with experience in ACT and breast cancer, in collaboration with members of the research team (SS and SG). PPI members provided feedback at the planning and drafting stages. The adaptation involved rewording the participant module booklets to be relevant for women taking AET, and providing additional exercises to foster self-compassion.

The resulting intervention component involves guided self-help, consisting of four distinct modules (Table 2.4). Module content is presented in four participant handbooks supplemented by audio files and home practice tasks, which are conceptualised to participants as enabling them to develop four specific skills related to psychological flexibility (Table 2.4). The four modules are supported by five individual sessions with a practitioner psychologist ranging from 15 to 25 minutes. The sessions provide a space to discuss the module content, to reflect on experience of practising the skills in everyday life, and to consider their helpfulness.

2.5.4.4 Website development

The side-effect management website was developed as part of an existing intervention for women taking AET (71). The content of the website was informed by an umbrella review of self-management strategies for side-effects in AET (127) and suggestions from breast cancer survivors. Suggestions included the use of patient narratives (71), which have been shown to improve engagement (142, 143). To adapt the intervention, design elements were changed, and some sections were removed to ensure this was a standalone component only targeting side-effects (35).

2.5.5 Stage 5: Implementation planning

The optimisation objective chosen was to create the most effective intervention package achievable that costs no more than £3997 per patient. This optimisation objective was based on health economic modelling (15). An intervention that is effective at showing an absolute improvement of 10% in adherence would be considered cost-effective if it could be delivered

for less than £3997 per patient. The optimisation objective will be considered in the optimisation phase to ensure the intervention package developed is likely to be within cost-effectiveness thresholds.

Discussions with stakeholders highlighted the following considerations for potential implementation and maintenance of the intervention components. The SMS, information leaflet, and website components all represent relatively low-cost components with relatively modest maintenance needs. Therapist hours, cost and mode of delivery were considered in detail for the ACT component. There was a large amount of stakeholder engagement throughout the ACT adaptation process, involving patient representatives, clinical psychologists and service managers to consider feasibility of implementation within the NHS (71). A guided self-help intervention was chosen by the research team in collaboration with patient representatives, as it required a lower number of therapist hours to deliver. This follows a similar approach to the Improving Access to Psychological Therapies (IAPT) model, which uses brief guided self-help interventions and has been widely implemented in the NHS (144). Remote delivery was chosen as it can benefit patients through eliminating the need to travel to sessions. Remote delivery also reduces the need to identify clinic rooms which can be a constraint in NHS psychological services. The option of telephone or videoconferencing was chosen to reduce exclusion of those without access to videoconferencing software or a private space. Guidance for how to use videoconferencing platforms will be given.

2.5.6 Stage 6: Evaluation plan

2.5.6.1 Expected interactions between intervention components

Hypothesised synergistic interactions are displayed using dashed lines in Figure 2.1 and explained below. In a synergistic interaction, the presence of one component enhances the effect of another. In such a case, the effect of two or more factors (factors refer to independent variables in a factorial experiment) is greater than would be expected based solely on the main effects of these factors (145). No antagonistic interactions (the presence of a component reduces the effect of another) were hypothesised.

2.5.6.1.1 SMS messages and information leaflet

Habit formation consists of multiple phases (91, 94, 95). SMS reminders will specifically target initiation, and repetition conducive to formation of cue-behaviour associations. The other phase, deciding to take the medication, relies on motivation to engage in the behaviour (94), which could be influenced by a positive necessity-concerns differential (146). Therefore, we hypothesise the information leaflet will contribute to and enhance the process of habit formation, resulting in a greater overall effect on adherence.

2.5.6.1.2 ACT and information leaflet

Some processes in ACT will indirectly target emotional representations of illness, that are associated with medication beliefs (37). For example, ACT-based skills that help one 'unhook' from distressing thoughts, could positively affect emotional representations, such as reducing fear of recurrence (147). Reducing emotional representations such as worry may synergistically reduce concerns about AET (59). Therefore, ACT and the information leaflet together may have a greater effect on medication adherence than each component alone.

2.5.6.1.3 Website and information leaflet

A major concern women have with AET is side-effects (17, 55, 61, 148). From a causal learning theory perspective to adherence, bottom-up learning (where actual experiences shape beliefs) may occur in which experiences with side-effects could shape medication beliefs (107). The website may have a positive effect on experience of side-effects, while the information leaflet may reduce concerns, leading to a more positive necessity-concerns differential (146). Consequently, combining the website and information leaflet may have an overall greater impact on adherence.

2.5.6.1.4 ACT and website

Engagement in ACT techniques may increase willingness to tolerate side-effects when medication-taking is consistent with values, and can reduce symptom interference (116, 120, 121, 149). Engagement in the ACT component in combination with self-management strategies from the website, may therefore increase one's ability to live well alongside side-effects, reducing their interference with meaningful functioning, consequently leading to greater adherence.

Additionally, use of the website may reduce side-effects. If the impact of side-effects is reduced, participants may be able to focus on life-enriching activities consistent with their values (121, 126, 149). Therefore, use of the website may enhance engagement in the ACT component, leading to a greater overall effect upon adherence.

2.5.6.2 Specification of plans for evaluation design

We prepared a protocol for an external exploratory pilot trial using a 2^{4-1} fractional factorial design, with a nested process evaluation, to determine the acceptability and fidelity of the intervention components, and the feasibility of evaluating them in a larger optimisation trial (46, 150). If progression criteria are met, we will proceed to an optimisation trial using a 2^4 factorial design. A full factorial design is likely to be needed for the optimisation trial. This is because we have specified multiple 2-way interactions in Stage 6, which would be aliased with other potentially important effects in a fractional factorial design (151).

2.6 Discussion

We have demonstrated a transparent and systematic approach to the development of a complex behavioural intervention designed to support medication adherence in women with breast cancer. Using an iterative IM approach, and informed by the MOST framework, we used existing evidence, behavioural science theory, and patient experience to design an intervention package consisting of four intervention components (SMS, information leaflet, ACT, website) targeting key determinants of AET adherence.

Our study illustrates how intervention development can be guided by both IM and the MOST framework (34, 35, 46). Our plans to use a factorial design to optimise the intervention package will help delineate the individual contributions and interactions between the intervention components. This optimisation process aims to develop interventions that are more effective, efficient and scalable (34, 46, 152). This approach could accelerate knowledge in intervention development through improved understanding of which aspects of an intervention work and why (153). Combining IM with MOST could therefore be a more efficient method to develop and evaluate interventions, than using IM alone.

The MOST framework influenced key points in the intervention development process, namely, ensuring each component targeted a specific mediator, consideration of how the intervention components fit together as a package, and ensuring each component was

distinct. Using a staged approach such as IM enabled us to consider these points throughout development. To avoid the possibility of developing a disjointed intervention package we ensured continuity in the aesthetics of each component.

Targeting all barriers to adherence identified in the needs assessment was a challenge. A pragmatic decision was made not to include all barriers identified in Stage 1 in the conceptual model. Firstly, adding more intervention components increases the number of experimental conditions required in a factorial design. For example, adding three extra components would lead to a 2^7 factorial design requiring 128 experimental conditions if using a full factorial design. This may not be feasible to deliver. If we demonstrate that it is feasible to undertake a 2^{4-1} experimental design in the proposed pilot trial, additional intervention components could be considered in the future, as fractional factorial designs can be more efficient in these circumstances. Secondly, barriers such as social support and patient-physician communication are likely to require complex designs. For example, while the ACT component does provide a degree of social support, it could be argued that this could be more adequately addressed with a group-based psychotherapy intervention. However, evaluating group-based intervention components using a factorial experiment may necessitate more complex, multilevel designs (154). While such designs exist, they have rarely been used and methodological expertise and guidance are lacking. This issue led to uncertainty in deciding between a group-based or an individual psychotherapy component. Importantly, the conceptual model presented in this paper has not yet been tested, and can be refined in the future as further information is collected. For example, should we receive strong feedback from women receiving these interventions within the planned pilot trial that they would have preferred a group-based approach, we will give further consideration to evaluating it in a future optimisation trial. This decision will also be guided by the results of a separate pilot trial testing a group-based ACT intervention currently being undertaken by the authors (LH, SS, CG, JC) (155), alongside qualitative feedback within our planned process evaluation.

A further challenge of our approach was related to coding the active ingredients of the isolated intervention components. We felt it was important to use the same taxonomy to allow comparisons across intervention components. Therefore, we chose the BCTTv1 as this was the most widely used approach for coding behavioural interventions (47). However, the taxonomy was more challenging to apply to the ACT component than others, and several ACT

specific intervention methods could not be positioned in the BCTTv1. This highlighted that the BCTTv1 taxonomy does not comprehensively cover all techniques that are involved in ACT based interventions; a limitation also acknowledged elsewhere (156).

In using theory to develop the intervention components, we identified barriers to AET adherence to be targeted, and then considered psychological theories relevant to each barrier. This enabled us to consider theories specific to each identified determinant. An alternative approach could be to begin with a theory, and develop intervention components based on the constructs of that theory. However it has been recommended not to rely on singular theories when developing interventions to target medication adherence as single theories do not fully explain this behaviour (157). Our approach enabled exploration of multiple theories to inform the development of our intervention components.

Using factorial trials to evaluate multiple intervention components, as suggested by the MOST framework, is a relatively new approach in health services research. We made adaptations to IM based on time available and to include important considerations guided by MOST (28, 31). Strengths of our approach include applying an established intervention development method within the MOST framework, and the systematic reporting of the intervention development process. The differing formats of the intervention components allowed each determinant to be targeted using the most appropriate modality for that determinant. However, evaluating different formats of components may confound the mechanism of the intervention with the content. For example, participants may find the ACT component more engaging due to interaction with a therapist, rather than due to the content of the component. Future work could account for this by using a placebo control; for example by comparing ACT delivered by a therapist with an equivalent amount of time with a therapist discussing a different topic.

2.6.1 Conclusions

We have developed a complex behavioural intervention package aiming to support AET adherence in women with breast cancer, made up of four intervention components. We have also demonstrated how IM can be harnessed to develop an intervention package that targets known determinants of medication-taking behaviour in this population. Guided by MOST, this intervention package will be optimised in further trials with the aim of defining effective, efficient and scalable strategies to support behaviour change.

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Chapter 3 : Co-development of a text messaging intervention to support adherence to adjuvant endocrine therapy in women with breast cancer: mixed-methods approach

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3.1 Abstract

Background: Adjuvant endocrine therapy (AET) reduces breast cancer recurrence and mortality in women with early-stage breast cancer. Unintentional non-adherence to AET is common (e.g., forgetting to take medication). Forming habits surrounding medication-taking could reduce reliance on memory and improve AET adherence. SMS text messaging interventions may offer a low-cost approach for promoting medication-taking habits. To optimise the likely effectiveness of such SMS text messages, the content should be developed using a transparent approach to ensure fidelity to relevant psychological theory and with user input to increase acceptability.

Objective: This study aimed to develop a pool of brief SMS text messages promoting habit formation to support AET adherence, which are acceptable to women with breast cancer and show fidelity to theory-based behaviour change techniques (BCTs).

Methods: According to published literature, we selected 6 BCTs derived from the habit formation model: action planning, habit formation, restructuring the physical environment, adding objects to the environment, prompts/cues, and self-monitoring of behaviour. In study A[3], behaviour change experts (n = 10) created messages, each based on 1 of the 6 BCTs, in a web-based workshop and rated the fidelity of the messages to the intended BCT. In study B, women with experience of taking AET discussed the acceptability of the messages in a focus group (n = 5), and the messages were refined following this. In study C, women with breast cancer rated the acceptability of each message in a web-based survey (n = 60). In study D, additional behaviour change experts rated the fidelity of the remaining messages to the intended BCT in a web-based survey (n = 12). Finally, a consultant pharmacist reviewed a selection of messages to ensure that they did not contradict general medical advice.

Results: In study A, 189 messages were created targeting the 6 BCTs. In total, 92 messages were removed because they were repetitious, unsuitable, or > 160 characters, and 3 were removed because of low fidelity (scoring < 5.5/10 on a fidelity rating scale). Following study B, we removed 13 messages considered unacceptable to our target population. In study C, all

[3] Note: The studies included in the published version of this paper were labelled, Study 1, 2, 3, and 4. These have been renamed for the purpose of this thesis to study A, B, C and D to avoid confusion with the four studies that make up chapters 2-5 of this thesis.

remaining messages scored above the midpoint on an acceptability scale (1-5); therefore, no messages were removed (mean = 3.9/5, SD 0.9). Following study D, we removed 13 messages owing to low fidelity (scoring < 5.5/10 on a fidelity rating scale). All the remaining messages showed fidelity to the intended BCTs (mean = 7.9/10, SD 1.3). Following the pharmacist review, 2 messages were removed, and 3 were amended.

Conclusions: We developed a pool of 66 brief SMS text messages targeting habit formation BCTs to support AET adherence. These showed acceptability to women with breast cancer and fidelity to the intended BCTs. The delivery of the messages will be further evaluated to assess their effect on medication adherence

3.2 Introduction

Adjuvant endocrine therapy (AET) is routinely prescribed for 5 to 10 years to women with early-stage oestrogen receptor-positive (ER+) breast cancer to reduce recurrence and mortality (1-4). It is an oral tablet taken once daily. Despite its benefits, up to three-quarters (75%) of women do not take AET as prescribed (5-7), with up to half of women discontinuing it within 5 years (6, 8). Non-adherence to AET increases the risk of breast cancer-related recurrence and mortality and increases health care costs (4, 9, 10).

Non-adherence to AET can be intentional or unintentional. Intentional reasons for non-adherence include difficulties with side-effects, concerns about AET, and psychological distress (11-15). Unintentional reasons include forgetfulness, being away from home, and difficulty refilling a prescription (16). Unintentional non-adherence is reported more frequently than intentional non-adherence in women with breast cancer taking AET (16, 17). Subjective cognitive impairment, including impaired memory, is commonly reported by breast cancer survivors following chemotherapy (18, 19), which may contribute to unintentional non-adherence (7, 12, 20, 21).

A Cochrane review of 182 randomised controlled trials on medication adherence interventions across multiple long-term conditions highlighted the need for more effective and novel interventions to support medication adherence (22). Existing interventions supporting AET adherence tend to focus on educating women about AET and breast cancer and often solely use written information (23-26). Most of these interventions do not focus on unintentional barriers to adherence, despite their prevalence (26). Most existing interventions have been minimally effective in improving adherence (23-26).

Making medication-taking behaviours habitual could address unintentional non-adherence, as habits reduce reliance on memory. A habitual behaviour is an action triggered by exposure to a contextual cue (27). Habitual behaviours are learned through a process of context-consistent repetition: consistently repeating a behaviour (e.g., taking medication) in the presence of a specific context cue (e.g., a time of day) strengthens a specific cue-behaviour association (28-33). Habit theory suggests that although initial performances may require conscious effort, as the association is reinforced, the behaviour can be activated automatically with minimal dependence on conscious memory or attention (30). The

formation of a habit is initially rapid, plateauing over time as the habit is formed (33, 34). Although there is individual variation in the timescale in which a behaviour becomes habitual, habit formation tends to occur most notably within the first 2 weeks of attempting to change the behaviour (33, 35, 36). This highlights the need for support in the early phases of a behaviour change intervention aimed at supporting habit formation (31, 34).

According to habit theory, if habits for medication-taking behaviours are formed, taking medication could become more automatic, thereby reducing reliance on memory or the motivation to take AET (37). In a meta-analysis including 771 interventions supporting medication adherence in a variety of clinical contexts, larger effect sizes were observed for habit-based interventions than for those using simple prompts or educational materials alone (38, 39). However, a recent review highlighted that many medication adherence interventions described as “habit based” are not theoretically informed and do not promote the process of context-consistent repetition, which is fundamental to habit formation (40).

SMS text messaging interventions are a low-cost method for supporting habit formation. They can serve as an initial reminder to take the medication and could lead to sustained behaviour change through prompting medication-taking in the same context repeatedly to support habit formation (41). Meta-analyses of SMS text messaging interventions in other long-term conditions have reported positive effects on adherence (odds ratios 1.39-2.11) (42, 43). However, to date, no habit-based interventions to support medication adherence have exclusively used SMS text messages (40).

Outside of habit-based interventions, SMS text messaging interventions aimed at improving adherence to AET among women with breast cancer have shown mixed results (44-47). In these interventions, the same messages are often repeated, potentially causing response fatigue (45, 46). The use of simple prompts in some of these interventions fails to make use of the range of known behaviour change strategies and, therefore, may be unlikely to produce sustained behaviour change once the messages have ceased (46). Behaviour change techniques (BCTs) are described as irreducible, active ingredients of an intervention that can be used to label the content of behavioural interventions (48). Existing SMS text messaging interventions based on simple prompts use only 1 of the 93 BCTs identified in version 1 of the behaviour change taxonomy (BCTTv1) (48). Additional BCTs, beyond prompts and cues, should be used to promote sustained behaviour change.

The message development processes for existing SMS text messaging-based interventions targeting AET adherence generally lack detail and transparency, and there is rarely a theoretical justification for the message content. Intervention development guidance highlights the importance of having a theoretical basis for an intervention and advocates for detailed reporting of intervention development to improve transparency (49-52). Therefore, we sought to address these limitations in the field by developing SMS text messages based on specific, theory-based BCTs chosen to target habit formation, in line with habit theory (34).

3.2.1 Objectives

Using an established process (53, 54), we aimed to develop a pool of brief SMS text messages that promote habitual medication-taking, are acceptable to patients, and show fidelity to explicit BCTs. This process involved (1) an expert workshop to create the messages, (2) a patient focus group to determine message acceptability, (3) a web-based patient survey to assess message acceptability, and (4) a web-based expert survey to assess the fidelity of the final messages to the intended BCTs (Figure 3.1). The studies in this paper form part of a broader research programme, which aimed to develop and optimise a multicomponent intervention to support adherence to AET in women with breast cancer (26, 55). The multicomponent intervention includes 4 components targeting a range of known barriers to AET adherence. SMS text messages targeting memory and forgetfulness are one of these components (26, 55).

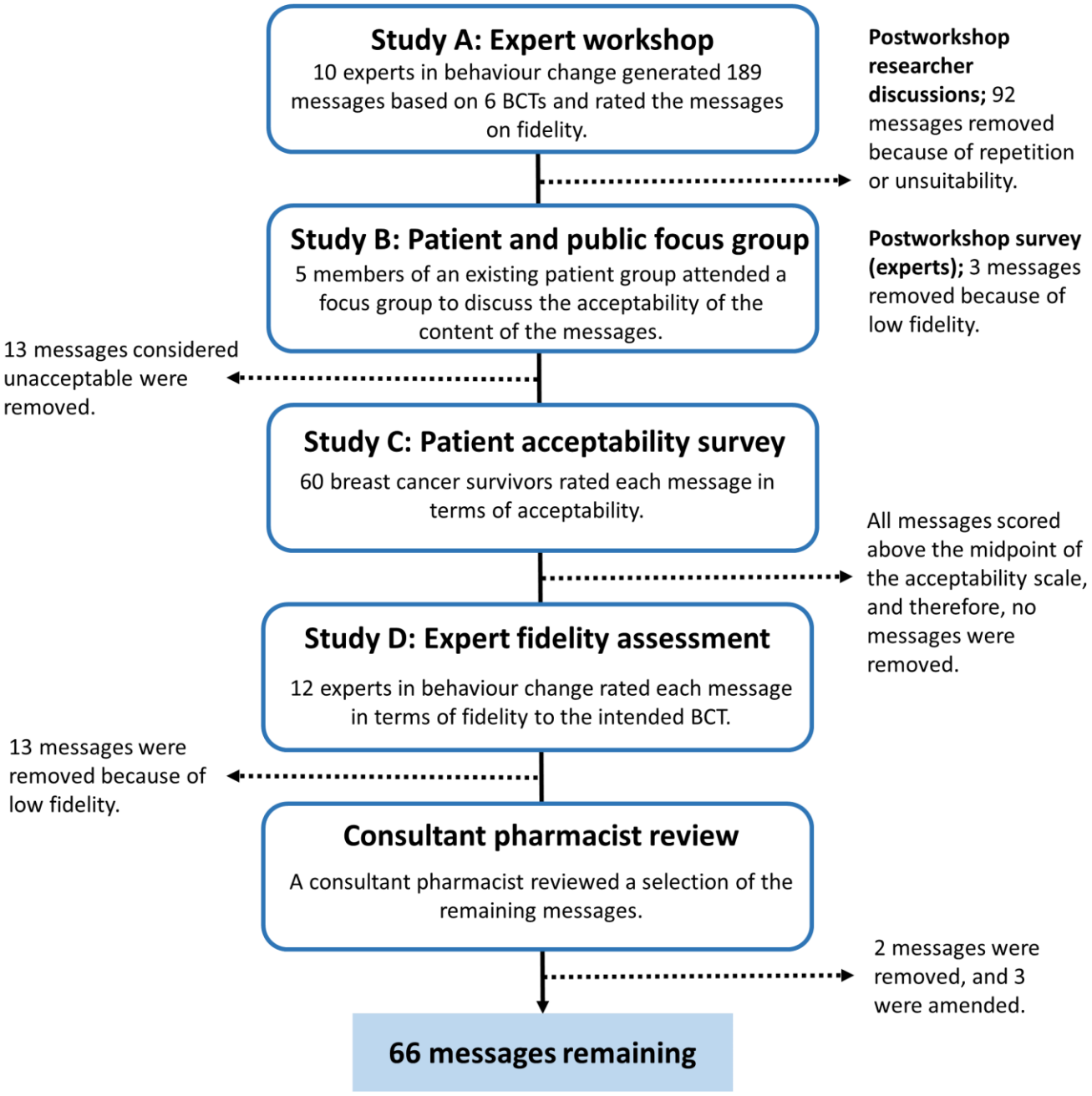

Figure 3.1. Development of SMS text messages
Key- BCT: behaviour change technique.

3.3 Methods

In preparing this manuscript, we followed the guidance for reporting intervention development studies in health research (52).

3.3.1 Target behaviour

Using the Target, Action, Context, Time framework for behaviour specification (56), the target behaviour is defined as women with breast cancer prescribed AET (target), taking their AET tablet (action) daily (time) in a consistent context (context). To achieve the behaviour of adherence (i.e., taking AET daily), ordering and collecting prescriptions is also required. Therefore, we targeted these associated behaviours to facilitate the performance of the overall behaviour of taking medication daily.

3.3.2 Selection of behaviour change techniques

On the basis of evidence suggesting that habit interventions could be effective for improving medication adherence (38, 39), and the potential for habitual medication-taking to reduce forgetfulness of taking AET, SMS text messages were designed based on habit theory. The process of habit formation involves multiple stages: deciding to undertake a behaviour, initiating and repeating the behaviour, and acting consistently in the same context (28-33). Although the first 2 stages are necessary for any long-term behaviour change attempt, the final stage promotes the formation of cue-behaviour associations, which is unique to habit formation (29, 32). On the basis of published guidance, we selected 6 BCTs from the BCTTv1 to be used in the intervention (29, 32, 34, 57). Using BCTTv1 enabled us to develop a theoretically informed intervention specified in a way that will improve generalisability and replicability. The 6 chosen BCTs included a BCT explicitly promoting context-dependent repetition (habit formation [also known as context-dependent repetition]), BCTs promoting the use of feasible environmental cues for medication-taking (prompts/cues, restructuring the physical environment, and adding objects to the environment (32, 34, 57)), a BCT specifying behavioural responses to these cues (action planning) (34, 57, 58), and a BCT promoting monitoring successful implementation of these responses (self-monitoring of behaviour (34, 48, 57)). The BCTs were identified by 1 author (SMCG) and discussed and agreed by consensus with 4 other members of the research team (SGS, DPF, YKB, and ER).

3.3.3 Development studies

We followed an established process using a series of studies to develop the pool of SMS text messages (53, 54). This approach involved developing SMS text messages based on theory with experts in behaviour change before gaining qualitative and quantitative feedback from the patient population. The final stage involved checking whether the messages still targeted the BCTs they intended to target after any adaptations had been made.

3.3.4 Study A: Expert workshop

Aim: The aim was to generate 12 to 15 messages for each of the 6 chosen BCTs targeting habit formation and to assess message fidelity to the intended BCTs.

Participants: We emailed 25 UK experts in behaviour change, identified through the research team's networks and by searching university websites and Twitter profiles. We sent a reminder email to non-respondents after 1 week. The participants were given a £100 honorarium for their time. A currency exchange rate of GBP £1 = US $1.25 is applicable.

Procedure: We sent a web-based questionnaire asking for e-consent, demographic information, and expertise in behaviour change. Participants who completed this questionnaire were sent the schedule for the 1-day web-based workshop. The schedule included the aims for the day, target behaviours for the messages, and the names and descriptions of the 6 target BCTs. The workshop was hosted on Zoom (Zoom video communications) and was split into 3 sections. For each section, participants were split into 2 groups (5 participants per group), facilitated by 2 researchers per group (SMCG, SGS, ER, and LHH). Each group was introduced to a BCT with a short description and an example taken from the BCTTv1 (48). Participants were informed that messages must be < 160 characters to fit in a single SMS text message. Participants were asked to generate SMS text messages to support AET adherence and enter the messages into a web-based real-time platform to collate uploaded content (Padlet). Participants then had 15 minutes to discuss the SMS text messages and BCT in their group. SMS text messages could be modified within this time, and new suggestions were added. This process was repeated 3 times such that across 2 groups, messages were generated for all 6 BCTs. The experts were allocated to a different group after each round of message generation. One workshop participant is an author of this manuscript (BG).

Following the workshop, 4 research team members (SMCG, SGS, ER, and LHH) removed messages deemed unsuitable for the intervention (e.g., they were substantially > 160 characters or made unrealistic suggestions that could not be actioned by the patient). Then, each researcher rated each message based on how well it addressed the target behaviours on a scale of 1 to 10 (coherence to the behaviour).

Two working days after the workshop, the participants were sent a survey containing the remaining messages. Participants were asked to rate how relevant they felt the BCT was to support medication adherence within this population, how well they thought the aim of generating 12 to 15 good-quality messages had been achieved, and the fidelity of each message to the BCT it was intended to target. All 3 questions were assessed on a scale of 1 (not relevant or not very well) to 10 (very relevant or very well).

Analysis: We removed messages scoring < 5.5 on the research team's coherence rating, as this was the midpoint of the scale. Participant characteristics were summarised. We calculated the means and SDs of each SMS text message on fidelity, and an *a priori* threshold of < 5.5 on the fidelity scale was used to remove messages, as this was the midpoint on the scale and has been used as a cut-off in a previous similar study (53). We summarised the responses regarding the relevance of the BCT and the aim of generating 12 to 15 good-quality messages per BCT.

3.3.5 Study B: Focus group

Aim: The aim was to assess the acceptability of the SMS text messages generated in study A to women taking AET.

Participants: Participants were recruited from a pre-existing patient and public involvement group. Patient and public involvement group members were originally recruited via an advertisement circulated in a newsletter for a charity that supports people with cancer. All members had a diagnosis of ER+ breast cancer and were currently taking AET. All members were offered £37.50 compensation for their time, in line with the published guidelines (59).

Procedure: All participants completed demographic and clinical questions and were sent a copy of the SMS text messages 2 weeks before the meeting. The focus group was hosted on Microsoft Teams, lasted 90 minutes, and was facilitated by SMCG and ER. Each BCT was presented along with a short description taken from the BCTTv1 and the SMS text messages

relating to that BCT. The participants were asked to discuss the acceptability of the messages and suggestions for rewording. A topic guide was used to structure the discussion (Appendix B.1).

Analysis: The focus group was recorded and transcribed verbatim. One author (SMCG) extracted all suggestions from the transcript and made amendments to the messages when there was no disagreement between participants. If there was disagreement among participants, these instances were discussed within the research team (SMCG, ER, SGS, and LHH). Where the research team could not reach an agreement, the message was retained and included in study C.

3.3.6 Study C: Patient survey

Aim: The aim was to determine the acceptability of SMS text messages remaining after studies A and B.

Participants: In total, 60 women diagnosed with ER+ breast cancer were recruited via a recruitment company, Dynata, to participate in a web-based survey. Dynata provided the women with a small monetary incentive on completion of the survey.

Procedure: Dynata sent the web-based survey link to their panel members. The survey contained information on the study, an e-consent form, and demographic questions. Participants who were eligible and provided e-consent were asked to rate the SMS text messages based on their acceptability, with responses on a 5-point Likert scale (1 = completely unacceptable and 5 = very acceptable). The order in which the messages appeared was randomised.

Analysis: We summarised participant demographics, means, and SDs for the acceptability of each SMS text message. We calculated an acceptability score for each BCT by averaging the acceptability scores of the messages related to that BCT. On the acceptability scale, any messages scoring below an *a priori* threshold of 3 were removed, as this was the midpoint of the scale and has been used as a cut-off in a previous similar study (53).

3.3.7 Study D: Expert survey

Aim: The aim was to assess the fidelity of the remaining SMS text messages to the intended BCTs.

Participants: We emailed 41 UK experts in behaviour change. This included 15 experts who had not responded to the study A invitation or could not attend the workshop. In total, 26 additional potential participants were identified from the research team's networks and through further searching of university websites and Twitter profiles. Study A participants were ineligible and were not contacted. A £25 Amazon voucher was offered upon completion of the survey.

Procedure: We emailed a link to a web-based survey containing information about the study and an e-consent form. If the participants consented, they were asked to rate each message on fidelity to the intended BCT on a scale of 1 (not very well) to 10 (very well). A description and an example from the BCTTv1 were provided.

Analysis: We summarised participant demographics and the means and SDs for each text message and BCT. We removed messages scoring below an *a priori* threshold of 5.5 on fidelity, as this was the midpoint of the scale and has been used as a cut-off in a previous similar study (53).

3.3.8 Clinical review

A selection of 20 messages were sent to a consultant clinical pharmacist with experience of AET to ensure advice in the messages was appropriate and not conflicting with general medical advice. The consultant pharmacist was a member of the trial management group for the larger program of research that this study is part of. The 20 messages to be reviewed included all messages in which there could be any risk of conflicting or dangerous advice. The review occurred at this stage to ensure that the final versions of the messages were checked.

3.3.9 Ethics approval, informed consent and participation

Ethics approval was granted by the University of Leeds School of Medicine Ethics Committee (MREC 20-038 July 2021). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all the participants included in this study. All data from the study were de-identified. Participants were compensated in the following ways: study A: £100, study B: £37.50, study C: small incentive provided directly from the market research company, and study D: £25 Amazon voucher.

3.4 Results

The flowchart of the 4 studies is shown in Figure 3.1. The 12-item "Template for Intervention Description and Replication" checklist describes the final pool of SMS text messages (60) (Appendix B.2).

3.4.1 Study A: Behaviour change expert workshop

Demographics: Of the 10 participants, 8 (80%) were research scientists and 2 (20%) were research scientists and health care professionals. Participants had been in paid research-related posts for between 10 and 25 (mean = 16.3, SD = 4.8) years. Each participant had published between 3 and 71 papers related to behaviour change, medication adherence, and/or breast cancer (mean = 36.1, SD = 21.1). Behaviour change interventions were the research focus for most participants (8/10, 80%). Half of the participants (5/10, 50%) described medication adherence as central or somewhat central to their work, and 1 participant described breast cancer as central to their work.

SMS text message generation: In total, 189 SMS text messages were created for the 6 BCTs during the expert workshop (Table 3.1).

Table 3.1. Generation and refinement of SMS text messages in study A

Behaviour change technique	Messages created in workshop, n	Coherence[a], mean (SD)	Messages removed (research team)[b], n
Restructuring the physical environment	42	7.5 (1.0)	18
Adding objects to the environment	27	7.4 (1.1)	13
Habit formation	33	8.3 (0.8)	17
Prompts/cues	34	7.8 (0.9)	18
Action planning	28	7.6 (0.7)	15
Self-monitoring of behaviour	25	7.9 (0.8)	11

[a]Coherence score ranged from 1 to 10, with higher scores indicating better coherence.
[b]Reasons for message removal include unsuitability for the intervention, repetition, scoring < 5.5 on coherence to the behaviour.

Refinement of SMS text messages by the research team: In total, 92 messages were removed because they were considered unsuitable (Table 3.1); for example, they seemed unrealistic, confusing, or exceeded 160 characters. Where multiple messages were similar within a BCT (e.g., the suggestion to put your medication by your toothbrush; target BCT: restructuring the

physical environment), the messages were combined and agreed upon by the research team (SMCG, SGS, LHH, and ER). On the basis of the research team's ratings of coherence to the behaviour, 4 messages were removed: 2 from "restructuring the physical environment," 1 from "habit formation," and 1 from "self-monitoring of behaviour."

Post-workshop survey message decisions: We removed 3 messages because they scored below the midpoint (5.5) on the 1 to 10 fidelity scale. These are related to "action planning" and "restructuring the physical environment" (Table 3.2). Messages related to the BCTs "action planning," "prompts/cues," and "habit formation" were considered the most relevant when targeting medication adherence. The individual messages rated highest on fidelity were "Buy yourself an attractive pillbox for your medication" (target BCT: "adding objects to the environment"; mean = 9.1, SD = 1.1), and "At the end of each day, try ticking off whether you have taken your medication in a diary or calendar, to help you keep track" (target BCT: "self-monitoring of behaviour"; mean = 9.1, SD = 0.9). A total of 94 messages remained after study A.

Table 3.2. Post-workshop survey behaviour change expert ratings

Behaviour change technique	Relevance[a], mean (SD)	Aim to have 12 to 15 messages that reflect the BCT well[b], mean (SD)	Fidelity[c], mean (SD)	Fidelity after exclusions, mean (SD)
Action planning	9.0 (0.9)	7.1 (1.5)	6.9 (1.2)	7.3 (0.9)
Prompts/cues	9.2 (0.8)	8.4 (0.7)	8.1 (0.7)	—[d]
Habit formation	9.4 (0.8)	8.1 (1.4)	7.8 (0.8)	—
Restructuring the physical environment	7.9 (1.1)	6.6 (2.1)	6.8 (0.7)	6.9 (0.7)
Self-monitoring of behaviour	7.8 (1.4)	8.3 (1.2)	8.1 (0.6)	—
Adding objects to the environment	7.8 (1.5)	7.6 (1.3)	7.7 (1.0)	—

[a]Relevance scores ranged from 1 to 10, with higher scores indicating the behaviour change technique was more relevant to medication adherence.

[b]Scores ranged from 1-10, with higher scores indicating the aim of generating 12 to 15 messages reflecting the behaviour change technique had been better met.

[c]Fidelity scores ranged from 1 to 10, with higher scores indicating better fidelity to the intended behaviour change technique.

[d]No message excluded.

3.4.2 Study B: Patient and public focus group

Demographics: In total, 5 women aged between 41 and 79 years participated in the focus group (Table 3.3). All participants were White, had been taking AET for an average of 7 years, and reported using their mobile phone more than once a day.

Table 3.3. Demographics and clinical characteristics of study B and C participants

Demographics	Study B (n = 5)	Study C (n = 60)
Age (years), mean (SD)	54 (15)	51 (16)
Time since diagnosis (years), median (range)	8 (2-20)	2 (0-41)
Ethnicity, n (%)		
White British	5 (100)	49 (82)
Asian or Asian British	0 (0)	7 (12)
Black or Black British (African)	0 (0)	2 (3)
Black or Black British (Caribbean)	0 (0)	1 (2)
Mixed	0 (0)	1 (2)
Educational Level, n (%)		
General Certificate of Secondary Education or equivalent[a]	2 (40)	5 (8)
National vocational qualification level 1 and 2 (NVQ1+2)	1 (20)	8 (13)
A-Level	0 (0)	6 (10)
Higher educational qualifications (below degree)	0 (0)	12 (20)
Degree level education	2 (40)	25 (42)
No formal qualifications	0 (0)	3 (5)
Still Studying	0 (0)	1 (2)
Number of children, median (range)	2 (0-2)	2 (1-7)
Marital Status, n (%)		
Single	1 (20)	1 (2)
Married or living together	4 (80)	47 (78)
Divorced or separated	0 (0)	10 (17)
Widowed	0 (0)	2 (3)
Menopausal status, n (%)		
Premenopausal	1 (20)	26 (43)
Postmenopausal	1 (20)	29 (48)
Unsure	2 (40)	5 (8)
Other	1 (20)	0 (0)
Stage of breast cancer at diagnosis, n (%)		
1	0 (0)	24 (40)
2	3 (60)	16 (27)
3	1 (20)	9 (15)
4	0 (0)	1 (2)
Unsure	1 (20)	10 (17)
Treatment received, n (%)		
Surgery: lumpectomy	1 (20)	33 (55)

Demographics	Study B (n = 5)	Study C (n = 60)
Surgery: unilateral mastectomy	4 (80)	15 (25)
Surgery: double mastectomy	1 (20)	8 (13)
Chemotherapy	4 (80)	26 (43)
Radiotherapy	4 (80)	36 (60)
Other	2 (40)	3 (5)
Hormone therapy prescribed, n (%)[b]		
Tamoxifen	4 (80)	23 (38)
Letrozole	2 (20)	20 (33)
Anastrozole	0 (0)	14 (23)
Exemestane	0 (0)	7 (12)
Other	1 (20)	0 (0)
Not prescribed any of these	0 (0)	9 (15)
Time since first prescribed hormone therapy to the nearest year, median (range)	7 (1-20)	2 (0-21)
Frequency of mobile phone use, n (%)		
More than once a day	5 (100)	45 (75)
Once a day	0 (0)	8 (13)
More than once a week but not everyday	0 (0)	3 (5)
Once a week	0 (0)	0 (0)
More than once a month but not weekly	0 (0)	2 (3)
Less than once a month	0 (0)	2 (3)
Frequency of SMS use, n (%)		
More than once a day	2 (40)	31 (52)
Once a day	0 (0)	9 (15)
More than once a week but not everyday	3 (60)	11 (18)
Once a week	0 (0)	2 (3)
More than once a month but not weekly	0 (0)	0 (0)
Less than once a month	0 (0)	7 (12)

[a]Includes General Certificate of Education Ordinary Level (O level) and Certificate of Secondary Education (CSE).

[b]Totals > 100% due to some participants switching medications.

Decisions for message development: All suggestions from the focus group in which there was no disagreement between participants were implemented, resulting in the removal of 13 messages (Appendix B.3). Amendments were made to the wording of certain messages. Example suggestions included using less directive wording, which resulted in phrases such as "you could…." being added. All references to AET were standardised to use "medication," as agreed by focus group members and researchers.

3.4.3 Study C: Patient survey

Demographics: In total, 60 women with ER+ breast cancer completed the web-based survey (Table 3.3). The average time that the participants had been prescribed hormone therapy was 2 years. Most of the women (53/60, 88%) used their mobile phones at least once per day.

Decisions for message development: All individual messages and BCTs scored above the midpoint on the acceptability scale (3); therefore, none were removed (Table 3.4). The mean acceptability ratings for individual messages ranged from 3.52 to 4.28 (scale 1-5). The message scoring highest on acceptability was "Try keeping your medication somewhere visible so that you are reminded to take the medication every day," targeting the BCT "prompts/cues" (mean = 4.28, SD = 0.99). The message rated lowest on acceptability was "If you find it hard to remember whether you've taken your medication, buying an electronic medication dispenser could help," targeting the BCT "adding objects to the environment" (mean = 3.52, SD = 1.11).

Table 3.4. Study C acceptability ratings and study D fidelity ratings per behaviour change technique

	Study C	Study D		
Behaviour change technique	**Acceptability[a], mean (SD)**	**Fidelity[b], mean (SD)**	**Messages removed, n**	**Fidelity after exclusions[b], mean (SD)**
Action planning	3.9 (0.9)	6.9 (1.7)	4	8.0 (1.3)
Prompts/cues	3.9 (0.9)	8.2 (1.2)	1	8.4 (1.3)
Habit formation	4.0 (0.9)	7.0 (1.3)	3	7.8 (1.2)
Restructuring the physical environment	3.9 (0.8)	6.9 (1.2)	3	7.2 (2.2)
Self-monitoring of behaviour	3.9 (0.9)	8.0 (1.3)	0	—[c]
Adding objects to the environment	3.8 (0.9)	7.3 (1.7)	2	7.8 (1.8)

[a]Acceptability score ranged from 1 to 5, with higher scores indicating better acceptability.
[b]Fidelity scores ranged from 1 to 10, with higher scores indicating better fidelity to the intended behaviour change technique.
[c]No messages were removed.

3.4.4 Study D: Expert survey

Demographics: In total, 12 experts in behaviour change participated in the survey: 11 were research scientists and 1 was a research scientist and health care professional. All participants

described behaviour change interventions as central or somewhat central to their work. A total of 5 participants described medication adherence as central or somewhat central to their work. In addition, 3 participants described breast cancer as central or somewhat central to their work. The participants had been in paid research-related posts for between 5 and 16 (mean = 9.3, SD = 3.3) years and had published between 5 and 25 papers related to medication adherence, behaviour change, and/or breast cancer (median = 10.5).

Decisions for message development: We removed 13 messages because they scored below the midpoint (5.5) of fidelity to the intended BCT (scale 1-10; Table 3.4). The 2 highest-scoring messages were "If you notice your medication is low, you could leave the empty box on the kitchen table to remind you to call the pharmacy," targeting the BCT "prompts/cues" (mean = 9.25, SD = 0.87), and "As a suggestion, when you brush your teeth in the morning, follow it immediately by taking your medication," targeting the BCT "action planning" (mean = 9.25, SD = 0.75). After removing messages scoring below the fidelity threshold, the 2 messages with the lowest fidelity were "If you take your medication in different places you may be more likely to forget to take it. By leaving your tablets in one place you're less likely to forget," targeting the BCT "restructuring the physical environment" (mean = 5.58, SD = 3.26), and "If you might forget to collect your prescription, you could add an appointment into your phone calendar to remind you," targeting the BCT "adding objects to the environment" (mean = 5.58, SD = 2.81).

3.4.5 Clinical review

We removed 2 messages and amended 3 messages following the advice of a consultant pharmacist (Table 3.5). Messages related to taking the AET tablet with hot drinks were removed, as this is not recommended.

Table 3.5. Reasons for message amendments or removal following clinical review

Behaviour change technique	Message	Action	Reason	Amended message
Action planning	"If you take your medication with a hot drink in the morning, then try getting the medication when you are boiling the kettle."	Removed	Medication is recommended to be taken with a glass of water, not hot drinks.	–[a]
Habit formation	"Taking your medication can be as routine as a morning coffee. Try taking your medication at the same time in your routine so it becomes easier to remember."	Removed	Not recommended to take medication with hot drinks- message could imply this.	–
Restructuring the physical environment	"As a suggestion, always keep some spare medication in your bag/coat, just in case you realise you haven't taken them later on that day and are not at home."	Amended	Not recommended to put medication in coat pocket as it is easy to fall out.	"As a suggestion, always keep some spare medication in your bag, just in case you realise you haven't taken them later on that day and are not at home."
Prompts/cues	"If you notice your medication is low, you could leave the empty box on the kitchen table to remind you to	Amended	You need to ring the GP[b] practice for a repeat prescription, not the pharmacy.	"If you notice your medication is low, you could leave the empty box on the kitchen table to remind you to call the GP."

	call the pharmacy."			
Prompts/cues	"Notice your medication is nearly out in the evening? We suggest that you put a Post-it note on the bathroom mirror to call the pharmacy in the morning."	Amended	You need to ring the GP practice for a repeat prescription, not the pharmacy.	"Notice your medication is nearly out in the evening? We suggest that you put a Post-it note on the bathroom mirror to call the GP in the morning."

[a]Message was removed, not amended.
[b]GP: General practitioner.

3.4.6 Final pool of messages

After all the studies, a pool of 66 messages remained (examples in Appendix B.4). The full pool of messages is available to research teams upon reasonable request. All messages are 1-way and are designed to be sent by an automated message system. Overall, the messages have a readability score of 8.2 on the Flesch-Kincaid reading grade level scale, which corresponds to the reading age of an eighth grader (aged 13 years) (61).

3.5 Discussion

3.5.1 Principal findings

In 4 linked studies involving behaviour change experts and women with breast cancer, we developed a pool of 66 SMS text messages to promote habitual medication-taking. The text messages were considered acceptable to women with breast cancer and had adequate fidelity to the target BCTs. The BCTs were chosen based on habit theory to promote context-dependent repetition of medication-taking behaviours so that habits may form. Next, we will examine the extent to which these messages can support adherence to AET in women affected by breast cancer (55). If SMS text messages are effective in improving AET, they could form part of a multicomponent support program for women with breast cancer.

This study builds on previous attempts to use SMS text messaging interventions in women taking AET by developing explicitly theory-based messages. Previous SMS text messaging interventions aimed at improving AET adherence have produced equivocal findings (45-47). One trial reported statistically significant effects at 6-month follow-up (p = .03), but these effects were not sustained at 12 months (p = .62) (46). This null result at longer follow-up may be explained by the use of atheoretical, simple text prompts. Although simple prompts may be effective for short-term behaviour change, they may create reliance on the text message as a prompt. In turn, behaviour change may not be sustained upon message cessation. To address this issue, our messages encourage taking medication in the same context repeatedly to form cue-behaviour associations, in line with habit theory (28-33). Forming context-dependent associations for medication-taking can lead to sustained behaviour change even if the messages are stopped (28-33).

Our iterative text message development process using 4 interlinked studies enabled us to continually optimise the pool of messages throughout the development process. We used the key steps recommended by the intervention development guidelines (51). For example, we included stakeholder involvement at multiple points throughout the development process, drew on existing theories, and continually refined the intervention. This advances on previous interventions that tend to be limited in their reported development process and therefore lack justification for the content of the intervention. Owing to our process, our pool of text messages quantitatively demonstrated acceptability in our target population and adequate fidelity to the intended BCTs. Consequently, the messages could be used to test habit theory in future evaluations.

The final pool of text messages demonstrated prospective acceptability in women with breast cancer. This was based on a single assessment of acceptability. Our approach was effective in ensuring that no messages considered unacceptable to women with breast cancer were included in the final pool of text messages. Previous studies involving SMS text messages to support adherence to diabetes medications found prospective and experienced acceptability to be correlated (54). In the subsequent evaluation of these messages, our focus will turn to assessing experienced acceptability, including the satisfaction and usefulness of the messages when delivered over a prolonged period (54). The theoretical framework of acceptability

conceptualises acceptability as a multifaceted construct composed of 7 components and could therefore provide a useful basis for the assessment of experienced acceptability (62).

Despite our rigorous intervention development process, some key uncertainties remain. First, there are uncertainties surrounding how these text messages should be used in an intervention; which messages to use, the frequency with which messages should be sent, and the duration for which they need to be sent to support habit formation (63). Such uncertainties surrounding implementation could be explored further to build an optimal intervention using our pool of SMS text messages. Our approach to implementation, including justifications for our proposed frequency of messages, is explained elsewhere (26). Second, some messages may show fidelity to other BCTs in the BCTTv1 outside of the 6 specified BCTs they were generated to target, for example, “problem-solving” To aid transparency, the messages chosen to be used in any intervention should be coded using the BCTTv1 to reflect any additional BCTs that the messages may target (26, 48).

3.5.2 Strengths and limitations

We adapted an established approach previously used to develop SMS text messages to support diabetes self-management and demonstrated how the process can be conducted remotely (53). Our approach can act as a guide for other researchers conducting remote co-development work. However, our study had limitations. In the web-based workshop in study A, it was difficult to facilitate conversations between behaviour change experts to collaboratively generate SMS text messages as planned. Consequently, the messages were largely developed individually. To encourage more collaboration during the workshop, researchers could consider allocating a period devoted to anonymously editing other participants’ messages on the web-based platform (e.g., Padlet), which may facilitate collaboration better than discussion alone. In addition, all women (5/5, 100%) in study B and most women (49/60, 82%) in study C were of White ethnicity. This limits generalisability, as the acceptability of digital health interventions may be influenced by ethnicity and cultural norms (64). Further developmental studies are needed to explore the acceptability and appropriateness of these messages in a wider range of sociodemographic groups.

3.5.3 Conclusions

In conclusion, we conducted a series of 4 linked studies using mixed-methods to develop a pool of 66 brief messages to support medication adherence to AET in women with breast cancer. The messages were based on 6 BCTs theorised to support habit formation. The messages were rated as acceptable to women with breast cancer and showed fidelity to the intended BCTs. Further evaluation of these messages is needed to establish whether they can support medication adherence behaviours.

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Data Availability: The data generated in this series of studies are not publically available as they contain the full list of SMS messages, which have not been publically shared to protect our Intellectual Property. The data, and final list of SMS messages, are available from the corresponding author on reasonable request.

Authors' Contributions: Conceptualisation: SGS, SMCG, DPF, YKB, BG. Methodology: SMCG, SGS, DPF, YKB, NR, LHH, CP, BG, ER. Supervision: SGS, LHH, NR, DPF. Funding acquisition: SGS. Analysis: SMCG, SGS, LHH, NR, DPF, ER. Writing (original draft): SMCG. Writing (review and editing): all authors.

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Chapter 4 : Optimisation of an information leaflet to influence medication beliefs in women with breast cancer: a randomised factorial experiment

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4.1 Abstract

Background: Adherence to adjuvant endocrine therapy (AET) is low in women with breast cancer. Negative beliefs about the necessity of AET and high concerns are barriers to adherence.

Purpose: To use the multiphase optimisation strategy to optimise the content of an information leaflet intervention, to change AET beliefs.

Methods: We conducted an online screening experiment using a 2^5 factorial design to optimise the leaflet. The leaflet had five components, each with two levels: (i) diagrams about AET mechanisms (on/off); (ii) infographics displaying AET benefits (enhanced/basic); (iii) AET side-effects (enhanced/basic); (iv) answers to AET concerns (on/off); (v) breast cancer survivor (patient) input: quotes and photographs (on/off). Healthy adult women (n = 1,604), recruited via a market research company, were randomised to 1 of 32 experimental conditions, which determined the levels of components received. Participants completed the Beliefs about Medicines Questionnaire before and after viewing the leaflet.

Results: There was a significant main effect of *patient input* on beliefs about medication (β = 0.063, $p < .001$). There was one significant synergistic two-way interaction between *diagrams* and *benefits* (β = 0.047, $p = .006$), and one antagonistic two-way interaction between *diagrams* and *side-effects* (β = −0.029, $p = .093$). There was a synergistic three-way interaction between *diagrams, concerns,* and *patient input* (β = 0.029, $p = .085$), and an antagonistic four-way interaction between *diagrams, benefits, side-effects,* and *concerns* (β = −0.038, $p = .024$). In a stepped approach, we screened in four components and screened out the side-effects component.

Conclusion: The optimised leaflet did not contain enhanced AET side-effect information. Factorial experiments are efficient and effective for refining the content of information leaflet interventions.

4.2 Lay Summary

Adjuvant endocrine therapy (AET) is a medication given to women to stop breast cancer from returning. Many women do not take AET every day or stop taking it before they should. Some women do not take AET because they do not believe it will help them, or they have concerns about the side-effects. We ran an online study aiming to create the best information leaflet to help women understand how AET is helpful and to reduce their concerns. The leaflet had five sections; diagrams explaining how AET works, visual pictures of the benefits of AET, information about the side-effects, answers to common concerns, and quotes from other women with breast cancer. 1,604 healthy women filled in a questionnaire before and after looking at an information leaflet about AET. Women received different combinations of the five sections of the information leaflet. We found quotes from other women with breast cancer led to more positive beliefs about AET. Some sections of the leaflet worked better in combination, while other sections were worse in combination. Our results led us to remove the detailed side-effect information from the leaflet, as in combination with the other sections this negatively affected women's beliefs about AET.

4.3 Introduction

Breast cancer is the most common cause of cancer death in women worldwide (1). Adjuvant endocrine therapy (AET) is prescribed to women with oestrogen receptor-positive (ER+) breast cancer for 5-10 years to prevent recurrence and mortality (2-4). However, many women do not take AET as prescribed (5-7). Non-adherence to AET increases the risk of recurrence and reduces survival and quality-adjusted life years (8, 9).

Medication beliefs, in the form of low perceived personal need for AET and high concerns about AET (e.g., burden of side-effects), are associated with lower AET adherence (6, 10-16). The Necessity-Concerns Framework (NCF) suggests women weigh up their personal perceived need for AET, against their concerns in a cost-benefit analysis to decide whether to take AET (17).

An extended version of the self-regulation model of illness suggests illness representations could influence key medication beliefs regarding the necessity or concerns of medication (17, 18). For example, stronger beliefs that AET can reduce the risk of recurrence (treatment control) have been associated with increased necessity beliefs, and reduced concerns (19). Similarly, better understanding of how AET works (coherence) has been associated with fewer AET concerns, while attributing more physiological sensations (identity) to AET (e.g., side-effects) has been associated with increased AET concerns (19). It has been hypothesised that necessity and concern beliefs mediate the relationship between illness perceptions (e.g., treatment control, coherence) and medication adherence (18-20). Therefore, illness representations may be potential intervention targets, which could consequently influence necessity and concern beliefs.

There is little understanding regarding effective strategies to target medication beliefs (21-23). A randomised controlled trial (RCT) found small to moderate effect sizes on medication beliefs using a three-session cognitive behavioural approach (24). RCTs involving single intervention and control arms can tell us whether the intervention package as a whole is more effective than a comparator, but they do not provide information on which components are affecting the outcome, or whether any components are interacting. This limits our understanding of how we can effectively target medication beliefs.

Medication beliefs are complex, and therefore a multicomponent intervention may be needed to target all aspects of the construct. The multiphase optimisation strategy (MOST) is a framework used to optimise multicomponent interventions (25, 26). MOST consists of three phases. The first and final phases reflect a classical approach in which an intervention package is prepared, and then evaluated, typically with a parallel groups RCT. MOST advocates for an additional optimisation phase between the preparation and evaluation phases. In this optimisation phase, highly efficient, fully powered experimental designs are used to estimate the main and interaction effects of intervention components (27). Optimisation trials allow intervention developers to screen out components having a negative or null effect on an outcome, or that are not justified based on resource demands. This has the potential to create more effective, affordable, scalable, and efficient intervention packages (28).

We aimed to prepare and optimise an information leaflet intervention, aiming to increase necessity beliefs and reduce concerns about AET. We had three objectives: (i) to evaluate the main effects of each component of the information leaflet on beliefs about AET, (ii) to estimate interactions between components of the information leaflet on beliefs about AET, (iii) to establish an optimal combination of information leaflet components with regard to changing beliefs about AET.

4.4 Methods

4.4.1 Preparation phase: Information leaflet intervention development

As part of a wider program of research, we used intervention mapping combined with MOST to develop a written information leaflet to change AET medication beliefs (29). A written information leaflet was chosen, as it is a low-cost, implementable method that can provide accurate information about the benefits and risks of AET, which could encourage more balanced medication beliefs (30-35). We chose five distinct intervention targets, based on the NCF, self-regulation model, causal learning theory, and existing literature (17, 18, 36). Our conceptual model details how we hypothesised each component to influence medication beliefs (Figure 4.1). The content of the leaflet was developed with our patient group, consisting of five breast cancer survivors with experience taking AET, and a consultant pharmacist with clinical experience of AET. A professional design company designed the leaflet.

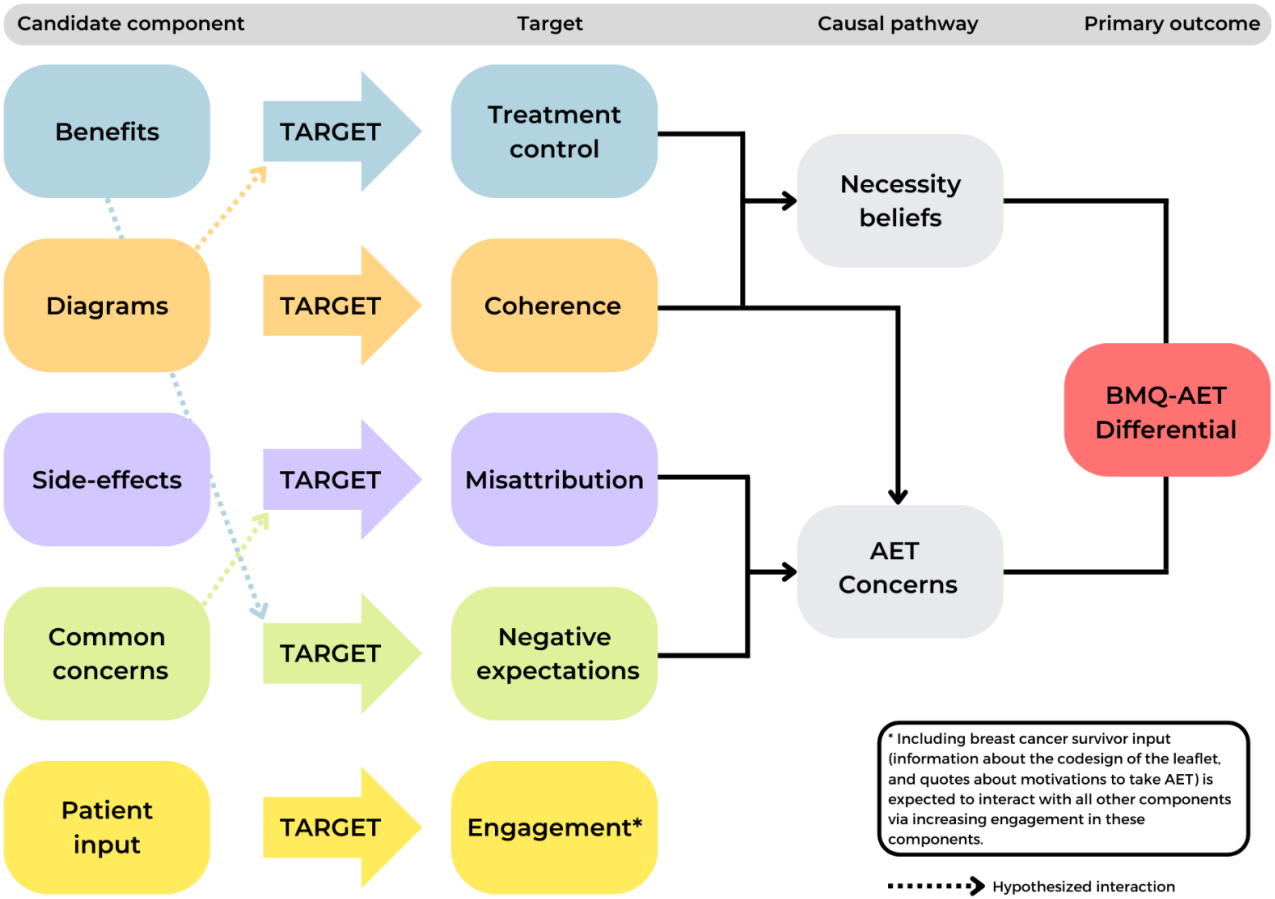

Figure 4.1. Conceptual model of information leaflet intervention

4.4.2 Optimisation phase: Randomised factorial screening experiment

4.4.2.1 Experimental design

We conducted an online, 2^5 (2x2x2x2x2) factorial experiment. The primary outcome was participant's beliefs about AET. Five candidate components were used as factors with two levels (on vs. off, or enhanced vs. basic). We randomised participants to 1 of 32 experimental conditions, which determined which levels of the components of the information leaflet participants would view (Table 4.1). Participants could receive any combination of the five components. One author (SG) created information leaflet versions corresponding to the experimental condition. A second author (SS) reviewed 20% (6 information leaflets) of the intervention information leaflets to check the correct levels of each candidate component were included. The reading level for the 32 versions of the information leaflet ranged from 6.8 to 7.6 on the Flesch-Kincaid reading grade level; between "easy to read" and "fairly easy to read" respectively (37).

Participants answered demographic questions followed by a scenario asking them to imagine they had been diagnosed with breast cancer and had been prescribed AET (Appendix C.1). This scenario aimed to reflect the information received when women are prescribed AET, and received patient input. Participants could not proceed until 30 seconds had passed to encourage them to read the scenario. Participants then completed a questionnaire regarding their beliefs about AET, before being randomised to one of 32 experimental conditions. The relevant information leaflet was displayed, and they could not proceed until three minutes had passed. Following this, participants were asked to complete the same questionnaire about their beliefs about AET. Data were collected in May 2022.

Table 4.1. Experimental conditions in 2^5 factorial design and number randomised to each condition

Condition	Constant Component	Diagrams	Benefits	Side-effects	Common concerns	Patient input	Number randomised
1	Yes	Yes	Enhanced	Enhanced	Yes	Yes	55
2	Yes	Yes	Enhanced	Enhanced	Yes	No	54
3	Yes	Yes	Enhanced	Enhanced	No	Yes	53
4	Yes	Yes	Enhanced	Enhanced	No	No	38
5	Yes	Yes	Enhanced	Basic	Yes	Yes	53
6	Yes	Yes	Enhanced	Basic	Yes	No	56
7	Yes	Yes	Enhanced	Basic	No	Yes	47
8	Yes	Yes	Enhanced	Basic	No	No	58
9	Yes	Yes	Basic	Enhanced	Yes	Yes	45
10	Yes	Yes	Basic	Enhanced	Yes	No	57
11	Yes	Yes	Basic	Enhanced	No	Yes	42
12	Yes	Yes	Basic	Enhanced	No	No	50
13	Yes	Yes	Basic	Basic	Yes	Yes	54
14	Yes	Yes	Basic	Basic	Yes	No	41
15	Yes	Yes	Basic	Basic	No	Yes	49
16	Yes	Yes	Basic	Basic	No	No	63
17	Yes	No	Enhanced	Enhanced	Yes	Yes	45
18	Yes	No	Enhanced	Enhanced	Yes	No	55
19	Yes	No	Enhanced	Enhanced	No	Yes	56
20	Yes	No	Enhanced	Enhanced	No	No	42
21	Yes	No	Enhanced	Basic	Yes	Yes	61
22	Yes	No	Enhanced	Basic	Yes	No	52
23	Yes	No	Enhanced	Basic	No	Yes	54
24	Yes	No	Enhanced	Basic	No	No	58
25	Yes	No	Basic	Enhanced	Yes	Yes	44
26	Yes	No	Basic	Enhanced	Yes	No	51
27	Yes	No	Basic	Enhanced	No	Yes	40
28	Yes	No	Basic	Enhanced	No	No	50
29	Yes	No	Basic	Basic	Yes	Yes	46
30	Yes	No	Basic	Basic	Yes	No	39
31	Yes	No	Basic	Basic	No	Yes	43
32	Yes	No	Basic	Basic	No	No	52

Note. Each component had two levels: on vs off, or enhanced vs basic.

4.4.2.2 Participants and setting

A market research company sent out the survey link to their panel of profiled respondents in the UK who have signed up to participate in market research. Participants confirmed they were female, over 18 and could read English. The market research company provided participants with a small incentive. The experiment took place online. We used a sample of healthy women as a pragmatic decision based on recruitment costs. This reflects the resource management principle in the MOST framework, which emphasises the importance of making the best use of available resources through balancing cost and scientific yield (38).

4.4.2.3 Candidate intervention components

Constant component. This information was not empirically examined, as all participants received this component. It consisted of a title page, a description of the types of AET, an explanation about how AET works, and how to take AET.

Diagrams detailing the mechanisms of AET (diagrams). Better understanding of how AET works has been associated with fewer concerns about AET (19). Visual information, in the form of medical diagrams, may aid understanding as to how a medication works and can be easier to remember (39-41). This component consisted of two levels; on, in which medical diagrams supplemented text explaining how AET works, and off, in which text alone explained the mechanisms of AET.

Information about the benefits of AET (benefits). Beliefs about treatment control have correlated negatively with medication concerns, and positively with necessity beliefs (19). Visual aids, such as icon arrays, can help readers understand information, and are helpful for those with low numeracy (42). In the enhanced level, information was provided regarding the benefits of AET, with two icon arrays to support this. In the basic level, one statement acknowledged that AET reduced the risk of recurrence and mortality.

Information about the prevalence of side-effects (side-effects). Misattributing symptoms to AET contributes to the nocebo effect, which can influence the formation of medication beliefs (31, 43-45). Displaying frequencies of side-effects using numerical values, positively framing side-effect information (e.g., 99% of people will not experience this side-effect) and informing people about the nocebo effect could lead to reduced attribution of symptoms to a medication (43, 46-48). The enhanced level details the prevalence of side-effects of AET, using

positive framing. Additional text challenges attribution of side-effects to the medication. The basic level includes a side-effect table indicating which side-effects are possible, but no information about their prevalence or attribution.

Answers to common concerns about AET (concerns). Negative expectations about a medication contribute to the nocebo effect, and have been associated with increased side-effect reporting in women taking AET (32, 44, 45). Addressing common concerns could reduce negative expectations of AET. This component is made up of answers to four common concerns informed by existing qualitative studies and suggestions from our patient group (14-16). For example, worry about not being able to cope with side-effects was addressed by suggesting that for many women side-effects are manageable, but that further support can be sought if they are disruptive. This component was either present or absent.

Input from breast cancer survivors (patient input). Narrative information, such as patient stories, can increase engagement with educational materials (49). This component comprises four quotes, photos from women with experience taking AET, and a statement highlighting the leaflet has been co-designed. This component was present or absent.

4.4.2.4 Measures

Participant characteristics. Information was collected regarding participant's age, marital status, education level, ethnicity, menopausal status, and previous breast cancer diagnoses. If participants reported a breast cancer diagnosis, they were asked the stage and whether they had ever taken AET. All participants were additionally asked whether any close relations had been diagnosed with breast cancer.

Beliefs about Medication Questionnaire- AET (BMQ-AET). The 10-item BMQ-AET was used to assess specific medication beliefs (50). Participants responded on a 5-point scale ranging from "strongly disagree" to "strongly agree". The BMQ-AET consists of two subscales; specific concerns and necessity beliefs, with five items relating to each subscale. As suggested by the authors of the original BMQ (17), and to reflect the need for a singular outcome capturing both necessity beliefs and concerns for a factorial experiment, we decided *a priori* to calculate a BMQ-AET differential score. This was calculated by subtracting concern from necessity scores (range -20 to +20).

4.4.2.5 Statistical considerations

Sample size. Sample size was calculated using the "MOST" package in R Studio (51). To detect an effect size of 0.15, with 0.9 power and alpha set to 0.1, a sample size of 1,524 was required. It was assumed that 5% of participants would enter 'nonsense' responses (defined as completing the survey in less than a third of the median time taken to complete the survey). Therefore, the sample size was increased to 1,604. The effect size chosen was based on the minimum effect of interest. Alpha was set to 0.1 rather than the traditional 0.05. This is due to the aim of this study being to screen components; incorrectly screening out and incorrectly screening in a component (the result of Type I and II error rates) are equally detrimental. This reflects the decision-priority perspective taken in the optimisation phase of MOST (52).

Randomisation. Simple randomisation was used in which each participant was randomly assigned to one of 32 experimental conditions (53). The randomisation was conducted automatically in the online survey platform, Qualtrics.

Missing data. Data for participants who did not complete the survey was not recorded. All fields in the survey were mandatory and therefore there was no missing data.

4.4.2.6 Statistical analysis

Primary analyses. The primary outcome was the BMQ-AET differential score after viewing the information leaflet. Descriptive statistics were used to summarise necessity belief, concern, and BMQ-AET differential scores overall and by component. Multiple linear regression with effect coding (-1, +1) was used to directly assess the main effects and the interaction effects of the components on the BMQ-AET differential. The model included all main effects and all interactions, and baseline BMQ-AET differential scores and age as covariates. Coefficients are reported as they originate from the model, which is half what they would traditionally be defined to be, due to the use of effect coding. Data were analysed using R Statistical Software (R version 4.2.0, 2022-04-22) (54) on an intent-to-treat basis (R packages detailed in Appendix C.2).

Sensitivity analyses. We repeated the primary analysis removing speed responders, defined as anyone who fit one of three criteria: (i) completed the whole survey in less than a third of the median time it took participants to complete the survey, (ii) answered the same response to all items in the BMQ-AET pre-test, and (iii) answered the same response to all items in the

BMQ-AET post-test. Our second sensitivity analysis removed participants who reported a diagnosis of breast cancer, to assess if decisions would change without this group. Sensitivity analysis was not conducted for only participants reporting a breast cancer diagnosis due to the low number of participants (n = 79).

Screening decisions. A decision-priority perspective was taken to select components to include in the optimised information leaflet (52). The all-active components criterion was used to make screening decisions, which is defined as the best expected outcome irrespective of cost or other constraints (52). The criteria for a component to be considered for inclusion in the optimised package was set *a priori* at $p < 0.1$ for main effects and interaction effects. Any main effects and interaction effects which were considered important (i.e., $p < 0.1$) were added into the parsimonious prediction model. Coefficients for all other effects not considered important (i.e., $p > 0.1$) were set to zero.

Decision-making followed a stepped approach (52). Following the principle of "effect hierarchy", which suggests that main effects and lower-order interaction effects are the most scientifically important, main effects were considered initially to screen components in and out (55). Decisions were reconsidered in light of interaction effects, prioritising lower-order interactions and those containing a component where a main effect was present. After considering all interactions, any components on the screened-in list were set to the higher level, and any components on the screened-out list were set to the lower level to make up the optimised information leaflet.

4.5 Results

4.5.1 Participant characteristics

A total of 1,604 participants were randomised and completed the survey. One participant was removed due to being under 18 years old (Condition 29), leaving a primary population of 1,603 participants (Table 4.2). Most women were White British (88.8%), either married or living with a partner (61.9%), and around a third (34.1%) reported degree-level education. Seventy-nine (4.9%) women had a diagnosis of breast cancer, with 67/79 (84.8%) being oestrogen or progesterone receptor-positive. Fifty-eight women were currently taking AET or had previously taken AET. Table 4.3 displays the mean beliefs about medicines scores overall and by factor.

Table 4.2. Demographics of participants

Demographics	**Total sample (n = 1,603)**
Age, mean (SD, range)	47.93 (16.29; 18-83)
Marital Status (%)	
Single	398 (24.8)
Married	749 (46.7)
Cohabiting/ living with a partner	244 (15.2)
Divorced/ separated	159 (9.9)
Widowed	53 (3.3)
Education (%)	
GCSE/O-Level/ CSE	374 (23.3)
Vocational Qualifications (NVQ1+2)	142 (8.9)
A-Level	269 (16.8)
Higher educational qualifications (below degree)	190 (11.9)
Degree-level education	547 (34.1)
Still Studying	9 (0.6)
Other	18 (1.1)
No formal qualifications	54 (3.4)
Ethnicity (%)	
Asian or Asian British	78 (4.9)
Black or Black British (African)	16 (1.0)
Black or Black British (Caribbean)	10 (0.6)
Mixed	27 (1.7)
Chinese	6 (0.4)
White British	1,424 (88.8)
Other	36 (2.3)
Do not wish to answer	6 (0.4)
Menopausal status (%)	
Premenopausal	697 (43.5)
Postmenopausal	684 (42.7)
Unsure	222 (13.9)
Previous breast cancer diagnosis (%)	79 (4.9)
Stage of breast cancer (%)[a]	
Stage 0	3 (3.8)
Stage 1	25 (31.7)
Stage 2	22 (27.8)
Stage 3	11 (13.9)
Stage 4	1 (1.3)
Unsure	17 (21.5)
ER+ Breast cancer (%)[a]	
Yes	67 (84.8)
No	12 (15.2)
Experience with AET[a]	
Currently taking	35 (44.3)
Previously taken	23 (29.1)
No experience	15 (19.0)

Demographics	**Total sample (n = 1,603)**
Unsure	6 (7.6)
Type of hormone therapy[a]	
Tamoxifen	29 (36.7)
Anastrozole	22 (27.8)
Letrozole	17 (21.5)
Exemestane	3 (3.8)
Other	1 (1.3)
Close relations experience of breast cancer	732 (45.7)
Parent	167 (10.4)
Sibling	72 (4.5)
Grandparent	114 (7.1)
Partner	15 (0.9)
Close friend	311 (19.4)
Other	143 (8.9)

[a]Percentages calculated only from those who have had breast cancer (n = 79).

Table 4.3. Descriptives for baseline and follow-up beliefs about medicines scale scores (n = 1,603)

	Baseline, mean (SD)			Follow-up, mean (SD)		
Factor level	Necessity[a]	Concerns[a]	Differential[b]	Necessity[a]	Concerns[a]	Differential[b]
Total Sample	17.99 (4.28)	16.47 (3.97)	1.52 (5.36)	18.73 (4.20)	16.43 (4.11)	2.31 (5.72)
Diagrams						
On	17.98 (4.36)	16.44 (4.03)	1.54 (5.46)	18.80 (4.27)	16.42 (4.16)	2.37 (5.93)
Off	18.00 (4.19)	16.50 (3.90)	1.50 (5.25)	18.67 (4.14)	16.43 (4.06)	2.24 (5.49)
Benefits						
On	17.99 (4.37)	16.60 (3.93)	1.39 (5.21)	18.70 (4.16)	16.54 (4.05)	2.16 (5.60)
Off	17.99 (4.18)	16.33 (4.00)	1.67 (5.52)	18.78 (4.25)	16.31 (4.17)	2.47 (5.84)
Side-effects						
On	17.94 (4.31)	16.55 (3.94)	1.39 (5.25)	18.75 (4.21)	16.53 (4.00)	2.22 (5.51)
Off	18.04 (4.25)	16.39 (4.00)	1.64 (5.46)	18.71 (4.20)	16.33 (4.21)	2.38 (5.91)
Concerns						
On	17.88 (4.38)	16.34 (4.01)	1.54 (5.23)	18.60 (4.26)	16.27 (4.10)	2.33 (5.47)
Off	18.10 (4.17)	16.60 (3.92)	1.50 (5.49)	18.87 (4.14)	16.59 (4.11)	2.28 (5.96)
Patient						
On	18.09 (4.27)	16.51 (3.95)	1.59 (5.44)	18.94 (4.26)	16.22 (4.08)	2.72 (5.74)
Off	17.89 (4.28)	16.43 (3.98)	1.46 (5.29)	18.54 (4.14)	16.63 (4.13)	1.91 (5.67)

[a]Possible range: 5-25

[b]Possible range: -20 to +20

4.5.2 Engagement

The median time to complete the survey was 9.45 minutes (range = 4.87 to 85.25 minutes). The median time spent looking at the information leaflet (including the compulsory 3 minutes) ranged from 3.10 minutes (range = 3.02-29.28 minutes) in Condition 16, to 3.58 minutes in Condition 12 (range = 3.02- 37.67 minutes) (Appendix C.3).

4.5.3 Optimisation experiment

The number of participants randomised to each of the 32 conditions ranged from 38 to 63 (Table 4.1). One component, *patient input,* had a statistically significant positive main effect on beliefs about AET (β = 0.063, 90% CI 0.035, 0.091, $p < .001$) (Table 4.4). There was one significant synergistic two-way interaction: *diagrams × benefits* (β = 0.047, 90% CI 0.019, 0.075, $p = .006$), in which the effect of *diagrams* was greater when *benefits* was enhanced. There was an antagonistic two-way interaction: *diagrams × side-effects* (β = −0.029, 90% CI −0.056, −0.001, $p = .093$), in which the effect of *diagrams* was reduced when *side-effects* was enhanced. There was a synergistic three-way interaction: *diagrams × concerns × patient input* (β = 0.029, 90% CI 0.001, 0.057, $p = .085$), in which the presence of all three components set to on/enhanced was greater than would be expected from each component alone. Finally, there was an antagonistic four-way interaction: *diagrams × benefits × side-effects × concerns* (β = −0.038, 90% CI −0.066, −0.010, $p = .024$), in which *side-effects* being enhanced reduced the effect of *diagrams, benefits, and concerns* (Figures 4.2-4.5).

Based on this analysis, we constructed the parsimonious prediction model, containing only main effects and interactions meeting the threshold for importance ($p < .1$). Due to imbalance in the number of participants across conditions, the analysis was repeated including only the main effects and interactions of importance, and the covariates, baseline BMQ-AET and age (52). There was minimal change in the coefficient values (Table 4.4).

Table 4.4. Multiple linear regression showing the effect of candidate components on beliefs about AET

		Full regression model				*Parsimonious prediction model*			
		b-weight	**β (90% CI)**	***t***	***p***	**b-weight**	**β (90% CI)**	***t***	***p***
	Intercept	2.322		23.989	**<0.001**	2.319		24.219	**<0.001**
Main effects	Diagrams (D)	0.028	0.005 (-0.023, 0.033)	0.293	0.770				
	Benefits (B)	−0.047	−0.008 (−0.036, 0.020)	−0.486	0.627				
	Side-effects (SE)	0.018	0.003 (−0.025, 0.031)	0.185	0.853				
	Concerns (C)	−0.005	<0.001 (−0.029, 0.027)	−0.055	0.956				
	Patient (P)	0.362	0.063 (0.035, 0.091)	3.740	**<0.001**	0.361	0.063 (0.036, 0.091)	3.773	**<0.001**
Interactions	D × B	0.267	0.047 (0.019, 0.075)	2.757	**0.006**	0.266	0.047 (0.019, 0.074)	2.770	**0.006**
	D × SE	−0.163	−0.029 (−0.056, −0.001)	−1.683	**0.093**	−0.163	−0.028 (−0.056, −0.001)	−1.693	**0.091**
	B × SE	−0.102	−0.018 (−0.046, 0.010)	−1.051	0.293				
	D × C	0.031	0.005 (−0.022, 0.033)	0.324	0.746				
	B × C	−0.080	−0.014 (−0.042, 0.014)	−0.826	0.409				
	SE × C	−0.072	−0.013 (−0.040, 0.015)	−0.745	0.456				
	D × P	0.134	0.023 (−0.005, 0.051)	1.380	0.168				
	B × P	0.002	<0.001 (−0.028, 0.028)	0.022	0.983				
	SE × P	−0.121	−0.021 (−0.049, 0.007)	−1.253	0.210				
	C × P	−0.035	−0.006 (−0.034, 0.022)	−0.357	0.721				
	D × B × SE	−0.045	−0.008 (−0.036, 0.020)	−0.462	0.644				
	D × B × C	−0.042	−0.007 (−0.035, 0.021)	−0.437	0.663				
	D × SE × C	0.144	0.025 (−0.003, 0.053)	1.484	0.138				
	B × SE × C	0.032	0.006 (−0.022, 0.033)	0.327	0.744				
	D × B × P	0.086	0.015 (−0.013, 0.043)	0.888	0.375				
	D × SE × P	0.130	0.023 (−0.005, 0.051)	1.344	0.179				
	B × SE × P	0.061	0.011 (−0.017, 0.039)	0.632	0.527				
	D × C × P	0.167	0.029 (0.001, 0.057)	1.726	**0.085**	0.160	0.028 (0.000, 0.056)	1.664	**0.096**
	B × C × P	0.047	0.008 (−0.020, 0.036)	0.481	0.630				

	SE × C × P	−0.002	<0.001 (−0.028, 0.027)	−0.025	0.980				
	D × B × SE × C	−0.219	−0.038 (−0.066, −0.010)	−2.261	**0.024**	−0.224	−0.039 (−0.067, −0.012)	−2.332	**0.020**
	D × B × SE × P	−0.096	−0.017 (−0.045, 0.011)	−0.987	0.324				
	D × B × C × P	−0.157	−0.027 (−0.055, 0.001)	−1.614	0.107				
	D × SE × C × P	0.070	0.012 (−0.016, 0.040)	0.724	0.469				
	B × SE × C × P	0.107	0.019 (−0.009, 0.047)	1.105	0.269				
	D × B × SE × C × P	0.095	0.017 (−0.011, 0.045)	0.980	0.327				
Covariates	Baseline BMQ-AET	0.784	0.735 (0.707, 0.763)	42.842	**<0.001**	0.785	0.736 (0.708, 0.764)	43.291	**<0.001**
	Age	0.003	0.010 (−0.018, 0.038)	0.575	0.566	0.005	0.014 (−0.014, 0.042)	0.846	0.397

Note. Bold text indicates statistical significance ($p < 0.1$)

n = 1,603

Key: BMQ = Beliefs about medicines questionnaire.

4.5.4 Decision-making

Initially, the only component with an important main effect, *patient input,* was screened in. We then reconsidered the screened-in and -out lists based on the important interaction effects ($p < .1$). We examined the three-way *diagrams × concerns × patient input* interaction first, as this contained a component with a main effect (*patient input*). When *patient input* was set to on, the effect of *concerns* was higher when *diagrams* was also set to on. Setting all three components to the higher levels had the optimum effect (Figure 4.2). Therefore, *concerns* and *diagrams* were screened in.

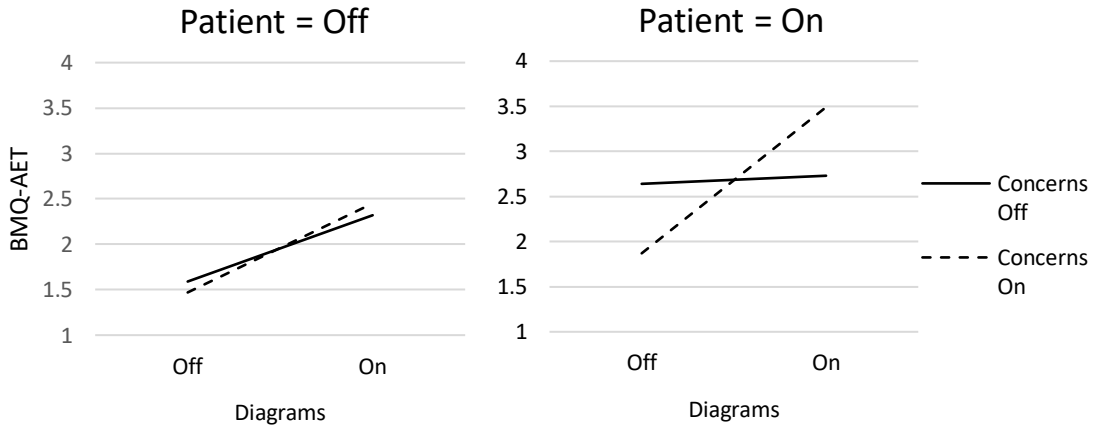

Figure 4.2. Three-way synergistic interaction between *patient input, diagrams*, and *concerns* components

Next, we examined the *diagrams × benefits* interaction (Figure 4.3). There was a significant synergistic interaction in which the effect of *diagrams* was increased when *benefits* was set to on. The optimum effect occurred when either both components were set to the higher or lower level. As *diagrams* was screened in previously, it was more beneficial to screen in *benefits*, rather than screen out both *benefits* and *diagrams*.

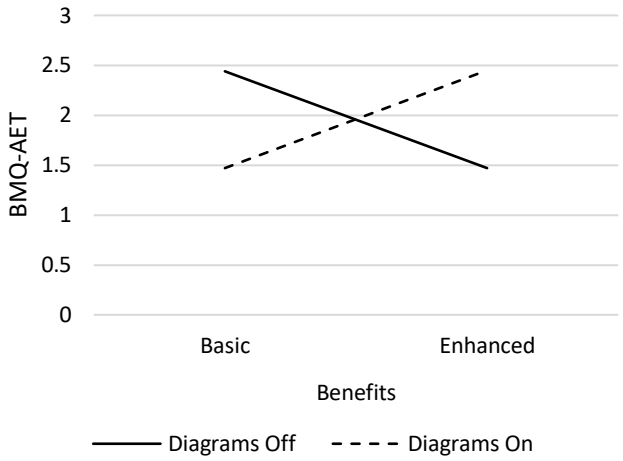

Figure 4.3. Two-way synergistic interaction between *benefits* and *diagrams* components

The antagonistic *diagrams × side-effects* interaction highlights the effect of *diagrams* was reduced when *side-effects* was set to the higher level (Figure 4.4). When both components were set to the higher level, the BMQ-AET differential was smaller than would be expected with no interaction. Therefore, *side-effects* remained screened out.

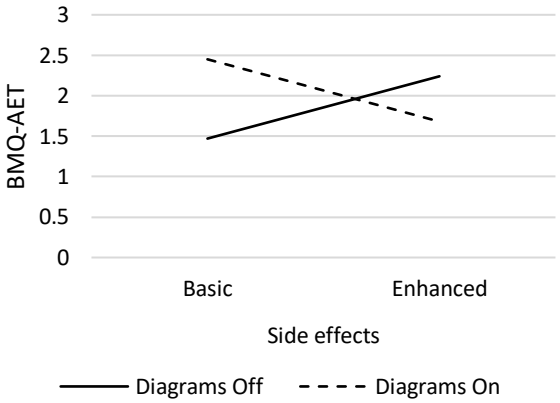

Figure 4.4. Two-way antagonistic interaction between *diagrams* and *side-effects* components

Finally, we examined the four-way *diagrams × benefits × side-effects* × *concerns* interaction (Figure 4.5). Here we examined what effect *side-effects* would have when all other components involved are set to the higher levels, as this reflected the screened-in and screened-out list at this stage. When *diagrams, benefits,* and *concerns* were set to their higher levels, *side-effects* being set to the higher level diminished the effect. Therefore, *side-effects*

remained screened out, meaning the basic level of *side-effects* was included in the optimised information leaflet.

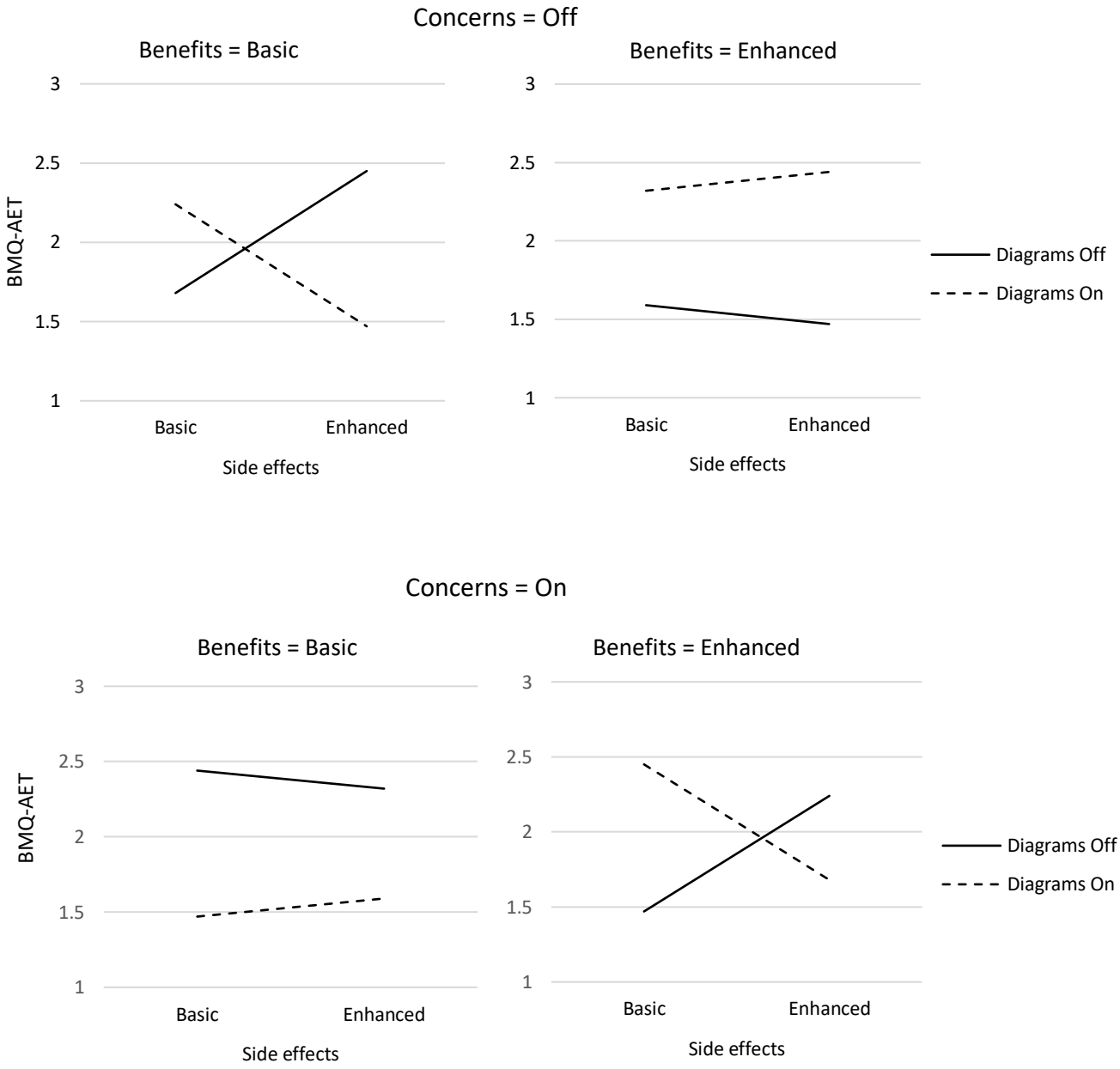

Figure 4.5. Four-way antagonistic interaction between *benefits, diagrams, concerns* and *side-effects* components

Table 4.5 lists the predicted outcomes for $\hat{Y}_{Beliefs}$ for all 16 conditions reflecting all combinations of the four screened-in components, computed using the expression for the parsimonious prediction model. Condition 5 had the greatest $\hat{Y}_{Beliefs}$ value, which represents

diagrams, benefits, concerns, and *patient input* being screened in, and *side-effects* screened out.

Table 4.5. Predicted beliefs about medications scores for each condition

Condition	Side-effects	Diagrams	Benefits	Concerns	Patient	$\hat{Y}_{Beliefs}$[a]	$\hat{Y}_{Beliefs}$[b]
5	**Basic**	**On**	**Enhanced**	**On**	**On**	**2.524**	**4.315**
6	Basic	On	Enhanced	On	Off	2.342	4.133
7	Basic	On	Enhanced	Off	On	2.390	4.181
8	Basic	On	Enhanced	Off	Off	2.320	4.111
13	Basic	On	Low	On	On	2.352	4.143
14	Basic	On	Low	On	Off	2.170	3.961
15	Basic	On	Low	Off	On	2.374	4.165
16	Basic	On	Low	Off	Off	2.304	4.095
21	Basic	Off	Enhanced	On	On	2.240	4.031
22	Basic	Off	Enhanced	On	Off	2.170	3.961
23	Basic	Off	Enhanced	Off	On	2.374	4.165
24	Basic	Off	Enhanced	Off	Off	2.192	3.983
29	Basic	Off	Low	On	On	2.412	4.203
30	Basic	Off	Low	On	Off	2.342	4.133
31	Basic	Off	Low	Off	On	2.390	4.181
32	Basic	Off	Low	Off	Off	2.208	3.999

[a]Predicted values calculated for the parsimonious model without covariates.
[b]Predicted values calculated for the parsimonious model with covariates.

4.5.5 Sensitivity analyses

When removing speed responders (n = 153), the results were consistent with the primary analysis (Appendix C.4.1). The only important effect to change was the three-way *diagrams × concerns × patient input* interaction which became non-significant (p = .103), but this did not impact which components were screened out. Demographic and clinical characteristics were comparable between women with and without breast cancer (Appendix C.4.2). There was no significant difference in baseline BMQ-AET differential scores between women with breast cancer (M = 2.19, SD = 5.93) and women without breast cancer (M = 1.49, SD = 5.33), $t(1,601) = 1.14$, p = .259. Women with breast cancer had significantly higher baseline necessity beliefs (M = 18.92, SD = 4.27) than those without breast cancer (M = 17.94, SD = 4.27), $t(1,601) = 1.99$, p = .047 (Appendix C.4.3). When removing participants reporting a diagnosis of breast cancer (n = 79), results were consistent with the primary analysis and decision-making did not change (Appendix C.4.4).

4.6 Discussion

Using an online factorial screening experiment, we optimised an information leaflet intervention to increase beliefs about the necessity of AET and reduce concerns about AET. The optimised information leaflet contained four out of five of the candidate components; diagrams explaining how AET works *(diagrams)*, icon arrays explaining the benefits of AET *(benefits)*, answers to common concerns about AET *(concerns),* and quotes and photographs of breast cancer survivors explaining their motivations for taking AET *(patient input)*. The side-effect component *(side-effects)* was screened out due to interacting negatively with the other candidate components. The optimisation process led to development of a more efficient and effective information leaflet.

We have demonstrated that it is feasible and beneficial to optimise an information leaflet using an online factorial experiment. Compared with a classical approach (i.e., using an RCT to evaluate the leaflet as a package), the optimisation phase provided an insight into the contributions of individual components of the leaflet in isolation and combined. From this, we know that the leaflet supports medication beliefs, which is a known barrier to AET adherence (6, 10-16). The resulting leaflet is optimised to increase efficiency (e.g., redundant components are not included) and effectiveness (e.g., only components reaching an *a priori* statistical significance are included).

The strategies we tested appear to be effective in changing medication beliefs, which builds on the limited existing evidence. These strategies could be applied in other contexts where medication beliefs are a barrier to adherence behaviours. However, our results suggest these strategies had more impact on increasing necessity beliefs than reducing concerns. While this was still effective in improving the cost-benefit analysis (differential) which has been found to be a more consistent predictor of non-adherence than necessity beliefs or concerns alone (56), future research could focus on developing components to better reduce concerns.

The patient input component was the only candidate component to demonstrate a main effect on beliefs about AET. In our conceptual model, we hypothesised that this component would interact with all other components, but it did not interact with the side-effects and benefits components. The main effect suggests that the patient-input component has an alternative mechanism for affecting beliefs about AET. One explanation is that the content of

the quotes could have led to social comparison; in which participants may have adapted their beliefs after comparing with others, which is common in a state of uncertainty (57, 58). Information about the main effects and interaction effects obtained in an optimisation experiment enables refinement of our conceptual model and understanding of how interventions may work.

The only candidate component screened out of the optimised information leaflet was the side-effects component. Informing participants of the nocebo effect (suggesting that not all physiological sensations may be caused by AET), and providing positively framed side-effect information did not affect medication beliefs, and interacted negatively with the diagrams, benefits and concerns components. The lower level of this component could have provided the "gist" of the information sufficiently (i.e., the bottom line meaning that different side-effects are possible for different types of AET). According to Fuzzy Trace Theory, health information may be encoded in two ways; a gist representation (the essence of the information), and a verbatim representation (literal, precise information e.g., specific statistics) (59). When making decisions, people tend to prefer to rely on the gist representation (59, 60). In this case, the lower level of the side-effect component may have been enough to form this gist-based representation, meaning the enhanced level of the component was redundant. Alternatively, participants may not have understood the enhanced side-effect information, or a written intervention may not be sufficient to reduce concerns. Screening out the enhanced side-effect component led to a more efficient information leaflet, with redundant information removed. Future work could explore alternative methods to reduce concerns further.

The synergistic interaction between the diagrams and benefits components was the only hypothesised interaction evident in our data. The lack of main effect but the presence of a synergistic interaction indicates these components only work together. Understanding how a medication works via the diagrams component may increase understanding and belief in the benefits of AET (61). Therefore, it may be appropriate to combine these components into a single, more robust component (52).

Our study had limitations. Women with breast cancer reported significantly higher necessity beliefs at baseline than women without breast cancer (Appendix C.4.3), which could limit the generalisability of the findings to women with breast cancer. However, the concerns and

differential scores were not significantly different between women with and without breast cancer at baseline or follow-up (Appendix C.4.3). BMQ-AET scores for the total sample and breast cancer subsample were comparable to previous published studies conducted with women with breast cancer (34, 62). Further evaluation of the leaflet will be conducted in women with breast cancer. The majority of participants were White British and had higher level educational qualifications. A more diverse sample may have generated different findings that reflected a different optimal combination of components. As a result of using simple randomisation, the number of participants in each experimental condition was not balanced which will have reduced statistical power. We optimised an information leaflet based on one singular outcome, but other outcomes could also be considered, such as women's satisfaction with the information they receive. Further work is needed to explore optimisation with multiple outcomes of interest. To limit the length of the survey, we did not include assessments of each component target (e.g., coherence). Future optimisation studies could include these assessments to enable causal pathway analyses to enhance our understanding of the underlying mechanisms of action (63).

We used a rigorous approach to optimise an information leaflet to increase necessity beliefs and reduce concerns in women taking AET. Our approach has enabled refinement of our conceptual model, and has led to the development of a more efficient information leaflet, removing components that are negatively impacting the outcome. Factorial experimental designs offer a highly efficient way of optimising multicomponent intervention packages such as information leaflets**.** Optimisation, guided by MOST, can enhance our overall understanding of behavioural interventions.

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Materials availability: Materials used to conduct the study may be available by emailing the corresponding author.

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Chapter 5 : Acceptability of four intervention components supporting medication adherence in women with breast cancer: A process evaluation of a fractional factorial pilot optimisation trial

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[4] **Note:** The intervention components developed in previous chapters were included in a pilot optimisation trial. I did not lead the pilot optimisation trial, and therefore it is not included as part of this thesis. I led the process evaluation of the pilot optimisation trial which is presented in Study Four.

5.1 Abstract

Background: Adjuvant endocrine therapy (AET) reduces mortality risk in early-stage breast cancer, but adherence is low. We developed a multicomponent intervention to support AET adherence comprising: text messages; information leaflet; acceptance and commitment therapy (ACT); side-effect management website. Guided by the multiphase optimisation strategy, the intervention components were tested in the ROSETA pilot optimisation trial. Our mixed-methods process evaluation investigated component acceptability.

Methods: The pilot optimisation trial used a 2^{4-1} fractional factorial design. Fifty-two women with breast cancer prescribed AET were randomised to one of eight experimental conditions, each containing a unique combination of components. An acceptability questionnaire was administered four months post-randomisation, and semi-structured interviews with 20 participants further explored acceptability. Assessments were guided by four domains of the theoretical framework of acceptability; affective attitude, burden, perceived effectiveness, and coherence. Quantitative and qualitative findings were triangulated to identify agreements/disagreements.

Results: There were high overall acceptability scores across components (median = 14-15/20, range = 11-20). Overall there was agreement between the qualitative and quantitative findings when triangulated. Most participants 'liked' or 'strongly liked' all components, and reported they generally required low effort to engage in. Perceived effectiveness was mixed, with 35.0% (text messages) to 55.6% (ACT) of participants 'agreeing' or 'strongly agreeing' that each component would improve their adherence. Interview data provided suggestions to improve acceptability.

Conclusion: The four components were acceptable to women with breast cancer, and will be refined prior to a full optimisation trial. Mixed-methods and triangulation were useful methodological approaches and could be applied in other optimisation trial process evaluations.

5.2 Introduction

Women with early-stage (I to III) hormone receptor-positive breast cancer are prescribed adjuvant endocrine therapy (AET) for 5-10 years to reduce the risk of breast cancer recurrence and mortality (1, 2). However, non-adherence is present in up to three-quarters of women (3-5), which increases risk of recurrence and reduces quality-adjusted life years (6-8). The most recent meta-analysis of interventions to support AET adherence found a small overall significant effect on adherence (9). However, several limitations with existing research were identified; the frequent use of educational interventions that are unlikely to be sufficient to change behaviour when used alone, the limited use of theory to guide intervention development and the lack of focus on key barriers to adherence. This meta-analysis identified little progress in improving effectiveness of interventions to support AET adherence over time, possibly due to limited understanding of which intervention components contribute to effectiveness (9).

As part of the 'Refining and Optimising a behavioural intervention to Support Endocrine Therapy Adherence' (ROSETA) program, we developed four theory-informed intervention components that aimed to target key barriers to AET adherence (10). The ROSETA program is guided by the Multiphase Optimisation Strategy (MOST), an engineering inspired framework to optimise multicomponent behavioural interventions (11, 12). The MOST framework consists of three phases: preparation, optimisation, and evaluation (11). In the preparation and evaluation phases, intervention components are typically developed and tested for feasibility and evaluated as a package against a suitable comparator, often using a parallel group randomised controlled trial (RCT). The MOST framework advocates for an additional optimisation phase between preparation and evaluation. In this optimisation phase, efficient, fully powered experimental designs are used to estimate main and interaction effects of intervention components (11). These effect estimates can be used to build an optimal intervention package within set constraints, such as time or cost (11, 13-15). The optimisation phase aims to balance the effectiveness of an intervention with affordability, scalability and efficiency.

In the preparation phase of MOST, we conducted an external, multi-centre exploratory pilot optimisation trial, using a highly efficient 2^{4-1} fractional factorial design (11-13, 16). In this pilot trial we assessed the feasibility of undertaking a fully powered optimisation trial, and the acceptability of intervention components (ISRCTN: 10487576) (16). Participants were randomised to one of eight experimental conditions which determined the unique combination of components they received. Each intervention component had two levels: 'on' or 'off.' Participants received usual care plus a combination of the four intervention components (Table 5.1). In total, 52 adult women with stage I-IIIa breast cancer taking AET across five UK hospital sites were randomised. Participants were followed up at 2- and 4-months post-randomisation. Progression to a full optimisation trial is based on criteria regarding consent rates, intervention component adherence and availability of outcome data (16).

Medical Research Council guidance for developing and evaluating complex interventions and process evaluations suggests assessing acceptability in the feasibility stage of intervention development (17, 18). During the feasibility phase, quantitative and qualitative assessments of acceptability can inform potential adaptations and improvements to intervention components prior to further evaluation (18-20). Improving acceptability is beneficial at this stage, as greater adherence is more likely with an acceptable intervention (19). In this process evaluation of the ROSETA pilot optimisation trial, we assessed the acceptability of the four intervention components, to identify any necessary adaptions prior to further evaluation.

Table 5.1. Experimental conditions in ROSETA pilot trial

Condition	Usual Care	SMS	Information leaflet	ACT	Website	Randomised, n = 52	Interviewed, n = 20
1	Yes	Yes	Yes	Yes	Yes	8	1
2	Yes	Yes	Yes	No	No	7	4
3	Yes	Yes	No	Yes	No	7	3
4	Yes	Yes	No	No	Yes	6	2
5	Yes	No	Yes	Yes	No	6	3
6	Yes	No	Yes	No	Yes	6	1
7	Yes	No	No	Yes	Yes	6	3
8	Yes	No	No	No	No	6	3

Key: ROSETA = Refining and optimising a behavioural intervention to support endocrine therapy adherence. SMS = Short message service. ACT = Acceptance and commitment therapy.

5.3 Methods

5.3.1 Design

We used quantitative and qualitative methods to assess the acceptability of each intervention component, guided by the Theoretical Framework of Acceptability (TFA), which defines acceptability as being composed of seven constructs (19). The seven constructs are (1) affective attitude; *how an individual feels about the intervention*; (2) burden; *perceived amount of effort required to participate in the intervention*; (3) ethicality; *extent to which the intervention has a good fit with an individual's value system*; (4) intervention coherence; *the extent to which the participant understands the intervention and how it works*; (5) opportunity costs; *the extent to which benefits, profits or values must be given up to engage in the intervention*; (6) perceived effectiveness; *the extent to which the intervention is perceived as likely to achieve its purpose*; and (7) self-efficacy; *the participant's confidence that they can perform the behaviour(s) required* (19).

For the quantitative assessment, all trial participants were invited to complete an adapted version of the general acceptability questionnaire four months post-randomisation (20). The qualitative assessment involved a semi-structured interview with a sub-sample of trial participants, which took place at least four months post-randomisation. The interview focused on acceptability of the intervention components, in addition to fidelity and trial experience related to the wider aims of the process evaluation (21). As an additional indicator

of acceptability, withdrawals from intervention components were recorded, together with the reason for withdrawal (where available).

5.3.2 Intervention components

The four intervention components assessed for acceptability were: (1) SMS messages to target forgetfulness; (2) an information leaflet to increase beliefs about the necessity of AET and reduce concerns; (3) acceptance and commitment therapy (ACT) based guided self-help to increase psychological flexibility and reduce psychological distress, and (4) a side-effect self-management website to support management of AET side-effects (Table 5.2).

Table 5.2. Summary of intervention components in the ROSETA pilot trial

Component	Target	Description
SMS	Forgetfulness/habit formation	SMS messages were sent over 4 months providing practical strategies to support regular medication-taking each day. The messages were sent daily for two weeks, twice weekly for 8 weeks and weekly for 6 weeks.
Information Leaflet	Medication beliefs	A written information leaflet containing five elements; an explanation of how AET works with diagrams to supplement, visual displays of the benefits of AET, accurate information about the side-effects of AET, answers to common concerns about AET and quotes and pictures of breast cancer survivors.
ACT	Psychological flexibility/psychological distress	A guided self-help intervention based on ACT principles involving four skills; mindfulness, unhooking, following values and living beyond labels. The modules consist of a participant booklet, home practice tasks and audio files. The modules are supported by five individual sessions with a psychologist; 1 x 15 minute opening session, 3 x 25 minute sessions following modules 1, 2 and 3, and 1 x 15 minute closing session following module 4.
Website	Side-effect self-management	A website containing strategies to self-manage common AET side-effects including; arthralgia, fatigue, vulvovaginal symptoms, gastrointestinal symptoms, hot flushes, sleep difficulties. The website uses a rating system to summarise the strength of evidence for each strategy.

Key: ROSETA = Refining and optimising a behavioural intervention to support endocrine therapy adherence. SMS = Short message service. AET = Adjuvant endocrine therapy. ACT = Acceptance and commitment therapy.
This table is taken, with permission, from Green et al., (21)

5.3.3 Participants

Participants were recruited from five UK NHS hospitals. All participants were women, over 18, taking AET (tamoxifen, raloxifene, anastrozole, letrozole or exemestane) for early-stage (I to IIIa) breast cancer who had completed their last hospital treatment in the previous 12 months. Full eligibility criteria and recruitment methods are available in the published protocol (16).

5.3.4 Procedure

5.3.4.1 Quantitative assessment measures

A validated acceptability questionnaire (AQ) based on the TFA was used to assess intervention component acceptability (20). We removed three constructs of acceptability (ethicality, self-efficacy and opportunity cost) we deemed less relevant, to reduce participant burden. The remaining four constructs (affective attitude, burden, perceived effectiveness, and intervention coherence) and general acceptability were assessed via five items. Participants answered on a 5-point Likert scale, with higher scores indicating greater acceptability for all items except for burden, whereby a lower score indicated greater acceptability.

All trial participants were sent a link to complete the questionnaire at four months post-randomisation. Non-respondents were prompted via email after one week and via phone after two weeks. Participants were given a separate AQ specific to each intervention component they had been randomised to receive. Where a participant was randomised to receive the ACT component, they were asked 15 extra items specifically about the individual ACT modules and elements of the ACT component (e.g., support sessions, home practice tasks). Participants randomised to the SMS component were asked one additional item regarding the frequency of the SMS messages.

5.3.4.2 Qualitative interviews

All participants willing to be contacted about an optional interview were emailed with further information about the interview and a consent form approximately three months post-randomisation. Non-respondents were prompted via phone and/or email after one week. Participants either returned a written consent form, or a time was arranged to take consent over the phone.

Semi-structured interviews investigated the acceptability of each intervention component relating to TFA constructs (19). The same TFA constructs were included as the quantitative assessment; affective attitude, burden, perceived effectiveness and intervention coherence. The interview schedule was developed with input from our patient and public involvement group consisting of five women with experience of taking AET (available at https://doi.org/10.17605/OSF.IO/8DWRN). The interview schedule was used as a guide, with flexibility in the order of questions asked and follow-up questions, guided by participant responses. We used a rapid qualitative analysis approach to allow findings to be communicated quickly to inform the next phase of the research (22, 23). All interviews were conducted via telephone or Microsoft Teams and were recorded either using an encrypted Dictaphone or inbuilt recording software in Microsoft Teams. Interviews took place between December 2022 and April 2023. All interviews were conducted by a researcher (SG) with experience in conducting qualitative interviews.

Due to the digital nature of the intervention components, we aimed to interview a mix of participants above and below 50 years old. We planned to cease interviewing once we felt the sample held sufficient information power: a concept which suggests data collection should stop when the collected data is sufficiently 'information-rich' (24). Continuation of data collection and information power was discussed at regular team meetings. As the number of participants recruited to the ROSETA pilot trial was lower than expected (80 planned, 52 participants randomised, due to a limited recruitment period and low volume of patients eligible to be approached), sampling was opportunistic, as we invited all consenting participants to be interviewed.

5.3.5 Data analysis

A quantitative analysis plan was pre-specified prior to qualitative analyses commencing. Qualitative analyses were completed before quantitative analyses began, both led by one author (SG).

5.3.5.1 Qualitative analysis

The TFA guided our deductive approach to analysis. The interviewer (SG) took notes during each interview and completed a Rapid Research Evaluation and Appraisal Lab Rapid Assessment Procedure (RAP) sheet for each individual participant immediately following the

interview (22, 23, 25). The RAP sheet was a two-column table based on the TFA (Appendix D.1). RAP sheets were collated into four higher level RAP sheets: one per intervention component.

For interviews taking place on Microsoft Teams, quotes were taken directly from the inbuilt transcript and added to individual and higher-level RAP sheets. Telephone interviews were recorded using an encrypted Dictaphone. After each interview, SG transcribed specific sections of the interview considered important to the research question and added these quotes to the individual and higher-level RAP sheets. Throughout the data collection period, members of the research team (SG, SS, LH and CG) met monthly (approximately after 4-5 new interviews had taken place) for the purpose of rapid qualitative analysis. We discussed key findings, adaptations to be made to the intervention components, and any areas to prioritise and explore in upcoming interviews.

5.3.5.2 Quantitative analysis

We used descriptive statistics to summarise each individual construct on the AQ, and for additional items relating to the ACT and SMS components. An overall acceptability score was calculated by summing items relating to the TFA constructs affective attitude, burden (reverse coded), perceived effectiveness, and coherence. Missing data were summarised descriptively and were not included in the overall acceptability score calculation.

5.3.5.3 Triangulation of quantitative and qualitative findings

Once qualitative and quantitative analyses were complete, findings were triangulated (26, 27). Quantitative findings were summarised into qualitative statements to aid comparison with qualitative findings. All statements were generated by one author (SG). For each of the four TFA constructs used (affective attitude, burden, perceived effectiveness, and coherence), key findings from the quantitative and qualitative data were compared for each intervention component. The relationship between the qualitative and quantitative data was marked as either silence (only one data set contained information on a topic), dissonant (conflicting findings), partial agreement (datasets provide complementary findings on a topic) or agreement (full convergence in the data). Two authors (SG and KL) triangulated the findings independently and resolved any disagreements through discussion.

5.4 Results

A total of 141 patients were eligible, of which 52 (36.9%) participants were randomised in the ROSETA pilot trial (Table 5.1). Participants had a mean age of 55.2 (SD = 10.8), most (86.5%) were of White ethnicity, and a third (32.7%) had degree level education or above (Table 5.3). Twenty-one (42.0%) participants had stage I breast cancer, 23 (36.0%) had stage II breast cancer, and 6 (12.0%) had stage IIIA breast cancer. Of the 52 participants, 28 were randomised to receive the SMS component, 27 to the information leaflet, 27 to the ACT component, and 26 to the website (Table 5.1). Rates of completion for the AQs were 71.4% (n = 20) for the SMS component, 74.1% (n = 20) for the information leaflet, 70.4% (n = 19) for the ACT component and 73.1% (n = 19) for the website. The quantitative assessment of acceptability for each intervention component is summarised in Table 5.4.

Table 5.3. Participant demographics

Demographics		**Component**				
	Overall, n = 52	SMS, n = 28	Leaflet, n = 27	ACT, n = 27	Website, n = 26	Interview sample, n = 20
Age, mean (SD)	55.2 (10.8)	52.5 (12.4)	56.1 (12.1)	55.4 (11.0)	54.1 (12.0)	57.7 (8.34)
Marital Status, n(%)						
Married	32 (61.5)	16 (57.1)	16 (59.3)	17 (63.0)	15 (15.7)	16 (80.0)
Single	6 (11.5)	3 (10.7)	3 (11.1)	3 (11.1)	3 (11.5)	2 (10.0)
Living with a partner	5 (9.6)	4 (14.3)	2 (7.4)	3 (11.1)	3 (11.5)	1 (5.0)
Divorced or separated	7 (13.5)	4 (14.3)	5 (18.5)	3 (11.1)	4 (15.4)	1 (5.0)
Widowed	2 (3.8)	1 (3.6)	1 (3.7)	1 (3.7)	1 (3.8)	0 (0.0)
Employment status, n(%)						
Full time	22 (42.3)	9 (32.1)	9 (33.3)	13 (48.1)	9 (34.6)	9 (45.0)
Part time	9 (17.3)	7 (25.0)	6 (22.2)	2 (7.4)	3 (11.5)	4 (20.0)
Not currently working	9 (17.3)	5 (17.9)	3 (11.1)	6 (22.2)	6 (23.1)	1 (5.0)
Other	12 (23.1)	7 (25.0)	9 (33.3)	6 (22.2)	8 (30.8)	6 (30.0)
Education, n(%)						
Postgraduate qualification	7 (13.5)	5 (17.9)	5 (18.5)	4 (14.8)	4 (15.4)	3 (15.0)
Degree level education	10 (19.2)	7 (25.0)	4 (14.8)	4 (14.8)	3 (11.5)	6 (30.0)
Higher educational qualifications (below degree)	12 (23.1)	5 (17.9)	6 (22.2)	7 (25.9)	6 (23.1)	6 (30.0)
Vocational Qualifications (NVQ1+2)	6 (11.5)	3 (10.7)	4 (14.8)	3 (11.1)	4 (15.4)	0 (0.0)
A-Level or equivalent	5 (9.6)	2 (7.1)	3 (11.1)	2 (7.4)	3 (11.5)	1 (5.0)
GCSE/ O-Level/CSE	11 (21.2)	6 (21.4)	5 (18.5)	6 (22.2)	5 (19.2)	4 (20.0)
No formal Qualifications	1 (1.9)	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.8)	0 (0.0)
Ethnicity, n(%)						
White British	43 (82.7)	25 (89.3)	22 (81.5)	23 (85.2)	20 (76.9)	19 (95.0)
White Irish	1 (1.9)	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.8)	1 (5.0)

Demographics		**Component**				
	Overall, n = 52	SMS, n = 28	Leaflet, n = 27	ACT, n = 27	Website, n = 26	Interview sample, n = 20
Any other white background	1 (1.9)	0 (0.0)	1 (3.7)	0 (0.0)	1 (3.8)	0 (0.0)
Mixed- White and Black Caribbean	1 (1.9)	1 (3.6)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed- White and Black African	1 (1.9)	0 (0.0)	1 (3.7)	0 (0.0)	1 (3.8)	0 (0.0)
Asian/ Asian British- Indian	1 (1.9)	1 (3.6)	1 (3.7)	1 (3.7)	1 (3.8)	0 (0.0)
Asian/ Asian British- Chinese	1 (1.9)	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.8)	0 (0.0)
Black/ Black British- Caribbean	2 (3.8)	0 (0.0)	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)
Black/Black British- African	1 (1.9)	1 (3.6)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Number of children, n(%)						
0	10 (19.2)	7 (25.0)	7 (25.9)	6 (22.2)	8 (30.8)	1 (5.0)
1	8 (15.4)	4 (14.3)	5 (18.5)	3 (11.1)	6 (23.1)	3 (15.0)
2	23 (44.2)	12 (42.9)	10 (37.0)	13 (48.1)	9 (34.6)	9 (45.0)
3	9 (17.3)	4 (14.3)	4 (14.8)	4 (14.8)	2 (7.7)	7 (35.0)
4	2 (3.8)	1 (3.6)	1 (3.7)	1 (3.7)	1 (3.8)	
Stage of diagnosis, n(%)						
Stage IA	19 (38.0)	8 (30.8)	12 (44.4)	9 (36.0)	7 (26.9)	7 (35.0)
Stage IB	2 (4.0)	0 (0.0)	1 (3.7)	1 (4.0)	0 (0.0)	2 (10.0)
Stage IIA	15 (30.0)	11 (42.3)	7 (25.9)	7 (28.0)	11 (42.3)	5 (25.0)
Stage IIB	8 (16.0)	4 (15.4)	2 (7.4)	4 (16.0)	4 (15.4)	4 (20.0)
Stage IIIA	6 (12.0)	3 (11.5)	5 (18.5)	4 (16.0)	4 (15.4)	2 (10.0)
Missing[a]	2	2	0	2	0	0
Tumour type, n(%)						
Primary	52 (100.0)	28 (100.0)	27 (100.0)	27 (100.0)	26 (100.0)	20 (100.0)
Year of diagnosis, n(%)						
2020	3 (5.8)	3 (10.7)	1 (3.7)	1 (3.7)	3 (11.5)	0 (0.0)
2021	33 (63.5)	18 (64.3)	16 (59.3)	20 (74.1)	18 (69.2)	13 (65.0)
2022	16 (30.8)	7 (25.0)	10 (37.0)	6 (22.2)	5 (19.2)	7 (35.0)

Demographics		**Component**				
	Overall, n = 52	SMS, n = 28	Leaflet, n = 27	ACT, n = 27	Website, n = 26	Interview sample, n = 20
Treatment received, n(%)						
Surgery: lumpectomy	43 (82.7)	23 (82.1)	23 (85.2)	26 (96.3)	20 (76.9)	18 (90.0)
Surgery: unilateral mastectomy	5 (9.6)	3 (10.7)	1 (3.7)	0 (0.0)	4 (15.4)	1 (5.0)
Surgery: double mastectomy	2 (3.8)	1 (3.6)	2 (7.4)	1 (3.7)	2 (7.7)	0 (0.0)
Neoadjuvant chemotherapy	5 (9.6)	4 (14.3)	3 (11.1)	4 (14.8)	5 (19.2)	1 (5.0)
Adjuvant chemotherapy	18 (34.6)	10 (35.7)	8 (29.6)	13 (48.1)	9 (34.6)	3 (15.0)
Adjuvant radiotherapy	43 (82.7)	23 (82.1)	22 (81.5)	23 (85.2)	20 (76.9)	17 (85.0)
Monoclonal antibody-based therapy	4 (7.7)	1 (3.6)	1 (3.7)	3 (11.1)	3 (11.5)	1 (5.0)
Other	13 (25.0)	8 (28.6)	8 (29.6)	7 (25.9)	3 (11.5)	5 (25.0)
Current hormone therapy, n(%)						
Tamoxifen	12 (23.1)	9 (32.1)	5 (18.5)	7 (25.9)	5 (19.2)	8 (40.0)
Anastrozole	8 (15.4)	3 (10.7)	4 (14.8)	6 (22.2)	3 (11.5)	1 (5.0)
Exemestane	3 (5.8)	1 (3.6)	2 (7.4)	1 (3.7)	2 (7.7)	1 (5.0)
Letrozole	29 (55.8)	15 (53.6)	16 (59.3)	13 (48.1)	16 (61.5)	10 (50.0)
Menopausal status, n(%)						
Premenopausal	12 (23.1)	10 (35.7)	8 (29.6)	5 (18.5)	7 (26.9)	2 (10.0)
Peri-menopausal	3 (5.8)	2 (7.1)	0 (0.0)	2 (7.4)	2 (7.7)	3 (15.0)
Postmenopausal	30 (57.7)	11 (39.3)	17 (63.0)	15 (55.6)	15 (57.7)	11 (55.0)
Unsure	7 (13.5)	5 (17.9)	2 (7.4)	5 (18.5)	2 (7.7)	4 (20.0)

[a]Missing data was not included in percentage calculations.

All clinical data was completed by the site.

Key: SMS = Short message service. ACT = Acceptance and commitment therapy.

Table 5.4. Acceptability questionnaire scores per component

Acceptability construct	Intervention components			
	SMS, n = 20	**Information Leaflet, n = 20**	**ACT, n = 19**	**Website, n = 19**
Overall acceptability, median (range)	14 (11-20)	14.5 (12-17)	15 (11-19)	15 (12-20)
General Acceptability, n(%)				
Completely unacceptable	0 (0.0)	1 (5.0)	2 (11.1)	0 (0.0)
Unacceptable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No opinion	1 (5.0)	4 (20.0)	1 (5.6)	5 (26.3)
Acceptable	11 (55.0)	9 (45.0)	3 (16.7)	6 (31.6)
Completely acceptable	8 (40.0)	6 (30.0)	12 (66.7)	8 (42.1)
Missing	0	0	1	0
Affective attitude, n(%)				
Strongly dislike	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dislike	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
No opinion	8 (40.0)	9 (45.0)	2 (11.1)	5 (26.3)
Like	10 (50.0)	10 (50.0)	5 (27.8)	9 (47.4)
Strongly like	1 (5.0)	1 (5.0)	11 (61.1)	5 (26.3)
Missing	0	0	1	0
Burden, n(%)				
No effort at all	11 (55.0)	10 (50.0)	1 (5.6)	6 (31.6)
A little effort	6 (30.0)	5 (25.0)	10 (55.6)	8 (42.1)
No opinion	3 (15.0)	4 (20.0)	1 (5.6)	5 (26.3)
A lot of effort	0 (0.0)	1 (5.0)	3 (16.7)	0 (0.0)
Huge effort	0 (0.0)	0 (0.0)	3 (16.7)	0 (0.0)
Missing	0	0	1	0
Perceived effectiveness, n(%)				
Strongly disagree	3 (15.0)	1 (5.0)	1 (5.6)	0 (0.0)
Disagree	3 (15.0)	0 (0.0)	1 (5.6)	4 (21.5)
No opinion	7 (35.0)	11 (55.0)	6 (33.3)	8 (42.1)
Agree	6 (30.0)	8 (40.0)	5 (27.8)	6 (31.6)
Strongly agree	1 (5.0)	0 (0.0)	5 (27.8)	1 (5.3)
Missing	0	0	1	0
Coherence, n(%)				
Strongly disagree	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
Disagree	2 (10.0)	0 (0.0)	3 (16.7)	1 (5.3)
No opinion	5 (25.0)	10 (50.0)	4 (22.2)	8 (42.1)
Agree	11 (55.0)	10 (50.0)	6 (33.3)	8 (42.1)
Strongly agree	2 (10.0)	0 (0.0)	4 (22.2)	2 (10.5)
Missing	0	0	1	0

Note. Only data from participants who completed the acceptability questionnaires were included. Percentages were calculated excluding missing data.

Key: SMS = Short message service. ACT = Acceptance and commitment therapy.

Overall, 46 (88.5%) participants consented to be approached for interview. Of these, 5 withdrew from the trial and the remaining 41 participants were invited for interview. A total of 20 (48.8% of those invited) participants were interviewed; 6 declined (14.6%), and 15 (36.6%) did not respond. Of the 20 participants interviewed, 10 participants received the SMS component, 9 received the information leaflet, 10 received the ACT component and 7 received the website (Table 5.1). Three interviewed participants were from condition eight; as they did not receive any intervention components their data did not contribute to analysis. The interviews took place between 0 and 46 days after the 4-month follow-up questionnaire was sent out and lasted between 11 and 62 minutes. The interview sample held sufficient information power to determine the acceptability of the four intervention components (24). A summary of the key findings from the interviews in terms of the acceptability of each intervention component is displayed in Table 5.5.

Table 5.5. Summary of rapid qualitative analysis of each intervention component across constructs of the theoretical framework of acceptability

Acceptability construct	SMS	Leaflet	ACT	Website
Affective attitude	• Most women felt the messages were a good idea and found the content interesting and informative. • A minority felt some messages were too much like common sense or out of place.	• Several aspects of the leaflet were liked, including the quotes from other women, and information about side-effects. • One participant felt they already knew the information but liked having the information written down.	• Participants liked the practical, skills focus. • A number of ACT skills were liked and applied. Examples included using mindfulness to reduce hot flushes and identifying values to get back to enjoyed activities such as volunteering. • Support sessions from the therapist were liked by all participants overall. • Most participants felt the timing of the sessions were good, as other support had ceased. One participant felt they were not ready for the sessions. • One participant felt some pressure to talk	• Some women felt it was beneficial to see videos of what other women are experiencing. However, one participant felt the videos were too stereotypical. • One participant felt the website was not aesthetically pleasing. • A few participants found the information too general and vague in places. • Some women liked the honesty of the evidence ratings for the side-effect management strategies, but others did not feel this was helpful.

Acceptability construct	SMS	Leaflet	ACT	Website
			in the sessions to fill the time.	
Burden	• Overall low burden and not intrusive. • Two participants felt daily messages were too frequent. • Some participants may have opted out if not within trial setting.	• Many women felt the leaflet was concise and easy to read, without "medical jargon".	• Most participants liked the online delivery and flexibility of sessions. • Weekly sessions too close together- need more time to practice skills. • Therapy is emotionally challenging- having sessions in the morning and then going back to work was difficult.	• The website modality was acceptable.
Coherence	• The majority of women understood the messages were about building routines of taking medication. • Some women felt the messages were a prompt to take medication. • Some felt the messages emphasised the importance of taking medication.	• Most women understood the leaflet was aiming to provide information about AET.	• Overall understanding that ACT was teaching skills and coping mechanisms to move forwards. • Some participants were unsure about how ACT would help them when beginning the intervention, but gained more understanding after	• Participants generally understood the website was to provide side-effect self-management strategies.

Acceptability construct	SMS	Leaflet	ACT	Website
	• One participant felt the messages were a form of social support.		attending a few sessions.	
Perceived Effectiveness	• Most women felt they had routines to take AET, but that the messages would be effective for those that did not. • Some women felt personalising the timing of the messages would make them more beneficial.	• Some women reported being able to go back to the leaflet and re-read it to remind themselves of the benefits was helpful to remind them why they are taking AET.	Multiple experiences were shared regarding perceived effectiveness: • How ACT had helped take AET • Reduced psychological distress • Helped to return to work • Helped to cope with side-effects of AET	• Some women acknowledged the website would be helpful for those experiencing side-effects, who have not researched coping strategies. • Some women felt the website did not teach them anything new.
Other		• A number of women could not recall receiving the leaflet.		• Some women could not recall receiving website login details.

Key: SMS = Short message service; ACT = Acceptance and commitment therapy; AET = Adjuvant endocrine therapy.

In triangulation, 38 comparisons were made between the quantitative and qualitative findings (Table 5.6). There were 13 disagreements between the two coders which were resolved via discussion.

Table 5.6. Triangulation of quantitative and qualitative findings

Component	Triangulation	TFA Construct				
		Affective attitude	**Burden**	**Perceived effectiveness**	**Coherence**	**Total**
SMS	Silence	0	2	1	0	3
	Dissonance	0	0	0	0	0
	Partial agreement	2	2	1	4	9
	Agreement	0	2	0	0	2
Leaflet	Silence	0	0	0	0	0
	Dissonance	0	0	0	0	0
	Partial agreement	2	1	1	1	5
	Agreement	0	0	0	0	0
ACT	Silence	0	1	0	0	1
	Dissonance	1	0	0	0	1
	Partial agreement	4	2	1	2	9
	Agreement	0	0	0	0	0
Website	Silence	0	1	0	0	1
	Dissonance	3	0	0	0	3
	Partial agreement	1	0	2	1	4
	Agreement	0	0	0	0	0

Key: SMS = Short message service; ACT = Acceptance and commitment therapy.

5.4.1 Overall acceptability

All intervention components were considered acceptable, with overall acceptability scores ranging between 14/20 (SMS) and 15/20 (ACT and website), across components (range 11-20). For all components, the majority of participants rated each TFA construct at the midpoint or above (Table 5.4). The following sections summarise the quantitative and qualitative data and triangulation for each component individually.

5.4.2 SMS

In the quantitative assessment, 19 out of 20 (95.0%) participants reported the SMS messages were 'acceptable' or 'completely acceptable' *(general acceptability)* (Table 5.4). Burden was low, with no participants reporting the SMS messages were 'a lot of effort', or a 'huge effort' to engage with. Seven (35.0%) participants 'agreed' or 'strongly agreed' that the SMS messages would help them take AET, and a further seven (35.0%) had 'no opinion' *(perceived*

effectiveness). Thirteen participants 'agreed' or 'strongly agreed' that it was clear how the messages would help them to take AET *(coherence).* Two of the seven participants that withdrew/opted-out from the SMS component cited dislike of the SMS messages as their reason for withdrawal (Appendix D.2). The majority of participants (18/20, 90.0%) reported the frequency of SMS messages was 'acceptable' or 'completely acceptable' (Appendix D.3).

In the interviews, participants reported that overall they liked the SMS messages *(affective attitude)* (Table 5.5, Appendix D.4.1). Most participants reported they already had routines in place to take their medication and so did not feel the messages would have provided additional benefit to them, but acknowledged the potential effectiveness among women who may not have such routines *(perceived effectiveness).* No women interviewed opted out of receiving the messages, and only a minority felt the daily messages were too frequent *(burden).* Most participants understood the intended target for the messages, in that they were aiming to build routines in taking medication. Some women also perceived the aims to be to prompt daily medication-taking, to emphasise the importance of taking medication and to provide social support *(coherence).*

A total of 14 comparisons were made between the quantitative and qualitative data for triangulation of the SMS component. Most comparisons observed partial agreement (Table 5.6). There were three instances of silence, in which the qualitative data provided data on a topic that the quantitative data did not refer to, such as suggested improvements to the timing of the SMS messages (Appendix D.5.1).

5.4.3 Information leaflet

Of the 20 participants who completed the AQ, 15 (75.0%) found the leaflet 'acceptable' or 'completely acceptable' *(general acceptability)*, and the majority (15, 75.0%) felt it was 'no effort at all' or 'a little effort' to read *(burden)* (Table 5.4). Eleven out of 20 (55.0%) participants 'liked' or 'strongly liked' the leaflet *(affective attitude)*, while nine (45.0%) had 'no opinion'. Eight (40.0%) participants 'agreed' that the leaflet would help them to take AET, but 11 (55.0%) had 'no opinion' *(perceived effectiveness)*. Half the participants 'agreed' it was clear how the leaflet would help them take AET, while the other half had 'no opinion' *(coherence)* (Table 5.4).

In the interviews, participants reported liking aspects of the information leaflet, including the quotes from other women with breast cancer, information about AET side-effects and clear information about the benefits of AET *(affective attitude)*. However, several women randomised to receive the leaflet could not recall receiving it, often explaining that they received a lot of information at once regarding the trial. When asked about the perceived effectiveness of the leaflet, some women reflected on the usefulness being that they could re-read the leaflet to remind themselves why they were taking AET *(perceived effectiveness)* (Table 5.5, Appendix D.4.2).

Five comparisons were made for triangulation of the leaflet (Table 5.6). All comparisons were coded as partial agreement, with the qualitative data adding context to the quantitative data (Appendix D.5.2).

5.4.4 ACT

Of the 27 participants randomised to receive the ACT component, 24 (88.9%) attended session one, 21 (77.8%) attended session; two 17 (63.0%) attended session three; 17 (63.0%) attended session four, and; 16 (59.3%) attended session five. Of the eight participants who withdrew from the ACT component, only one cited dislike of the ACT component as the reason for withdrawal (Appendix D.2).

Of the participants who completed the ACT AQ, 15 (83.4%) felt the ACT component was 'acceptable' or 'completely acceptable' *(general acceptability)*. Most (16, 88.9%) participants 'liked' or 'strongly liked' the ACT component *(affective attitude)*. Burden was mixed; 11 (61.2%) participants felt engaging in the ACT sessions was 'no effort at all', or 'a little effort', one (5.6%) participant had 'no opinion', and six (33.4%) felt it was 'a lot of effort' or 'a huge effort'. Ten (55.6%) participants 'agreed' or 'strongly agreed' that the ACT component would help them to take AET (*perceived effectiveness)*, and that it was clear how the ACT component would help them to take their AET *(coherence)*. Acceptability of the ACT component overall, and individual aspects of the ACT intervention did not vary considerably across the five sites, each with different therapists delivering the intervention (Appendix D.3).

Interviewed participants were enthusiastic about the ACT component overall, citing several ACT skills that they liked, including mindfulness, unhooking and values-based exercises *(affective attitude).* The participants were positive about their therapeutic relationship, with

frequent reports of feeling comfortable opening up, and listened to *(affective attitude)*. One participant felt pressure to keep talking to fill the time in the sessions *(affective attitude)*. For most participants, the burden of the intervention was perceived to be minimal; made easier through the online delivery and individual nature of sessions allowing flexibility *(burden).* However, one participant acknowledged the emotional burden of attending therapy, and some reported that the weekly sessions were too close together. Many participants reported understanding that the ACT sessions were skills focused, but a few participants were apprehensive prior to a session as they did not know what to expect or how this was going to help them *(coherence).* When asked about the perceived effectiveness of the ACT component, participants shared numerous experiences of their personal benefits, including improving their mental health, coping with AET side-effects, reducing stress on returning to work, and in adhering to AET *(perceived effectiveness).* Many participants felt the timing of the support was beneficial, at a time when other hospital-based support and appointments had ended (Table 5.5, Appendix D.4.3).

Eleven comparisons were made for triangulation of the ACT component, with most indicating partial agreement or agreement between the data (Table 5.6). The one instance of dissonance occurred whereby the qualitative data indicated some dislike of feeling pressure to talk in the sessions, whereas the quantitative data for affective attitude did not indicate any dislike of the component (Appendix D.5.3).

5.4.5 Website

Most (14/19, 73.7%) participants who completed the website AQ thought the website was 'acceptable' or 'completely acceptable' *(general acceptability)* and 'liked' or 'strongly liked' the website *(affective attitude)*. Most participants (14, 73.7%) felt the website was 'no effort at all' or 'a little effort' to read and the remainder (5, 26.3%) had 'no opinion' *(burden)*. Around a third of participants (7, 36.8%) 'agreed' or 'strongly agreed' that the website would help them to take AET, eight (42.1%) had 'no opinion' and four (21.1%) 'disagreed' *(perceived effectiveness).* Most (10, 52.6%) participants 'agreed' or 'strongly agreed' that it was clear how the website would help them take AET, and eight (42.1%) had 'no opinion' *(coherence)*.

In the interviews, there were mixed opinions about the website *(affective attitude).* Some women liked aspects of the website, including the videos of other women sharing their

experiences of taking AET. However, other women disliked certain aspects; feeling as if the website was not aesthetically pleasing, was not modern enough for younger participants, and that information was too vague in places *(affective attitude).* There were mixed opinions about the evidence ratings of each side-effect self-management strategy; some women liked the honest nature of this, while others felt it could be demotivating for women who are struggling with side-effects. Multiple women felt the website did not teach them anything new but acknowledged that the information could be helpful for women who have not already researched coping strategies *(perceived effectiveness)*. Some women could not recall receiving log in details for the website (Table 5.5, Appendix D.4.4).

A total of eight comparisons were made for triangulation of the website. There were three instances of dissonance between the data, which related to occasions whereby qualitative findings included some negative comments about the website, whereas the quantitative assessment did not indicate any dislike in the affective attitude construct (Appendix D.5.4).

5.5 Discussion

This nested mixed-methods process evaluation of a fractional factorial pilot optimisation trial demonstrated overall acceptability of four intervention components aiming to support medication adherence to AET in women with breast cancer. We identified key areas of each intervention component that could be adapted to further improve intervention acceptability prior to a larger optimisation trial.

Understanding the acceptability of each intervention component had several implications. In response to some participants feeling the ACT component was burdensome, we amended the delivery to fortnightly sessions rather than weekly, as recommended by interviewed participants. Similarly, a choice of time of day to receive the SMS messages will be offered in the full optimisation trial, in response to interview data. Due to some indifference toward the information leaflet, and a proportion of women not recalling receiving the leaflet or the website components, we have changed the timing of delivery of both of these components to one week after randomisation, to minimise the chance they are lost amongst other information. Undertaking this process evaluation provided important insights and an opportunity to make adaptations to improve acceptability.

A mixed-methods approach added value to understanding acceptability of the components, and triangulation strengthened the conclusions made. A high proportion of the data was coded as 'partial agreement' in triangulation, which reflected the qualitative data adding crucial context to the quantitative findings. For example, in the coherence construct of the TFA, we quantitatively assessed whether a participant felt they understood how the component would help them take their AET, but this did not provide insight into what their understanding was and whether it matched the intended design of the component. The qualitative data added important context to aid this interpretation. The use of quantitative data alone may have led to different interpretations; a mixed-methods approach and triangulation were needed to ensure a more thorough understanding of acceptability.

Perceived effectiveness of the components on medication adherence was rated lower than other TFA constructs across all components in the quantitative assessment. In some cases, this could be explained by interview data. For example, many women in the SMS component reported that they did not forget to take their medication and therefore felt the SMS messages would have no impact on their adherence. However, to some extent, lower perceived effectiveness may be expected in some components. We acknowledge that the more passive, educational components (information leaflet and website) may not be sufficient to change adherence behaviour alone (9). These components are most likely to have an effect on adherence via interactions with other components, which can be empirically estimated using a factorial design. Low perceived effectiveness could also reflect that many people do not have insight into exactly what changes their behaviour. When exploring acceptability of individual intervention components, the relevance of TFA constructs may vary dependent on the type of component.

Undertaking a mixed-methods process evaluation of a trial using a fractional factorial design required some key considerations. For participants randomised to receive multiple intervention components, completing an AQ for each component added burden. Investigators considering such an approach should be mindful of this, particularly if assessing four or more intervention components in a 2^k factorial design (11, 13, 14). The number of experimental conditions added complexity when considering participant sampling for the interviews. We felt it was important to interview at least one participant from each of the eight conditions, as experienced acceptability could differ dependent upon combinations of

intervention components. Attempting to interview participants from all eight experimental conditions while purposively sampling across multiple demographics was logistically complex, and therefore we planned to focus on purposive sampling across age only. If the primary aim is focused on the individual intervention components, sample size may need to be increased for qualitative studies in a factorial trial compared with those in a parallel group RCT. This is because, on average in a factorial trial, half the participants interviewed will have received a component and half will not (11, 13).

The resource management principle is a key principle of the MOST framework that emphasises the importance of making the best use of resources available (11). We applied this principle in our decision to use a rapid qualitative approach in the process evaluation, which was helpful in the context of limited time and resources (22). We had a short period of time to make adaptations to the intervention components before proceeding with a larger optimisation trial (16). We saved time by using automatic and selective transcription and commencing analysis after only a few interviews had taken place. This enabled early consideration of improvements to be made to the intervention components, to ensure adaptations could be implemented in the next phase of the research (22).

5.5.1 Limitations

We excluded three less relevant constructs of the TFA in our assessment of acceptability: ethicality, self-efficacy, and opportunity cost. This decision was made to reduce participant burden, as participants were asked to complete an AQ for each intervention component they were randomised to receive. Including all constructs of the TFA could have led to different insights on acceptability. The TFA constructs focused on acceptability of an intervention based on a primary outcome (e.g., perceived effectiveness on adherence) in the quantitative assessment. Secondary outcomes that may still be important to a participant, such as reduction in side-effects, were not considered. Quantitative assessments of acceptability should consider asking about intervention targets or mediators which may be more proximal to participants, rather than focusing solely on the primary outcome. Our sample consisted predominantly of White women, and therefore we have not captured the acceptability or appropriateness of the intervention components in a more diverse sample, in which acceptability may have differed. We were unable to interview participants who withdrew from receiving the intervention components as they were no longer eligible to be contacted,

which may have biased the qualitative findings to women who had a more positive experience. However, we have included relevant data on withdrawals and reasons to aid overall understanding of acceptability across all trial participants. One interviewer (SG) conducted all the interviews, and was involved in intervention development, which allowed an in-depth assessment of acceptability but may have introduced bias to the interviews. Multiple researchers (SG, LH, SS, CG) attended qualitative analysis meetings, and a researcher independent to the trial team (KL) triangulated the findings in attempt to reduce bias.

5.5.2 Conclusions

Overall, we have demonstrated acceptability of four intervention components aimed at supporting medication adherence in women with breast cancer. Using a mixed-methods approach based on the TFA was helpful in providing a detailed assessment of acceptability of each of the intervention components. Our rapid qualitative approach enabled our findings to be analysed quickly to inform adaptations of the intervention components for the next phase of this research. We have demonstrated one approach to conducting a process evaluation which could be applied in other pilot optimisation trial process evaluations.

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Consent to participate: Informed consent was obtained from all individual participants included in the study.

Data availability: Data will only be shared for participants who have given consent to use of their data for secondary research, and will only be made available in such a way that recipients cannot identify individuals by any reasonable likely means. Requests to access quantitative data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Qualitative data is available on reasonable request by contacting the corresponding author.

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Chapter 6 : Discussion

6.1 Chapter summary

In this chapter, I first summarise the main findings from the four studies in this thesis. Specifically, I discuss the development of the intervention components in Studies One, Two and Three and the process evaluation determining intervention component acceptability in Study Four, followed by comparisons to the broader literature. I then discuss key considerations and challenges I encountered in this thesis, followed by the strengths and limitations of the methods I used. In the final section, I discuss clinical implications and directions for future research.

6.2 Summary of findings and contributions to the literature

In this thesis, I aimed to develop a complex intervention to support adherence to adjuvant endocrine therapy (AET) in women with early-stage breast cancer. Most women with early-stage breast cancer are prescribed AET, which is effective at reducing recurrence and mortality (1-5). Prior to this PhD, the extent of non-adherence to AET and the barriers to adherence had been reported extensively. However, existing interventions aiming to support AET adherence were mostly ineffective or yielded small effect sizes (6-9), similar to interventions to promote medication adherence more broadly (10). Moreover, effect sizes for interventions have not increased over time, potentially because we have little empirical understanding of which intervention components may be effective (6). To achieve the aim of this thesis, I undertook four studies that fall within the preparation and optimisation phases of the multiphase optimisation strategy (MOST) framework.

6.2.1 Intervention development and optimisation (Studies One, Two and Three)

Across Studies One, Two and Three I have demonstrated how intervention components can be developed and optimised, in line with the MOST framework. In Studies One and Two, I focused on the development of four intervention components to support adherence to AET. As the MOST framework does not provide explicit guidance for identifying and developing intervention components (11), in Study One, I adapted intervention mapping (IM) to incorporate the fundamental principles of MOST to guide the design of the conceptual model and intervention components. I have demonstrated that it is feasible to combine such

approaches; detail about key considerations in combining IM and MOST is discussed in section 6.4.2.

During Study One, I chose four determinants of AET adherence to be targeted in the complex intervention; forgetfulness, medication beliefs, psychological distress and side-effects. To target psychological distress and side-effects, two existing interventions were adapted; an acceptance and commitment therapy (ACT) intervention to increase psychological flexibility and reduce psychological distress, and a self-management website to manage side-effects. To target forgetfulness and medication beliefs, I developed two new intervention components, discussed below.

I identified habit theory as suitable for guiding the development of an intervention component to reduce reliance on memory (12, 13). A short message service (SMS) intervention component was proposed as a potential low-cost method to support habit formation. As no existing SMS interventions based on habit theory were identified (14), in Study Two I developed the content of a pool of SMS messages designed specifically to support habits for medication-taking using a series of quantitative and qualitative studies. This led to a pool of 66 text messages being developed, which were all considered acceptable to women with breast cancer, and showed fidelity to the behaviour change techniques (BCTs) they intended to target. The development of the content of these messages aligned with stage four of IM in Study One.

To address medication beliefs, I developed an information leaflet aiming to increase beliefs about the necessity of AET and to reduce concerns in stage four of IM, in Study One. The leaflet was formed of multiple components. Due to the limited evidence for effective strategies to address medication beliefs (6), in Study Three I sought to empirically optimise the leaflet to understand the effects of each component on beliefs about AET using a factorial experiment. This study had two key outcomes; (1) an optimised information leaflet that is more efficient and effective in improving the balance between necessity beliefs about AET and concerns; and (2) a demonstration of specific strategies to address necessity and concern beliefs that could be applied in other contexts.

6.2.2 Process evaluation (Study Four)

Following Studies One, Two and Three, a pilot optimisation trial using a fractional factorial design was undertaken, which aimed to assess the feasibility of a fully powered optimisation trial (15). I did not lead this pilot, and it is not included as part of this thesis. I led the process evaluation embedded within the pilot trial, which formed Study Four of this thesis. I chose to conduct a mixed-methods process evaluation, guided by the theoretical framework of acceptability (TFA), aiming to determine the acceptability of the intervention components developed in Studies One, Two and Three. All four components were considered acceptable to trial participants. I demonstrated how a mixed-methods process evaluation in a pilot optimisation trial can be conducted efficiently, incorporating rapid qualitative methods and triangulation of qualitative and quantitative findings.

6.3 Comparisons with existing interventions to support adherence to AET

Existing interventions to support AET adherence have typically shown no effect on adherence or have yielded small effect sizes (6-9). The most recent meta-analysis of interventions supporting AET adherence, published in 2023, was the first to find a significant overall intervention effect (6). However, the effect was small and, broadly, no single approach to supporting adherence was consistently better than others (other than educational approaches for side-effects that were consistently ineffective, and policy changes impacting the cost of AET that were consistently effective) (6). The intervention I developed in this thesis advances on previously evaluated interventions in four main ways; (1) by targeting a range of determinants of AET adherence; (2) by using theory and intervention development frameworks to guide the development of the intervention components; (3) by optimising an educational information leaflet component to understand the effects of more granular intervention components prior to inclusion in a larger trial; and (4) by developing the intervention components in such a way that they can be readily optimised using the MOST framework. The following sections explain these advances.

The intervention components developed in this thesis share similarities with existing and ongoing interventions (6). For example, many existing interventions include a psychoeducation element (16-21), some use SMS messages to prompt medication-taking and provide information (22-25), and others incorporate self-management strategies for side-

effects and include an element of relaxation training (26, 27). However, many interventions focus on a single barrier to adherence, with psychological distress and affective attitudes towards adherence rarely addressed (6). The intervention package I developed as part of this thesis targets a range of barriers to AET adherence, which may be necessary when attempting to change a complex behaviour such as medication adherence.

The lack of theory and limited use of intervention development frameworks are acknowledged limitations of interventions developed to support AET adherence (6-9). My use of intervention development (MOST) and intervention design (IM) frameworks provided a structured approach to intervention development, ensuring the intervention targeted key determinants of adherence (11, 28). I was guided by theory throughout this thesis, which has benefited the development of the intervention components. For example, while SMS messages have been used to support AET previously, they were not based on any underpinning theory (22). The SMS component I developed, however, was designed to support habit formation rather than to just prompt medication-taking, which has the potential to lead to sustained behaviour change. I further discuss the benefits of the use of theory in this thesis in section 6.5.1.1.

The optimisation experiment in Study Three advances our understanding of how to target medication beliefs through the factorial experimental design used to estimate the effects of intervention components with high granularity (e.g., mechanistic diagrams). Medication beliefs are often targeted within a larger complex intervention aiming to support AET adherence. Therefore, it has not been clear how effective strategies specifically targeting medication beliefs are (6). A recent systematic review, investigating which BCTs are most effective at changing medication beliefs, called for further research to understand whether individual techniques work best alone or in combination (29). The factorial experimental design I used enabled understanding of the individual and combined effects of specific strategies to target medication beliefs.

However, the reliance on solely educational intervention components is a consistent limitation of existing interventions aiming to support adherence to AET (6-9). Educational intervention components alone may not be sufficient to impact adherence to AET, but they may be a necessary part of a multicomponent intervention. The information leaflet I developed may provide necessary education about AET, but may not be sufficient on its own

to change adherence. However, it may interact with other intervention components to improve adherence. In Study One, I hypothesised that there would be a two-way interaction between the information leaflet and all three other intervention components. For example, the information leaflet might increase one's motivation to take AET. Motivation is the first phase of habit formation, which the SMS messages target, and therefore as outlined in Study One, I am hypothesising a synergistic interaction between the educational information leaflet and SMS messages (12, 30). Hypothesising interactions between components *a priori* was a challenge, as in using a typical approach to intervention evaluation, investigators have not been able to empirically test how educational intervention components may interact with other components. As such there is a weak evidence base for hypothesising interactions (6). Conducting further optimisation trials, informed by the MOST framework, will strengthen the evidence base for interactions between components that are likely to occur. Investigating interaction effects will improve our understanding of how interventions may work, and has the potential to advance intervention development.

6.4 Key challenges and considerations

Due to the novel methods used throughout this thesis, several points required thoughtful consideration, as there was little guidance to rely on. In the following section, I discuss challenges encountered and considerations that influenced key decisions throughout my PhD.

6.4.1 Intervention development considerations in the MOST framework

In the development of the conceptual model and intervention components throughout Studies One, Two, and Three, I needed to make considerations in relation to the MOST framework. Firstly, I had to consider that each intervention component should ideally target one specific mediator (31). If an intervention component targets more than one mediator, this can cause difficulty in decision-making in the optimisation phase. For example, if the ACT and information leaflet components were combined into one component (Figure 6.1), which was hypothesised to target both psychological flexibility and medication beliefs, this may create difficulties. If the combined component (ACT + leaflet) successfully increased psychological flexibility but did not impact medication beliefs, it would be unclear how best to proceed; whether to leave the component as is, as it impacted one mediator, or whether to revise the component in attempt to also change medication beliefs. Moreover, it cannot

be determined which part of the intervention component was driving the effect observed on psychological flexibility. Therefore, ensuring each intervention component targeted one mediator was important during intervention development (31).

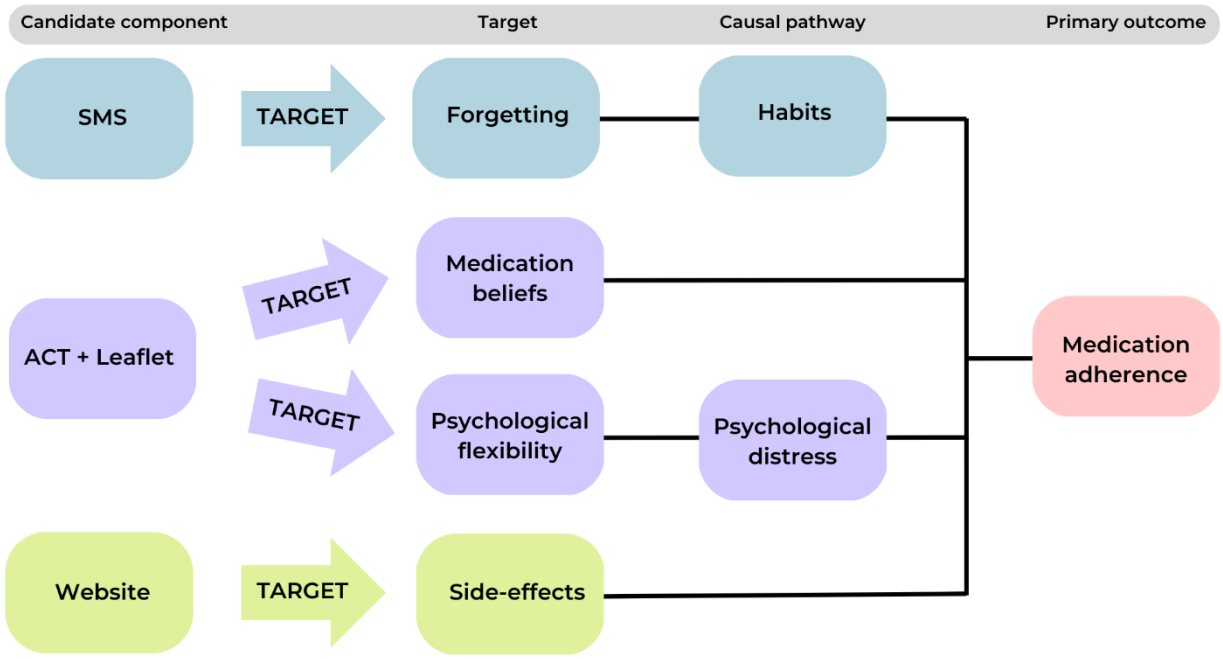

Figure 6.1. Conceptual model example with one intervention component targeting multiple mediators

Secondly, in the design of the four components in Study One, and the design of the information leaflet components in Study Three, I had to ensure that the intervention components were distinct from one another so that they did not duplicate large amounts of information and did not depend on the presence or absence of one another (32). Dependence on the presence of another component could be problematic, as not all participants will be randomised to receive all intervention components when using a factorial design. Moreover, duplication of information may be irritating to participants randomised to receive multiple intervention components, and in the worst case scenario may lead them to withdraw from the trial completely (32). In adapting the website component in Study One, I removed information about the mechanisms of AET, as this overlapped with the content of the information leaflet. To ensure independence of the information leaflet intervention components in Study Three, I added a constant component. The constant component provided key information to all participants regardless of what condition they were

randomised to, to avoid duplication of information across components. Visualising exactly what each participant in each condition would receive was a helpful way to ensure content was distinct and independent between components in Studies One and Three.

Furthermore, I needed to consider the granularity of intervention components in the preparation phase of MOST (31). In Study Three, the information leaflet components had high granularity, with small nuances between them. For example, the side-effects component contained information about the prevalence of side-effects and the nocebo effect, while the common concerns component provided answers to common concerns which largely centred on side-effects. In using more granular components, I had to allocate more time for the intervention development phase to ensure each component targeted a single mediator, and that the content of the components was distinct.

6.4.2 Integrating IM in the preparation phase of MOST

Study One was the first study to demonstrate how IM can be combined with the MOST framework. Investigators using MOST rarely describe the preparation phase activities they have completed in detail, but they can provide important rationale underpinning the development of intervention components (33). Using IM was beneficial to ensure I developed candidate components that target the determinants of medication adherence, and to ensure the conceptual model was theory- and evidence-based. The flexibility of IM enabled stages to be adapted to fit with the MOST framework. For example, stages one to three of IM focus on identifying and selecting key determinants of a behaviour to develop a logic model of change. I adapted these stages to focus on developing a conceptual model which is fundamental in the preparation phase of MOST to specify the causal pathway for each intervention component (31). The implementation stage of IM (stage five) provided an ideal opportunity to consider and specify an optimisation objective, which is a key activity in the preparation phase of MOST (31, 34). Overall, IM and MOST were successfully combined, and the use of these two approaches enhanced the intervention development process.

However, IM is just one framework that could be used in the preparation phase of MOST. The person-based approach (35) or the behaviour change wheel (36) could also be adapted to incorporate key aspects of intervention design in the MOST framework (28, 37, 38).

Investigators considering using these approaches should consider how to address the key challenges I have described in section 6.4.1.

6.4.3 Resource management principle

The resource management principle, which is a key principle of the MOST framework, advocates for using and realigning resources in the most efficient way to enhance scientific yield (34, 39, 40). Several decisions I made throughout this thesis were influenced by the resource management principle.

6.4.3.1 Rapid review

In Study One, I used literature reviews and rapid reviews in a needs assessment to summarise the extent of non-adherence to AET, the barriers to AET adherence, and existing and ongoing interventions aimed at supporting AET adherence. The decision to not conduct multiple full systematic reviews was a pragmatic one. At the outset of this PhD, it was evident that several reviews incorporating quantitative and qualitative studies exploring the barriers of AET adherence already existed (41-51). In addition, the most recent meta-analysis investigating existing interventions to support AET adherence was published recently in 2019 (8). Therefore, I used a rapid review as opposed to a full systematic review, to allocate resources more efficiently. While this approach may have led to studies or interventions being missed from inclusion in Study One, on reflection and based on the most recent full systematic review of interventions supporting AET adherence (6), the inclusion of additional studies would not have substantially altered the development of the intervention components.

6.4.3.2 Intervention mapping

A criticism of the intervention mapping (IM) approach is the length of time it can take, with some reports of months spent on a single stage, and years to complete the overall process (52). Authors have suggested IM can be adapted based on the time available (53). As this PhD was part of a larger project involving a pilot and full optimisation randomised controlled trial (O-RCT), I needed to complete the intervention development phase to align with the project's funding constraints and overarching project deadlines. As such, I did not complete some sub-stages of IM, in particular constructing matrices of change in stages two and five (53).

Nonetheless, I developed a theory- and evidence-based conceptual model and intervention components that target key determinants of adherence, in line with the MOST framework.

6.4.3.3 Factorial experimental design

An alternative approach to a factorial experiment in Study Three could have been to conduct five separate randomised controlled trials (RCTs) to evaluate each component individually, or to conduct a six-arm RCT, with each component as an arm in addition to a control. These approaches would have required more resources in terms of larger sample sizes, and interaction effects could not have been estimated. In an intervention package with such granular components, interactions between components are likely to be highly prevalent and important, as demonstrated. Therefore, a factorial experimental design was an appropriate realignment of resources to generate the greatest scientific yield.

6.4.3.4 Sample size in optimisation experiments

Determining an appropriate sample size for the factorial experiment in Study Three involved several considerations relevant to the resource management principle. To calculate a sample size, I had to consider three parameters; an expected effect size, required power, and chosen alpha (32). Often, an expected effect size is determined based on an effect size found in previous literature (54). However, if there are differences in the population or design of the study then the expected effect size would not be generalisable and could lead to an overestimation of effect size due to publication bias (54). A more appropriate method to consider the expected effect size is to determine what the smallest effect size of interest may be (54). Deciding the smallest effect size of interest in Study Three was a challenge, as there is very little existing evidence for individual components of an information leaflet. In a factorial design, it may be beneficial to first consider what the expected effect size of the overall package is. In Study Three, I used a conservative estimate of Cohen's d = 0.3 for the overall intervention effect, which is considered a small to medium effect size (55). This also reflects the expected effect size for the intervention components that will be used in the wider O-RCT that this leaflet will be tested in (15). Conservatively assuming two out of five components would affect beliefs about medication, I aimed to detect a main effect of 0.15 for each component. This approach assumed a simple additive effect of the effect sizes and did not account for ceiling effects of the main outcome. Considering ceiling effects, I could

have estimated an effect size of 0.1 for four components, to detect an overall effect size of d = 0.3 for the whole intervention package, for example. However, this would have required a larger sample size overall, and may not have been feasible. Sample size calculations for factorial trials are complex and require more guidance with regard to expected effect sizes. Investigators should balance the expected effect size of the overall intervention package and components with resource constraints.

A further consideration in calculating sample size is the estimated power and chosen alpha. Statistical power is the probability of concluding there is a statistical effect when there is one, i.e., making the correct decision to reject a null hypothesis. The widely accepted minimum level of statistical power is 0.8. A Type II error rate (β), is when a null hypothesis that is false, is not rejected. β = 0.2 is the widely accepted Type II error rate. Alpha reflects the Type I error rate, which is when a null hypothesis is wrongly rejected. The widely accepted alpha used in hypothesis testing is 0.05. These traditional values for Type I and II error rates reflect a conclusion-priority perspective which is used in a typical approach to evaluation (32). The conclusion-priority perspective aims to draw a robust scientific conclusion based on scientifically accepted rules of statistical significance (32). Using these cut-offs, it can be deduced that investigators generally agree that a Type II error (0.2) is four times more acceptable than a Type I error (0.05).

Taking a decision-priority perspective to optimisation involves using the data to make decisions about whether to screen in or screen out components. Here, hypothesis testing is an aid for decision-making, rather than a definitive conclusion (32). In the screening experiment in Study Three, I considered Type I and II errors to be equally detrimental to decision-making. As such, I balanced Type I and II error rates by increasing the alpha to 0.1, and power to 0.9. Alternatively, I could have increased the number of participants, which would increase the power and reduce the Type II error rate (32). However, in alignment with the resource management principle, I felt reducing Type I error was an appropriate trade-off to make the best use of available resources.

6.4.3.5 Rapid qualitative methods

For the qualitative component of the process evaluation in Study Four, I used rapid qualitative methods as opposed to more traditional qualitative analyses, such as thematic analysis (56).

The decision to use a rapid qualitative approach was based on the limited time and resources available to conduct the process evaluation prior to a full O-RCT.

Several studies have compared rapid qualitative approaches with more "in-depth" analytic approaches, reporting consistency between findings from in-depth analyses and rapid approaches (57-59). Where there were additional findings using thematic analysis, these were argued to be 'relevant but non-essential', suggesting a rapid analysis approach may be sufficient but may not capture every detail in the data (58). As the aim of the qualitative element in Study Four was to capture key aspects that could be adapted to improve intervention component acceptability, I felt a rapid qualitative approach was appropriate for this context.

6.4.4 Informed decision-making vs. behaviour change

A common challenge in designing medication adherence interventions is the distinction between whether the intervention should focus on behaviour change (e.g., improving adherence), or informed decision-making (whereby an informed choice is based on relevant knowledge, consistent with the decision-maker's values (60)). In a typical approach to intervention development and evaluation, an intervention package tends to be considered as a whole, and therefore a decision can be made about whether the intervention overall will focus on behaviour change or informed decision-making. However, when developing individual intervention components in the context of the MOST framework, the decision becomes more challenging, as each intervention component could have a different focus.

The aim of the overall intervention I designed was to improve adherence to AET, as improving AET adherence has known benefits in terms of reduction in recurrence, mortality and health care costs (1-5, 61-66). However, the individual components I developed incorporated varying levels of informed decision-making aspects within them. The SMS and information leaflet components focus on behaviour change explicitly, by encouraging habits around medication-taking and via promoting more positive beliefs about AET. The website component promotes the management of side-effects to improve medication adherence, but is more passive in its approach to behaviour change. In contrast, the ACT component focuses on aligning behaviour with one's values, which for some women may involve not taking AET (67). The ACT component is therefore more aligned with the informed decision-making approach. The

differing perspectives of the components could lead to conflicting information between some intervention components. For example, for those randomised to receive the ACT and SMS components; one component (SMS) is promoting behaviour change, while the other (ACT) acknowledges that adherence may not be the right choice for some. These interactions were not explored in the interviews in Study Four. However, this potential interaction may be interesting to explore in a process evaluation of a full O-RCT. Investigators designing intervention components to be included in O-RCTs should consider the focus of each component (e.g., behaviour change or informed decision-making) individually, and as a cohesive whole early in the intervention development process.

6.4.5 Qualitative analysis

6.4.5.1 Deductive approach

I used a deductive approach to guide data collection and analysis in Study Four. In this context, the interview questions were all guided by the TFA, and the deductive approach to analysis involved applying the TFA to the data in a 'top-down' manner (56). In comparison, an inductive approach would have involved generating codes and/or themes from the data in a 'bottom-up' approach (56). I felt a deductive approach was most appropriate, as the research question was very specific rather than exploratory, and the interview questions and rapid assessment procedure (RAP) sheets were designed using the TFA.

Using an inductive approach to data collection and analysis could have led to additional findings. A qualitative study investigating intervention acceptability in a different context used both a deductive approach guided by the TFA and an inductive approach to analysis and found value in both approaches, with different findings being generated by each (68). However, in that study, the interview guide was not originally designed based on the TFA. As the interview guide in Study Four was originally designed specifically using the TFA, the data naturally fell within TFA domains. Therefore it is less likely that alternative findings would have been generated using an inductive approach in Study Four. If I had used an inductive approach in the context of rapid qualitative approaches, more extensive and iterative revisions to the RAP sheet based on early findings in the data may have been warranted.

6.4.5.2 Data saturation vs information power

In Study Four, I considered information power *a priori* to make decisions about when to cease data collection. Information power focuses on the richness of the data, and proposes five factors that will affect the sample size required; (1) narrow or broad study aims; (2) dense or sparse sample; (3) presence of theory; (4) quality of the interview dialogue, and (5) use of case or cross-case analysis (69). Data is considered more 'rich', with higher information power when there are narrow study aims, a highly specific sample to answer the research question, the presence of theory informing the study, good quality dialogue and individual case analysis (69).

There were two main challenges I faced when applying the concept of information power. Firstly, while the five factors guide whether a larger or smaller sample is required, there is little guidance on what constitutes a large or small sample. As such, reliance on experience in qualitative research is needed. Secondly, defining a sufficient amount of information power is challenging. There is little guidance on how to assess whether the data is sufficiently 'information-rich', and therefore knowing when to cease data collection is a challenge.

An alternative to information power that I considered was the concept of saturation, which is a debated topic in the field of qualitative research (70). There are many different types of saturation that can be applied; (1) theoretical saturation, whereby data collection stops when no new theoretical categories are identified; (2) inductive thematic saturation whereby data collection ceases when there is no new identification of codes or themes; (3) *a priori* thematic saturation which considers whether identified codes are exemplified in the data; and (4) data saturation which considers whether new data is adding anything to the previous data (71). Applying these methods of saturation to rapid qualitative methods is difficult as data collection and analysis occur simultaneously, and 'themes' are not always generated in rapid qualitative research (72). On reflection, alternative approaches may have been beneficial. For example, a combination of information power and data saturation; using elements of information power to consider sample size *a priori*, followed by discussing whether the data have been sufficient for analysis (a concept previously termed 'analytic saturation' (72)).

An alternative approach to define sample size in theory-based interview studies, is to interview an initial number of participants (e.g., ten), and to set a stopping criteria (e.g., data collection stops once three further interviews generating no new ideas have been conducted)

(73). This approach may have been useful in combination with RAP sheets, as it was clear immediately following an interview whether new ideas were added to the overall RAP sheet. Further guidance for defining when to cease interviewing in rapid qualitative research would be useful.

6.5 Strengths and limitations

In this thesis, I used a variety of novel methods to develop and optimise the four intervention components to support adherence to AET. These methods had strengths and limitations as summarised below. Where relevant, future directions to address limitations are described.

6.5.1 Theory and theoretical frameworks

6.5.1.1 Developing a complex intervention grounded in theory

The majority of existing interventions aiming to support AET adherence have not incorporated (or reported) theory in their development process (6). The approach I took in this thesis advances on existing interventions, incorporating multiple psychological theories (e.g., habit theory, common-sense model of self-regulation) in the development of the intervention components. In stage three of IM, theory can guide how to target the behavioural determinants identified to be important in changing the behaviour (74). Combining multiple theoretical perspectives, as I demonstrated in Study One, may be beneficial in adherence interventions due to the complexity of the behaviour (38, 75).

There is mixed evidence as to whether incorporating theory in the development of an intervention increases the effectiveness of the intervention (76-78). However, the benefits of using theory are broader than the potential increased effectiveness of an intervention. The use of theory can aid explanation of why an intervention does or does not work in subsequent evaluation and can provide a framework for the exploration of determinants of behaviour in contexts in which there is limited existing research (76).

6.5.1.2 Behaviour change techniques

In Study One, I coded all four intervention components using the behaviour change technique taxonomy (BCTTv1), which helped to classify the content of the intervention components in a standardised way across all four components, using a taxonomy understandable to other

investigators (79, 80). In Study Two, the SMS messages were developed to target six BCTs hypothesised *a priori* to be important in habit formation, which was beneficial in ensuring the content of the SMS messages aligned with the proposed theoretical underpinning. Specifying the BCTs used in all four intervention components before the O-RCT will aid interpretation of any intervention component effects observed.

However, there are limitations to the use of the BCTTv1. Some BCT definitions are unclear and overlap with one another (81, 82). Coding BCTs does not provide any information about the dose of BCTs included in each intervention component. Some BCTs may be used multiple times in a component (e.g., restructuring the physical environment in the SMS component), whereas others may be incidentally targeted once (e.g., a single line of text in one ACT module booklet). Coding the dose of a BCT could further aid the interpretation of the active ingredients of an intervention component.

The recently developed behaviour change intervention ontology (BCIO) addresses some of the limitations of the BCTTv1. An ontology is a structure that can be used to represent knowledge (83). It defines entities (e.g., objects, processes) and the relationships between them. The BCIO is made up of 11 individual ontologies concerning different aspects of interventions that may need to be defined, such as delivery mode, schedule and dose, mechanisms of action, contextual influences and BCTs (84). The BCT ontology addressed feedback from behaviour change experts regarding the BCTTv1, leading to an updated BCT ontology consisting of 281 BCTs organised into 20 groups and five hierarchical levels (81). Updates included adding and removing BCTs, updating labels and definitions of multiple BCTs, and revising the structure and grouping of BCTs (81). The BCIO offers the potential to better define behaviour change interventions more extensively in the future.

6.5.1.3 Theoretical framework of acceptability

My use of the TFA in Study Four to guide the assessment of acceptability was a strength of this thesis. Assessments of acceptability have previously varied considerably, ranging from single items to in-depth qualitative assessments (85). In Study Four, the TFA provided an informed assessment of acceptability, as opposed to using an ad hoc assessment. The TFA elicited more detailed responses than if participants had been asked a more general question about acceptability, supporting the idea that acceptability is a multi-faceted concept (85).

However, there are limitations both in how I used the TFA, and the TFA itself. With regard to the use of the TFA in Study Four, I excluded three domains to reduce participant burden. I excluded the ethicality domain, as based on previous qualitative interviews I had conducted with a similar population, many participants were unsure how to respond when asked whether the intervention fit with their values. Of note, the interviews in this previous study explored the acceptability of a group based ACT intervention (86). Therefore it could have been expected that due to the focus on values in ACT, participants may have been more readily able to discuss whether the intervention aligned with their values, but this was not the case. Identifying and reflecting on values is challenging and this difficulty has been similarly reported in other qualitative studies (68, 87). Further guidance about how to discuss and elicit values in the context of acceptability would be beneficial. Alternatively, it is possible that ethicality may be more relevant to health care professionals delivering an intervention, in which they can reflect upon whether the intervention fits with their professional values.

I also did not use the self-efficacy domain of the TFA (confidence in doing the intervention) in Study Four, as three of the components involved predominantly reading intervention content, meaning this domain was considered less relevant. Opportunity costs was the final domain not to be included in Study Four; I had previously conducted interviews with women with AET for a similar purpose, and found opportunity costs overlapped considerably with the burden domain. Including all domains of the TFA could have led to a more detailed assessment of acceptability, but considering multiple intervention components were being assessed this could have become overly burdensome. A qualitative study using all domains of the TFA in a different context found there was insufficient information for the ethicality, self-efficacy and opportunity costs domains, suggesting removal of these domains may not have limited the assessment of acceptability (87). Guidance for the use of the TFA in different contexts would be helpful.

A further limitation is that the TFA itself does not distinguish whether acceptability refers to someone actively liking an intervention or if they are only willing to tolerate it; these nuances represent different cognitive states that could be important in terms of engagement or adherence to an intervention. Someone who actively likes an intervention is likely to engage more with that intervention compared to someone who is only willing to tolerate the intervention. Throughout this thesis, I considered acceptability as the latter, whereby a

component was considered acceptable if there was no active dislike. This guided the acceptability assessment I used in the SMS development in Study Two, whereby a message was considered acceptable if it scored above the mid-point of the scale. Similarly in Study Four, I concluded that all four intervention components were acceptable, despite some indifference reported in relation to the information leaflet component. If I had considered acceptability as needing to actively like an intervention component, conclusions of acceptability may have been different for some intervention components. Further clarification of this nuance in defining acceptability would be useful in future iterations of the TFA.

6.5.2 Individual and health system-level intervention components

In this thesis, I focused on patient-level factors associated with medication adherence, such as medication beliefs, side-effects and psychological distress. Individual determinants of adherence are extremely important in medication adherence research, as ultimately it is the patient who actively takes the medication (88). However, as highlighted in the medical research council (MRC) guidance to complex intervention development and evaluation, the wider context is important to consider, as complex interventions are considered as events within systems (89). Current health system interventions in the context of supporting AET adherence predominantly relate to reducing the cost of medication, which is less relevant in the UK where AET prescriptions are free (6). Quality of the patient-physician relationship is a commonly cited barrier to AET adherence but has rarely been addressed, perhaps due to the added complexity of addressing system-level factors (6, 41, 47, 49, 90, 91). Future research should explore the development of an intervention component targeting patient-physician communication or other relevant system-level factors, which have the potential to further improve adherence to AET and don't place all emphasis on the individual needing to change.

6.5.3 MOST framework

As the MOST framework is relatively novel, and is not widely used, there are some challenges in using the framework and associated experimental designs (e.g., the factorial experimental design I used in Study Three). Undertaking the optimisation phase adds an extra phase of research prior to definitive evaluation, compared with using a standard approach in which a pilot or definitive RCT is typically conducted immediately after developing the intervention.

In addition, there is relatively little guidance on the delivery and reporting of trials using a factorial design, and as such more time and resources must be devoted to planning and delivering an O-RCT using these designs. If the goal of an investigator is to conduct a definitive RCT quickly, then these factors could be viewed as limitations to the MOST framework. However, if the goal is to advance intervention science by gaining greater insight into how and why interventions work or do not work (as was the case in Study Three), and by developing interventions that are more readily scalable, then realigning resources to be used on conducting MOST-informed O-RCTs would be appropriate.

6.5.3.1 Decision-making in the optimisation phase of MOST

In Study Three, I used the component screening approach (CSA) to choose which candidate components were included in the optimised information leaflet. Components with main effects of importance (defined as reaching a fixed statistical significance cut-off of 0.1) were screened in originally, and all other components were screened out. Decisions were then reconsidered based on important interaction effects to choose the final screened-in and-out list for the optimal intervention package.

Since Study Three was conducted, limitations of the CSA have been highlighted (92). The CSA is embedded in frequentist statistical methods which use arbitrary thresholds to determine which main and interaction effects are important enough to contribute to decision-making. The consideration of an "important" effect in Study Three was one that reached the statistical significance threshold of 0.1. Using the CSA, any main or interaction effect not reaching this threshold, even marginally, was not considered further and was set to zero in the parsimonious prediction model. This means that not all available information was used to decide on the composition of the optimal information leaflet (92). Moreover, the systematic interpretation of interaction effects in the CSA is not always straightforward; unpicking higher-order interactions (e.g., four-way) is challenging and is subject to human judgements which are prone to errors. Furthermore, different interaction effects may provide conflicting information as to whether to include a component in the optimal package or not.

A further limitation of the CSA is that it is only compatible when using one primary outcome, as multiple outcomes cannot be incorporated into the decision-making process. This is problematic, as the optimal intervention may be different depending on the outcome used in

decision-making. It is common in applied health research to have multiple valued outcomes. In the context of AET adherence, lower knowledge about AET has been associated with lower adherence (43), and women prescribed AET frequently report not receiving sufficient information about the medication and its side-effects (93-96). Knowledge about AET and satisfaction with information about AET may be valued outcomes that warrant consideration in tandem. The CSA to decision-making I used in Study Three cannot incorporate these multiple valued outcomes.

Recent developments in decision-making methods in intervention optimisation have suggested an alternative approach. Using Bayesian principles, a posterior expected value (PEV) approach to decision-making overcomes the limitations of the CSA (92, 97). In a PEV approach, main and interaction effects are estimated using Bayesian models. Importantly, in the PEV approach, arbitrary thresholds for determining the importance of an effect are not used, and as such the model makes use of all main and interaction effect estimations without the need to unpick complex interaction effects (92). Multiple outcome variables can be incorporated through a process of weighting the relative importance of each outcome of interest (92). In a simulation study, the PEV approach outperformed the CSA in terms of detecting the true optimal intervention package (92). Future work should explore whether using the PEV approach would change which components make up the optimised information leaflet.

6.5.4 Recruitment and sampling

6.5.4.1 Diversity in samples

In all studies throughout this thesis, I recruited a largely homogenous sample, consisting of predominantly White, highly educated women. The large proportion of White women included in each sample partly reflects that age-standardised breast cancer incidence is higher in White women than in other ethnicities (98). However, the higher reported incidence rates in White women may reflect other factors, such as the increased likelihood of living in a more affluent area, in which screening uptake is higher.

The lack of diversity in the samples in this thesis is reflective of breast cancer and clinical trial research more broadly (99). In the context of adherence to AET, the homogenous sample

included in this thesis could be problematic, as women from ethnic minorities are less adherent to AET, across UK and US studies, and have increased rates of recurrence (100).

Different ethnic groups may also face different barriers to AET adherence. In a retrospective cohort study of women taking AET, side-effects including gastrointestinal symptoms, neuropsychological symptoms, vasomotor symptoms and musculoskeletal symptoms were more prevalent in Black women, and were more likely to increase during the course of AET prescription (101). Moreover, there is some evidence from a US study that non-Hispanic black people have higher fatalistic cancer beliefs, lower perceived risk of cancer and fewer cancer-related worries (102). These nuances in side-effect experiences and perceptions of cancer could impact how interventions such as those developed in this thesis are perceived and used.

In Studies Two and Four I aimed to determine the acceptability of intervention components. Acceptability can differ in different ethnic groups and literacy levels. For example, social and cultural norms may affect the acceptability of the intervention components (103), and people with lower literacy may find some intervention components less acceptable. The most recent systematic review of interventions aiming to support AET adherence reported that the only cultural adaptation to interventions made across 33 studies was changing the language of the intervention (6). Future studies incorporating more diverse samples should consider allocating resources to sufficiently adapt interventions to ensure suitability and acceptability for a wider demographic.

6.5.4.2 Methods to improve diversity

On reflection, I could have used a variety of efforts to recruit more diverse samples throughout this thesis. In Study Two(c) (survey to determine acceptability of a bank of SMS messages) and Study Three (optimisation of the information leaflet), I used a market research company to recruit participants. When using market research companies, a quota can be set to balance demographics to ensure diversity in the sample rather than one group of participants being overrepresented. However, using quotas increases recruitment costs and time. In future research, I should consider these increased costs and time earlier in the process to ensure involvement of a more diverse sample is a priority.

In Study Four, I could have used ethnicity as a purposive sampling criterion to increase diversity. When initially designing Study Four, purposive sampling strategies were considered

a priori in an attempt to recruit a more diverse sample. Initially, I considered aiming to sample participants from all eight experimental conditions in the pilot trial, across a range of ages and ethnicities. As discussed in Study Four, this was logistically complex. Due to the digital nature of the intervention components, I felt age should be the focus of the acceptability research. However, this resulted in a homogenous sample of White women. In future, attempting to purposively sample across multiple criteria would be useful to understand a wider range of perspectives from trial participants.

Sufficient time and resources should be devoted to involving diverse communities in research. Developing ongoing and meaningful relationships with more diverse communities to build up a level of trust between researchers and communities and break down power imbalances would be helpful (104). One potential method I could have used to engage with a more diverse range of communities is via a gatekeeper. A gatekeeper acts as a line of communication between a research team and a community. The gatekeeper can share study information with participants and facilitate connections between interested participants and research teams (105). Such an approach would have required additional resources, which I should have considered earlier in the process.

6.5.5 Patient and public involvement

Throughout my PhD, I met regularly with five women with breast cancer who have experience taking AET. Including patient perspectives has been fundamental to each stage of this PhD. During Study One, I consulted the patient representatives throughout multiple aspects predominantly in developing the content for each intervention component. During Study Two I held a focus group with the patient and public involvement (PPI) panel to determine the acceptability of the SMS messages. The PPI panel significantly contributed to the development of the information leaflet used in Study Three. I consulted them extensively on the components of the leaflet, the proposed conceptual model, and the design and content of the overall leaflet. They also contributed quotes and pictures to form the patient input component of the leaflet. Finally, in Study Four, the PPI panel were involved in the development of the interview guide for participants, in deciding to use rapid methods for the analysis, and were consulted on any proposed adaptations to be made to the intervention components. PPI work can improve the quality of research being conducted, alongside having positive impacts on the members of the public involved and the wider community (e.g.,

creating trust and acceptance of the research) (106, 107, 108). PPI work also has the potential to increase the impact of behaviour change research, but high-quality, robust research testing this hypothesis is needed (109).

The PPI group I worked with throughout this PhD included women of a range of ages and education levels. However, the group was composed entirely of White British women, and therefore similar limitations described in section 6.5.4.1 apply here. There was also a lack of diversity in terms of adherence to AET. All women were currently adhering to AET (while acknowledging some previous difficulties with adherence) and had a positive attitude towards adhering to AET. Recruiting a more diverse panel in terms of ethnicity and attitudes towards adherence at every stage of this research may have provided additional valuable perspectives and advice to support a wider population of women with breast cancer.

6.5.6 Beliefs about medicines outcome assessment (Study Three)

Choosing an appropriate outcome measure is a challenge across healthcare research. In Study Three, I chose to use the AET specific beliefs about medicines questionnaire (BMQ-AET) differential as the primary outcome measure. I chose this outcome as the necessity-concerns framework (NCF) has been widely used to explain women's beliefs about AET and their relation to medication adherence, and because the balance of necessity beliefs compared with concerns has been more consistently associated with medication adherence than necessity beliefs or concerns alone (110, 111). Assessing necessity beliefs or concerns completely in isolation would not incorporate the fundamental theory of the NCF, which suggests that the balance between necessity beliefs and concerns is important (111).

However, the differential score used to combine necessity and concern beliefs has received criticism (112). The differential score attempts to place two separate dimensions (necessity beliefs and concerns) onto a single dimension. In the context of Study Three, the single dimension differential score masked the finding that the leaflet mostly increased necessity beliefs rather than reducing concerns to achieve any significant main and interaction effects. In addition, this single dimension does not differentiate someone who has ambivalent beliefs (high necessity beliefs and high concerns) from someone indifferent to the medication (low necessity beliefs and low concerns) (112). It is possible that both the difference in necessity beliefs and concerns, as well as the strength in these beliefs could be important.

Polynomial regression is one method that has been suggested to overcome the aforementioned limitations of the BMQ differential (112). This method, when applied to medication beliefs, keeps necessity beliefs and concerns on two dimensions when predicting medication adherence. In several instances across conditions including stroke, asthma, diabetes, cardiovascular conditions, hypertension and people living with multi-morbidity, polynomial regression has rejected the differential model as the best fit (112-115). Often, ambivalent attitudes (high necessity beliefs and high concerns) are associated with lower adherence than indifferent attitudes (low necessity beliefs and low concerns) (112, 114). Polynomial regression has not been used to explore the relationship between medication beliefs and adherence in cancer patients but could provide a more comprehensive explanation of the relationship between medication beliefs and adherence. Exploring how BMQ outcomes could be used most effectively in the context of a factorial experiment, potentially considering the PEV approach with multiple outcomes of interest (as described in section 6.5.3.1), would be a useful future direction.

6.6 Implications and future research directions

6.6.1 Clinical implications

As this PhD is comprised of formative work to develop four intervention components, clinical implications are tentative, and may be more evident in the future. The complex intervention I have developed could support women in adhering to AET, subject to further optimisation (see section 6.6.2.1).

The individual studies have more immediate clinical implications. The work throughout this PhD supports the concept that adherence to AET is complex, and is likely to require varied approaches. In Study One I synthesised the evidence highlighting the need to support women prescribed AET, alongside identifying key barriers to AET adherence that women may need to be supported with. This synthesis could be a useful reference for healthcare professionals when supporting women with AET, to be aware of key barriers women may face.

The acceptability of all four intervention components, which was determined in Study Four, confirmed that varied approaches to supporting adherence are likely appropriate due to the multiple barriers to adherence. While comparing the acceptability of each intervention component against one another was not an aim of Study Four, tentatively, it is possible that

more active intervention components (e.g., ACT) could be more acceptable than more passive components (e.g., website), for which there was more indifference. Whether more active components are more effective in improving medication adherence could be identified in a full O-RCT (see section 6.6.2.1).

Medication beliefs are difficult to change, and a recent review has highlighted that many interventions aimed at modifying medication beliefs are resource intensive but yield small effect sizes. As such, effectiveness may not outweigh cost (29). The factorial experiment I conducted in Study Three, has demonstrated that medication beliefs can be changed using a low-cost information leaflet, demonstrating specific strategies that could be applied in clinical practice; mechanistic diagrams, icon arrays to emphasise medication benefits, answers to common concerns, and quotes from other people taking the medication. More basic side-effect information may be more beneficial if modifying medication beliefs is the aim of a leaflet. However, the strategies used in Study Three were more effective at increasing necessity beliefs compared with reducing concerns. My data show in contexts where the priority is to reduce concerns, leaflets should perhaps be provided in combination with other forms of support.

6.6.2 Research implications and directions for future research

A number of directions for future research have been highlighted within each chapter and throughout section 6.5. Further research implications and future directions are discussed below.

6.6.2.1 Full optimisation trial

Study Four provided valuable learning about the acceptability of the intervention components and informed several adaptations to improve acceptability prior to a full O-RCT. The most immediate next phase of this research will involve optimising the intervention package in a fully powered O-RCT to determine the optimal combination of components to support medication adherence. The O-RCT will use a 2^4 factorial design, whereby participants will be randomised to one of 16 experimental conditions. The main and interaction effects of the four intervention components will be estimated. Decisions on whether to include a component in the optimal package can focus on whether an increase in effectiveness is worth the increased cost or time associated with a different intervention package (116). As a result,

an intervention aiming to support adherence to AET will be optimised to balance effectiveness with efficiency, affordability and scalability.

6.6.2.2 Development of complex interventions

The methods used in this thesis have described a comprehensive method for intervention development. As suggested by MRC guidance, formative work should be completed to develop or adapt interventions, and different approaches to intervention development can be combined to utilise strengths from multiple approaches (38, 89). The combination of a broad intervention development framework (e.g., MOST), alongside an intervention design framework (e.g., IM) provides an overarching approach to intervention development and evaluation, alongside a more detailed approach to ensure an intervention is grounded in theory and targets relevant determinants of the health behaviour. I have demonstrated key aspects of IM that can be adapted to fit within MOST (e.g., specifying an optimisation objective in stage five of IM); these should be considered when combining other approaches with MOST. Combining approaches, such as IM and MOST or other appropriate frameworks, could be a useful method for other investigators to follow to enhance intervention development.

6.6.2.3 Using MOST to optimise health communication tools

The optimisation of the information leaflet in Study Three could act as guidance of how the MOST framework can be used to optimise health communication tools more broadly. Health communication tools are used to promote a wide range of health behaviours across chronic conditions. However, often information leaflets are used without a robust evidence base or evaluation (117, 118). O-RCTs of health communication tools, using intervention components with a similar granularity to those I used in Study Three, could provide empirical information of the effectiveness of health communication strategies. Accumulation of data from O-RCTs would build an evidence base of what specific intervention components are effective for health communication, and how they work in combination.

6.6.2.4 Process evaluations of complex interventions

Process evaluations of complex interventions require considerable thought and planning. In Study Four, I demonstrated an efficient method to conduct a mixed-methods process evaluation of a pilot trial, which other investigators could follow. In particular I highlighted

key considerations for a process evaluation embedded in a trial using a factorial design, such as considering participant burden and sampling methods. I also demonstrated how quantitative and qualitative data analysed using rapid methods could be triangulated. These methods could be applied to process evaluations more broadly, whether embedded in a factorial trial or not. Applying this mixed-methods approach to other focuses of process evaluations recommended in MRC guidance (119), for example to explore intervention fidelity, could be beneficial.

6.7 Conclusions

In summary, this thesis has developed four intervention components that aim to improve medication adherence in women with breast cancer prescribed AET: SMS messages, an information leaflet, acceptance and commitment therapy-based guided self-help, and a side-effect self-management website. The complex intervention developed was acceptable to women taking AET, and has advanced previous interventions by incorporating theory, targeting a range of barriers to AET using a variety of strategies, and being guided by a framework to ensure the intervention targeted appropriate determinants to adherence. The use of the MOST framework offers the potential to advance our understanding of the best ways to support women taking AET by improving our understanding of the effects that individual intervention components have on adherence. Using the MOST framework could lead to faster advances in behavioural intervention development, through developing interventions that are more effective, efficient, affordable and scalable.

6.8 References

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Appendix A : Study One supplementary material

Appendix A.1 : Registered clinical trials of interventions to support adjuvant endocrine therapy in breast cancer patients

Clinical Trial ID	Description of intervention	Intervention modality	Design	Population	Status	Adherence related outcomes
NCT03592771	Web-enabled app in which patients input their treatment-related symptoms or changes. Reported symptoms integrate into electronic health care records. Concerning symptoms trigger an alert to the care team and contact is made. App group: receive weekly reminders (via text or email) to use the app. App + Feedback group: receive weekly reminders and feedback about their use of the app.	App and text/email reminders	3 arm RCT; usual care vs app vs app plus feedback	AI or Tamoxifen	Recruiting	Electronic pillbox monitoring.
NCT04142476	Motivational, semi-directed interviews with pharmacists over 18 months, to motivate adherence to hormone therapy.	In person	No randomisation; Single group assignment	Any AET	Recruiting	Data from electronic pillboxes.
NCT04861896	Smartphone app with a 12-week program regarding psychoeducation about breast cancer and hormone therapy, stress awareness and management, social support, and enhanced communication and intimacy skills.	App	No randomisation; single group assignment	Hispanic/Latina women, any AET	Recruiting (for pilot trial)	Adherence to Refills and Medications Scale.

Clinical Trial ID	Description of intervention	Intervention modality	Design	Population	Status	Adherence related outcomes
NCT04824339	8 week aerobic and resistance program with virtual group-based supervised exercise sessions twice per week (60 minutes). Optional information on healthy eating.	Virtual exercise sessions via Zoom	Randomised, partial crossover; immediate intervention vs delayed intervention	Tamoxifen or AI	Recruiting	Voils DOSE non-adherence measure (secondary outcome).
NCT04651452	Values affirmation group: participants asked to write an essay monthly for 6 months about values important to them. Reflective journal group: Participants will be asked to write monthly essays for 6 months about their daily routines, and values not important to them that could be important to others.	Online website or postal	RCT; value affirmation vs reflective journaling	AI	Recruiting	Morisky measure of adherence, and electronic pill bottle monitoring.
NCT04719455	HCP visits; baseline visit will include motivation, collaborative goal setting and plans for adherence and physical activity. Follow-ups with HCP include personalised visual reports of medication intake, number of steps, and to identify any problems and solutions.	In person	Pilot RCT; usual care vs self-management intervention	Any AET	Recruiting (for pilot trial)	Number of days of missed medication (adherence is a secondary outcome).
NCT04176809	One compulsory workshop about AET benefits. Two optional workshops about nutrition and fatigue monthly. Monthly	In person, and letters	RCT; standard care vs routine HRQoL assessment and	Any AET	Not yet recruiting	Morisky Green

Clinical Trial ID	Description of intervention	Intervention modality	Design	Population	Status	Adherence related outcomes
	reminder letters sent including tips to deal with side-effects. Regular HRQoL assessments using a tablet before consultations.		therapeutic information			Levine scale.
NCT04554927	Web based application (no further information provided).	App	RCT; Web application vs active comparator (personalised schedule of medical follow-up)	Any AET	Recruiting	Morisky 8 item adherence scale.
NCT04086875	Twice weekly SMS messages providing educational information for 6 months to motivate adherence.	Text messaging	RCT; usual care vs text messages	Any AET	Recruiting	Smart pill bottles opening data.
NCT02883361	Motivational enhancement therapy. 4 in person counselling sessions over 12 months. Motivational interviewing to increase motivation and decrease ambivalence about change.	In person	RCT; Motivational interviewing vs attention control	AI	Not yet recruiting	Medication possession ration.
CN-01810939	Breast cancer information leaflet. Personalised letter to remind, motivate and inform patients about AET. Additional reminder phone calls from a study nurse.	Post, phone calls	3 arm RCT; standard information vs personalised letters telephone calls	No information	No information	Self-report and prescription refill.

Clinical Trial ID	Description of intervention	Intervention modality	Design	Population	Status	Adherence related outcomes
NCT03949270	Daily text messages asking whether the patient has taken their medication, Weekly messages asking about side-effects. Monthly messages asking about barriers to adherence. Contact from physician if there are any concerning responses.	Text messaging	RCT; usual care vs text messaging	AI	Recruiting	Persistence to therapy at one year.
NCT02707471	Self-management intervention. 10 calls over 6 months delivered by a nurse, and tailored interactive voice messages based on adherence data. Focus on strategies for managing side-effects, behavioural strategies to improve adherence and education.	Phone calls	RCT; self-management intervention vs general health education control	Any AET	Recruiting	Smart pill bottles (bottle opening and percent of pills remaining).
NCT02850939	Interactive smartphone app that was personalised and culturally tailored. Additional support from a patient navigator. Focus on patient education, reporting side-effects, delivery of self-care advice, simplified communication between patient and oncology team.	App and patient navigation	RCT; usual care vs app and patient navigation	Any AET	Recruiting	Prescribing and refill records and self-report data via mobile app.
NCT03837496	6 weekly one hour sessions in small groups of 2-3; psychoeducation, problem solving barriers to adherence, cognitive behavioural skills, relaxation training, coping strategies for side-effects, and mindfulness techniques. Two individual 15 minute semi-structured	Videoconferencing	RCT; STRIDE intervention vs medication monitoring control (pilot trial)	Any AET	Recruiting	MEMSCaps, MARS-5 (adherence is secondary outcome

Clinical Trial ID	Description of intervention	Intervention modality	Design	Population	Status	Adherence related outcomes
	interview with therapist one and two months after the intervention to problem solve ongoing challenges with adherence.					due to pilot trial).

Key: RCT = Randomised controlled trial; AI = Aromatase inhibitor; AET = Adjuvant endocrine therapy; DOSE = Domains of subjective extent of non-adherence; HCP = Health care practitioner; HRQoL = Health related quality of life; STRIDE = Symptom-targeted randomised intervention for distress and adherence to adjuvant endocrine therapy; MEMSCaps = Medication event monitoring system caps; MARS-5; Medication adherence report scale.
Note: Where there were multiple publications regarding an ongoing trial (e.g., study protocols and development papers), the trial is only displayed in the ongoing interventions table to avoid repetition.

Appendix A.2 : Intervention component examples

Appendix A.2.1 : SMS examples

- Take your medication consistently at the same point of your everyday routine. Within a couple of weeks, it should start to feel like 'second nature' to you.
- Try popping a pen and calendar next to where you take your medication, and tick when you've taken it - the tick will remind you if you've taken it already.
- Do you use your phone alarm to get you up in the morning? You could trying setting it with a daily message to take your medication.
- When you are down to your last weeks' worth of your medication, try to make it a rule that you order your new prescription at the same time.
- You can check the NHS app for when you can next order a repeat prescription. Pop a calendar entry in your phone to remind you when that is.
- If you go away, it could be useful to take your medication out of your bag and put it somewhere that you will see it

Appendix A.2.2 : Information leaflet example pages

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ROSETA

Refining and Optimising a behavioural intervention to Support Endocrine Therapy Adherence

Hormone therapy for treatment of early-stage breast cancer

Hormone Therapy

There are two main types of oral hormone therapy:

1. Tamoxifen.
2. Aromatase inhibitors (AIs), including anastrozole, letrozole and exemestane.

Four main factors can affect the hormone therapy you are given:

1. Menopausal status.
2. Your risk of cancer coming back.
3. Your experience of side effects.
4. Your other medical conditions.

This information leaflet has been designed with input from breast cancer survivors.

This information leaflet is independent research supported by the National Institute for Health Research NIHR Advanced Fellowship, Dr Samuel Smith, NIHR300588. The views expressed in this leaflet are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

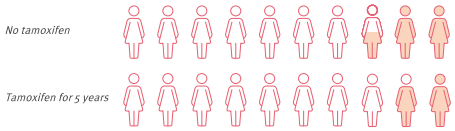
What are the benefits of taking this medication?

Unfortunately, there is a possibility that breast cancer can return. The good news is that taking hormone therapy is one thing you can do to reduce the chances of cancer returning, and to help you feel a sense of control over your health.

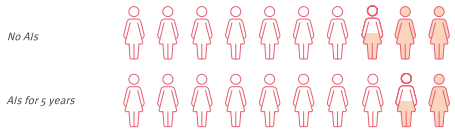
There are two main benefits of taking your hormone therapy as prescribed:

1. It can reduce the chance of breast cancer coming back.
2. It can reduce your risk of dying from breast cancer.

On average, taking tamoxifen for 5 years can reduce the risk of dying from breast cancer by around one third (33%) over the first 10 years.[1]



On average in post-menopausal women, taking AIs for 5 years can reduce the risk of dying from breast cancer by around 40% over the first 10 years.[2]



The benefits of hormone therapy can be different for each person. You can speak to your doctor to find out how hormone therapy will benefit you personally.

[1] Early Breast Cancer Trialist Collaborative Group et al. The Lancet. 2011; 378: 771-784.

[2] Early Breast Cancer Trialists' Collaborative Group. The Lancet. 2015; 386: 1341-1352.

Appendix A.2.3 : ACT participant manual example pages

2 INTRODUCTION TO SKILLS 1 AND 2

As you might have seen in Exercise 1, many of the unhelpful ways we manage tricky thoughts and feelings make common sense. For example, if we start worrying about something, we might say things like "stop thinking about that, think about something nice instead...".

If you have tried this, you may have found it doesn't usually get rid of unpleasant thoughts and feelings for good. It may get in the way of you enjoying your life. To explore what's going on here, **please try Experiment 1.**

EXPERIMENT 1: DON'T THINK OF THE POLAR BEAR

For the next minute I want you to do just one thing, one simple thing:

I want you to **NOT** think about a white polar bear. Do **NOT** think about a white polar bear. Don't think about its thick white fur; don't think about its massive size, or big white paws. I want you to start **NOT** thinking about a white polar bear for 1 minute...now.

*Were you able to **not** think of the polar bear?*

Most people find all they could think of was a white polar bear. This is surprising since you were specifically trying not to think of the bear. It seems like such an easy task, so why does this happen?

There seems to be an important difference between the best ways to deal with internal problems (problems within our thoughts or feelings) and external problems (practical problems in the outside world).

For example, if you do not like something going on in the outside world, you can simply find the problem and fix it. You can always get rid of an ugly sofa, clean a dirty house, or travel to the shops and buy groceries.

But, our internal worlds don't quite work this way, and getting rid of annoying thoughts and feelings isn't so easy. It can become a bit like trying to not think of a polar bear. It may not work, and even when it is possible, it takes lots of concentration. This can take time and energy away from doing things that matter to us.

Home Practice Task 2: Unhooking from thoughts and struggles

Please keep a diary of thoughts that hooked you in and what you did in response. We would like you to also describe what struggling feels like for you - so that you gradually start to recognise when you are, and are not, struggling. Also please describe any actions you took to unhook from thoughts. You can complete this diary each evening if you like - or another regular time that suits you.

Thought that hooked you	How long were you struggling before you noticed?	What did the struggling feel like?	What action did you take?
I look particularly unattractive today	About 2 minutes	• I kept following a train of thought and found that I wasn't really present where I was. • I found I was beginning to feel a little less comfortable	• I noticed I was struggling • Then put "I am having the thought that..." before it • Re-focused on chatting with my colleague

2 INTRODUCING YOUR OBSERVER SELF

Hopefully, over the past few weeks, you have been developing your ability to notice your thoughts and feelings. With this in mind, here is a short exercise that builds on this. Take a moment and do each of the following steps for 10 seconds.

1. Notice the sounds around you.
2. Notice the feelings in your body.
3. Notice your thoughts.
4. Notice that you are noticing sounds, feelings, and thoughts. Because you can notice these experiences, can you see that there is a part of you that is separate from each of the experiences?

So, how is it possible that we can step back and notice our own thoughts? What is this part of you that does the noticing? This isn't an easy question to answer. We call this part of ourselves 'the observer self'. If you are open to exploring this unique feature of being a human, **try Audio Task C**.

Please listen to audio file C

EXERCISE 3

FINDING WAYS TO CREATE AN EMPOWERING RELATIONSHIP WITH YOURSELF[1]

If you are willing, consider the most empowering relationship(s) that you have or have had.

This should be a rewarding relationship, with someone who has been supportive or helped you move forward in life. It could be a friend, family member, colleague, or even a spiritual relationship. If there is no one, then you are not alone, others will be in a similar position. In this case, imagine the type of person with whom you want to have an empowering relationship and what that relationship might look like.

Now I'd like you to reflect on what that person was like with you: what they did that allowed you to respond in such an empowered way? Some specific questions:

1. Did you, at least to some extent, feel accepted for who you are by this person?
2. Did you feel constantly judged or criticised by this person...?
3. When you were with this person were they present with you, or did they seem distracted and bored?
4. Did what you care about seem to matter to that person?
5. Did the relationship feel really unequal - like you always had to do what the other person said, or that you had no say in what was happening?

Looking at your reflections on this empowering relationship, is there anything you could try in your relationship with yourself. If there is, you may want to note them, and say them out loud. You can write them below if you like.

Things I could try in my relationship with myself, to help me move forward:

[1]Adapted from Hayes, (2019)

Appendix A.2.4 : Website example pages

ROSETA

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HOME MANAGING SIDE EFFECTS RESOURCES CONTACT

Home

Refining and Optimising a behavioural intervention to Support Endocrine Therapy Adherence.

This website aims to provide advice on managing some of the most common side-effects experienced when taking hormone therapy medication as part of your breast cancer treatment. For each side-effect, it states different strategies that might help. It also shows how much evidence there is to support each strategy.

We hope the website will provide support and improve quality of life for women like you.

ROSETA

MANAGING SIDE EFFECTS

Some women may experience side-effects from taking hormone therapies. Click here for strategies to help manage them.

RESOURCES

Lists of support groups, and additional online resources to help with managing side-effects.

CONTACT THE ROSETA RESEARCH TEAM

General Queries: roseta@leeds.ac.uk

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HOME MANAGING SIDE EFFECTS RESOURCES CONTACT

Home / Managing Side Effects / Side-effect management strategies

SIDE-EFFECT MANAGEMENT STRATEGIES

It is important not to suffer in silence if you feel your medications are causing side-effects. You should speak to your GP or breast care nurse if you experience any symptom that you find distressing.

We have outlined ways you can manage these side-effects without speaking with a healthcare professional. We have used a simple rating system to show how good the evidence is for these approaches.

Supportive
Overall, this strategy seems useful in helping to manage this side-effect.

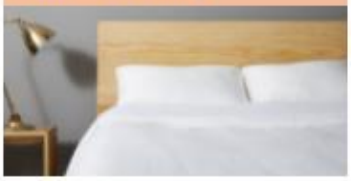
Limited / unclear
There may be some evidence to support this strategy. But it is not clear whether it will help with this side-effect.

No evidence
There is either no evidence for or against this strategy. OR the current evidence shows it is not helpful for this side-effect.

Harmful
This strategy may make the side-effect worse or cause unnecessary harm.

VULVOVAGINAL SYMPTOMS & SEXUAL FUNCTION

SLEEP DISTURBANCE



FATIGUE

HOT FLUSHES

NAUSEA & GASTROINTESTINAL PROBLEMS

JOINT PAIN

CONTACT THE ROSETA RESEARCH TEAM

General Queries: roseta@leeds.ac.uk

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ROSETA

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FATIGUE

Fatigue is a common symptom among women with breast cancer. This may be related to sleep disturbance (e.g. waking from night sweats) or after some treatments. Women may feel extremely tired, weak, or low in energy. Unlike fatigue you may have had before, resting does not always help.

The following are some recommended strategies for managing fatigue.

Side-effect management strategies

Vulvovaginal Symptoms & Sexual Function
Sleep disturbance
Fatigue
Hot Flushes
Nausea & Gastrointestinal Problems
Joint Pain

EXERCISE for fatigue

Evidence: Supportive. Overall, this strategy seems useful in helping to manage this side-effect.

Although it might not seem right, regular exercise can improve symptoms of fatigue. One high quality review found 22 studies testing the effect of exercise on fatigue. The conclusion supports this as a strategy. Exercise has also been shown to be safe, and has benefits for overall health.

If you are interested in increasing your levels of exercise, NHS resources might help. They include the 'Couch to 5K' programme, exercise tips and fitness guides. You can find them on our resources page.

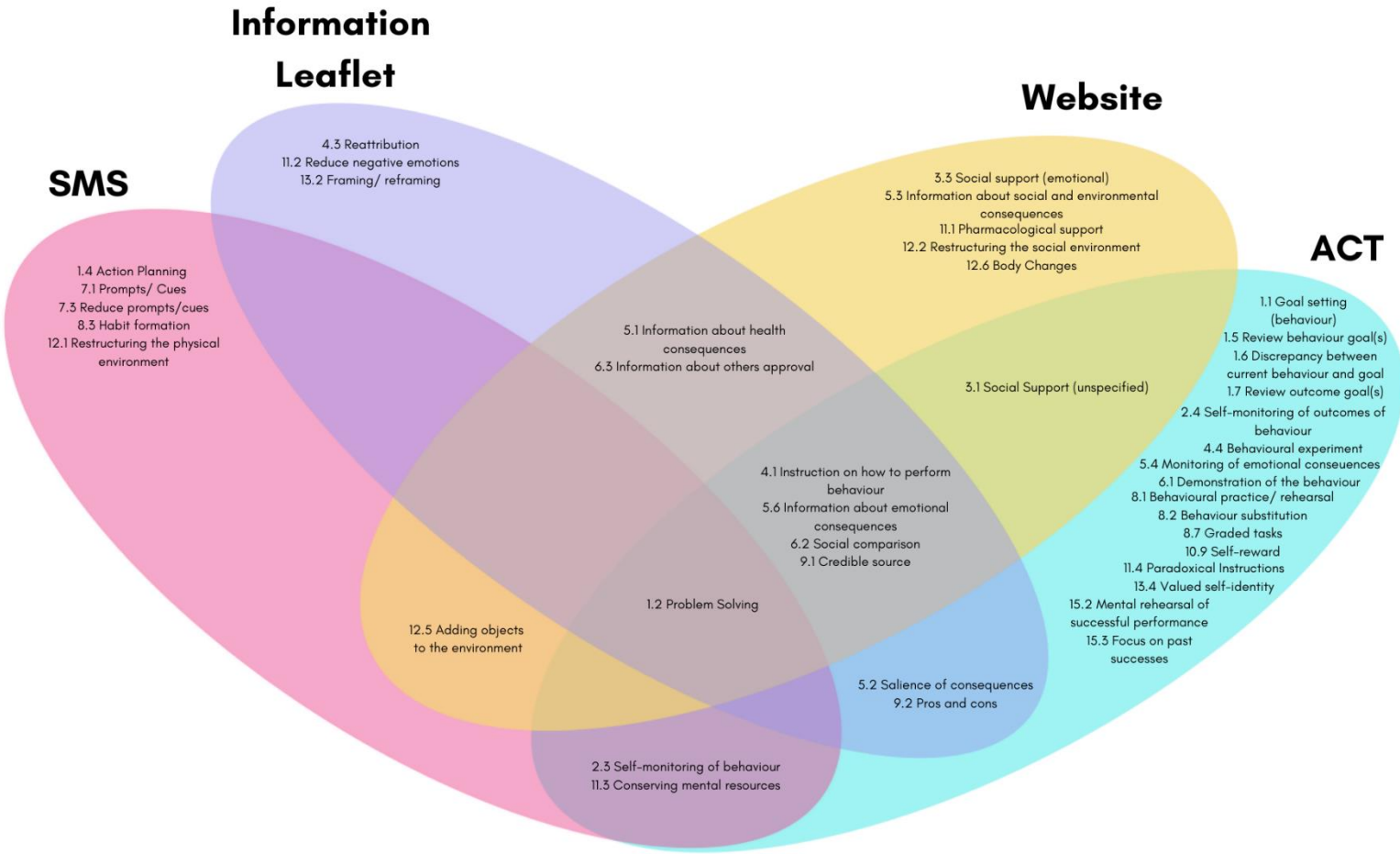
You may also find these tips from the Australian Cancer Council helpful:

- Start a gentle and regular exercise programme
- Start with a small activity, and include a rest period
- Vary the exercise so you don't get bored
- If you haven't exercised in a while, ask your GP about the type and amount of exercise to do
- Ask a friend to exercise with you to help with motivation
- Avoid long periods in bed
- Drink lots of water, as dehydration can be a cause of fatigue

ACUPUNCTURE for fatigue

Evidence: No Evidence. There is either no evidence for or against this strategy. OR the current evidence shows it is not helpful for this side-effect.

Appendix A.3 : Behaviour change techniques present in intervention components



Appendix A.4 : TIDieR (Template for Intervention Description and Replication) Checklist

No.	What	Details
1	**Name**	Refining and Optimising a behavioural intervention to Support Endocrine Therapy Adherence (ROSETA)
2	**Why: Rationale, theory, goal**	Adjuvant hormone therapies are prescribed at the end of hospital-based breast cancer treatment in order to prevent recurrence and mortality. However adherence to these medications is often poor, due to multiple factors, including forgetfulness, beliefs about medications, intolerable side-effects and psychological distress. Previous adherence interventions have tended to consist of solely educational based interventions that are not grounded in theory, and did not target the factors commonly associated with medication adherence. An intervention targeting a range of factors that have been highlighted as barriers to adherence in needed. *Memory and forgetting:* Mobile phone-based interventions are well suited to tackle forgetfulness as a barrier to adherence, through promotion of habit formation. SMS messages have been shown to be effective in improving medication adherence in other chronic illnesses but have not been widely tested in cancer patients. *Medication beliefs:* Accurate information about the necessity and risks of AET has the potential to increase women's perceptions of their need for AET, and to reduce unfounded concerns about the medication. Women with breast cancer have stated that they would like more accurate information about AET to overcome unfounded concerns. *Psychological Flexibility:* Acceptance and Commitment Therapy (ACT) has been shown to improve outcomes in those living with chronic illness, chronic pain, and cancer. ACT aims to increase a participant's awareness of their personal values, and to undertake more of the behaviours that support these values – a process that often involves developing a willingness to have painful thoughts and feelings (such as medication side-effects). ACT targets psychological flexibility, which can improve functioning during objectively difficult circumstances, and can often reduce psychological distress as a by-product. *Living with Side-effects:* One of the most commonly cited barriers to AET adherence is the impact of side-effects, and the lack of support for management of these is commonly cited. There are a number of strategies for these side-effects that have the potential to be effective in alleviating symptoms. However, these are typically not presented in a patient-friendly manner.

No.	What	Details
		Given the above, we have co-designed four intervention components for women with breast cancer who have been prescribed adjuvant endocrine therapies; SMS reminder messages to target forgetfulness, an information leaflet to promote necessity beliefs and reduce concerns, ACT therapy sessions to address psychological distress, and a side-effect management website to support living with side-effects. The aim of the intervention components are to support medication adherence to hormone therapy.
3	**What Materials**	*SMS component:* This component involves 43 SMS messages being sent over four months. This includes three opening messages, one closing message, 36 messages related to behaviour change techniques aiming to promote habit formation, and 3 messages (sent monthly) as a reminder that participants can stop any further SMS messages being sent. The content of the SMS messages was co-developed with experts in behaviour change and/or medication adherence, and women who have experienced breast cancer. *Information leaflet:* Participants will receive an information leaflet containing detailed information about AET. This includes information about how the medication works (with diagrams to supplement), information about the benefits and side-effects of AET, answers to common concerns that women have, and quotes from women with experience of taking AET. *ACT:* Participants will receive a participant manual consisting of information about the ACT skills and home practice tasks, in addition to corresponding audio files to assist with the home practice tasks. Each of the four modules focused on a different ACT-based skill: • Module 1: Mindfulness and unhooking • Module 2: Following your values • Module 3: Taking an observer perspective • Module 4: Recap, reflection, and staying committed *Therapists delivering ACT sessions:* Therapists delivering the intervention will receive two half days of bespoke training delivered by clinical psychologists with ACT experience. Alongside this, they will receive a training manual, with information about ACT generally, and specific session plans for the intervention sessions.

No.	What	Details
		Side-effect website: Participants will receive access to a bespoke website containing information and strategies for self-management of side-effects, and signposting to further sources of support.
4	**What Procedures**	***Intervention Delivery*** *SMS component:* Participants will receive 43 SMS messages over four months. The 36 messages relating to behaviour change techniques will be sent on the following schedule: • Daily messages for 2 weeks • Two messages per week for 8 weeks • Weekly messages for 6 weeks *Information leaflet:* Participants will be emailed the information leaflet. *ACT:* • 4x guided self-help modules consisting of information about ACT, home practice exercises and corresponding audio files • 1x 15-minute individual introductory session with a therapist • 3 x 25 minute individual support sessions with a therapist to discuss the module completed over the past week, their experiences of the home practice exercises, and to allow reflection on using the skills in their everyday lives. • 1x 15-minute closing session with a therapist *Side-effect website:* Participants will be emailed log in details to access the website.
5	**Who provided**	*SMS messages:* SMS messages will be sent automatically by the Leeds Clinical Trials Research Unit (CTRU). *Information Leaflet:* A research nurse will send the information leaflet via email. *ACT:* The therapists who will deliver the intervention will receive two half days of training in delivering ACT. The training will be delivered by Dr Chris Graham (CG), who has expertise in ACT applied to chronic disease. Training will include teaching about ACT and practice of intervention-specific therapy methods.

No.	What	Details
		Each site's therapists will have had a varied background that may or may not have included previous ACT training prior to our delivered training programme. However, all therapists will be Health and Care Professional Council (HCPC) registered practitioner psychologists (Clinical, Health or Counselling Psychologist). *Side-effect website:* Access to the bespoke website will be emailed by a research nurse.
6	**How: mechanisms of delivery**	*SMS component:* SMS messages will be sent in an automated fashion by the CTRU to the participants mobile phone based on the following schedule: • Daily messages for 2 weeks • Two messages per week for 8 weeks • Weekly messages for 6 weeks *Information leaflet:* Participants will be emailed a copy of the information leaflet. *ACT:* The individual sessions (five in total) will be delivered via phone or video conferencing. The participant manual containing information about each module, home practice tasks, and audio files will be emailed to each participant by the therapist following each session. *Side-effect website:* Participants will be given a login to the website and will be able to use this as they wish.
7	**Where: location of delivery**	*SMS Messages:* Not applicable. *Information Leaflet:* Not applicable. *ACT:* All sessions will be delivered remotely via phone or videoconferencing. *Website:* Not applicable
8	**When and how much**	*SMS component:* SMS messages will be sent by the CTRU based on the following schedule: • Three opening messages • Daily messages for 2 weeks • Two messages per week for 8 weeks • Weekly messages for 6 weeks

No.	What	Details
		• One closing message • One message after 4, 8 and 12 weeks indicating the participant can stop the SMS messages at any time *Information leaflet:* Participants will be emailed a copy of the information leaflet. *ACT:* The introductory session will last 15 minutes, three subsequent sessions will last 25 minutes, and the final closing session will last 15 minutes. The therapy sessions will be held weekly. *Side-effect website:* Participants will be given a login to the website and will be able to use this as they wish.
9	**Tailoring**	*SMS:* The same SMS messages will be sent in the same order to each participant. *Information Leaflet:* The same information leaflet will be sent to each participant. *ACT:* The deliverer may adapt the content to ensure it's relevant to each participant (e.g., through discussing specific individuals' values, goals, and behaviours). *Website:* The website will be the same for each participant.
10	**Modifications**	*<To be completed post study completion>*
11	**How well (planned)**	*SMS:* Successful delivery and receipt of the SMS messages will be recorded by the CTRU, alongside the number of SMS messages that were unable to be delivered. Participants will answer a single item asking whether they received the SMS messages, and another item asking how many of the SMS messages they read. Semi-structured interviews will be conducted to understand fidelity of receipt and enactment of the messages. *Information Leaflet:* The number of information leaflets sent out to participants will be recorded. Participants will be asked to self-report whether they received the information leaflet, and how much of the information leaflet they read. Semi-structured interviews will be conducted with participants to understand the fidelity of receipt and enactment of the information leaflet. *ACT:* Clinician fidelity to competently deliver the intervention in line with ACT will be assessed by an external rater with a background in ACT. They will complete the acceptance and commitment therapy fidelity measure (ACT-FM)

No.	What	Details
		therapist stance subscale checklist whilst listening to the audio recording of 10% of sessions. A score of > 4 on ACT consistent behaviours and < 5 on ACT inconsistent behaviours is considered competent. Additionally, an intervention specific metric of "Procedural Fidelity" will be completed, which measures other aspects of the intervention that are important for treatment fidelity but are not ACT-specific (e.g., reflecting on home practice tasks, sending module content etc.). Therapists will complete the procedural fidelity checklist following each session. A percentage score is created for each session by dividing the score achieved by the maximum possible score achievable within that session and multiplying by 100. Fidelity of ACT training will be monitored through Dr Graham assessing the recording of each therapists first ACT session, and rating competency based on the ACT-FM therapist stance subscale. Semi-structured interviews with the ACT therapists will assess the fidelity of training and delivery of the ACT component. Participant fidelity to the ACT component will be monitored by recording the number of sessions attended, missed and cancelled. The therapist will additionally report how much of the module materials the participant has read and engaged with (participant manual, audio files and home practice tasks). Participants will be asked to self-report receipt of the module content, and engagement with the participant manual, audio files and home practice tasks. Semi-structured interviews will additionally assess fidelity of receipt and enactment. *Side-effect website:* Website data will be tracked for each participant, including number of logins, time spent on pages, videos watched and clicked links. Participants will be asked a single item about their engagement with the website. Fidelity of receipt and enactment will be additionally assessed through semi-structured interviews.
12	**How well (actual)**	*<To be completed post study>*

Key: ROSETA = Refining and optimising a behavioural intervention to support endocrine therapy adherence; SMS = Short message service; AET = Adjuvant endocrine therapy; ACT = Acceptance and commitment therapy; CTRU = Clinical trials research unit; HCPC = Health and care professional council; ACT-FM = Acceptance and commitment therapy fidelity measure.

Appendix B : Study Two supplementary material

Appendix B.1 : Study B focus group schedule

Introduction

- The consent form will be read out and any participants who disagree with the statements will be able to leave the call.
- Aims of the focus group; to discuss the wording of SMS text messages generated by research scientists with the aim to support medication adherence in breast cancer patients
- Structure of the session; introduce a behaviour change technique, read out SMS messages relating to that behaviour change technique, and then to discuss wording of these messages.
- Right to withdraw at any time

Discussion of SMS Messages

Each behaviour change technique (BCT) will be introduced, giving the name and a short description of BCT, based on the v1 taxonomy. For example:

Name: Action Planning

Description: These messages have been created in order to prompt detailed planning of performance of the behaviour (including at least one of context, frequency, duration and intensity). Context may be environmental (physical or social) or internal (physical, emotional or cognitive). This also includes "implementation intentions" which are If….then… plans.

The SMS messages relating to this BCT will be read out and displayed on the screen, and there will be a discussion regarding the SMS messages. Discussion points will include:

- What do you think about the wording of these SMS messages?
- Is there anything you would change about the wording in any of these messages?
- Are there any messages that you would not want to receive and why?

This process will be repeated for each BCT.

Conclusion

Participants will be thanked for their time and informed that they will be sent a debrief letter.

Appendix B.2 : TIDieR (Template for Intervention Description and Replication) Checklist

No.	What	Details
1	**Name**	Brief SMS messages to support medication adherence to adjuvant endocrine therapy in women with breast cancer
2	**Why: Rationale, theory, goal**	Adjuvant endocrine therapy (AET) is routinely prescribed to women with early-stage breast cancer for 5-10 years once active hospital-based treatment has ended. AET prevents breast cancer recurrence and mortality. However, up to three-quarters of women prescribed AET are non-adherent. Unintentional non-adherence (e.g., forgetting to take your medication) is common in women taking AET. Previous interventions to support AET adherence tend to consist solely of educational based interventions, are not grounded in theory, and lack transparency in their development process. Promoting habits surrounding medication-taking could improve unintentional non-adherence as medication-taking will be less reliant on memory alone. SMS based interventions are a potential method to improve adherence and have been shown to be effective in other chronic illnesses. Therefore, we developed a pool of SMS messages to support adherence to AET that are based on habit formation theory.
3	**What Materials**	We developed a pool of 66 messages. Examples of these are available in Appendix B.4. The full pool of messages is available to research teams upon reasonable request. The pool contains the following messages based on selected BCTs from the BCTTv1. All messages are below 160 characters. • 17 messages targeting 'Restructuring the physical environment' • 10 messages targeting 'Adding objects to the environment' • 9 messages targeting 'Habit formation' • 13 messages targeting 'Prompts and cues' • 6 messages targeting 'Action planning' • 11 messages targeting 'Self-monitoring of behaviour' The messages chosen to be used, and the frequency and duration of messages to be sent can be determined by intervention developers.
4	**What Procedures**	The SMS messages are designed to be delivered to a participant's mobile phone device.

No.	What	Details
5	**Who provided**	The SMS messages are designed to be delivered by an automated system.
6	**How: mechanisms of delivery**	The SMS messages are designed to be sent in an automated fashion to a participant's mobile device.
7	**Where: location of delivery**	The SMS messages are designed to be delivered to a mobile device. All messages are under 160 characters to enable this.
8	**When and how much**	N/A. The current study has generated a pool of SMS messages that could be used in interventions with varying time periods.
9	**Tailoring**	N/A
10	**Modifications**	The pool of messages was modified following each individual study. Following study A, messages scoring below 5.5 on the fidelity subscale were removed. Following study B, messages deemed unacceptable were removed. Following study C, no messages were removed as no messages scored below 3 on the acceptability rating. Following study D, messages scoring below 5.5 on the fidelity subscale were removed.
11	**How well (planned)**	Messages were assessed for fidelity to the intended BCTs by experts in behaviour change in studies A and D. Experts in behaviour change were asked to rate each SMS message based on how well it targeted the BCT it was intended to target. Messages were rated on a scale of 1 (not very well) to 10 (very well). Any messages scoring a mean of below 5.5 (the midpoint on the fidelity scale) were deemed to have low fidelity and were removed from the pool of messages.
12	**How well (actual)**	N/A

Key: SMS = Short message service; AET = Adjuvant endocrine therapy; BCT = Behaviour change technique; BCTTv1 = Behaviour change technique taxonomy version 1.

Appendix B.3 : Justifications for deleting messages following Study B

Behaviour Change Technique	Message	Quote from focus group
Restructuring the physical environment	On days when you need to pick up your medication, place an empty medication pack in your purse as a reminder to pick your medication	"I don't know how big people's purses are, but you know, by all means put it in your handbag or put it on a shelf by the back door, or but yeah, I just wasn't sure about saying to put it in your purse."
	Store your medication on top of your usual breakfast items so that you remember to take them with breakfast	"some meds you're not meant to take with food"
	If leaving the house overnight then make life easier for yourself by putting your tablets somewhere you will see them to help remind you to take them	"that's a one-off, it's not like, oh you're going to be leaving the house every night, so I need to form a habit to leave the house every night overnight, do you know what I mean, it doesn't seem to fit there."
Adding objects to the environment	What object could you put in your house to remind you to take your medication?	"I didn't really sort of see the point, in a way it says an object, what are you going to get that's going to remind you other than leaving your pill box out, where you can see it. I just couldn't think of what you would use as an object to remind yourself"
	Buy your favourite drink to wash down your medication	"You know, lots of people would just wash it down with water, it's a small pill isn't it. I suppose it would work, there's some people maybe don't like water, so maybe buying your favourite drink would…a little bit pointless, so that's just me personally"
Habit formation	Try to always take your meds with your first meal of the day, so that it becomes part of your everyday routine	"Try to take your meds with the first food of the day, some meds you're not meant to take with food."

Behaviour Change Technique	Message	Quote from focus group
	A little poem, for you to commit to today, I'll take my medication during, the same activity every day	"I personally would just find that a little bit patronising, …., I think there's enough other messages which are kind of stronger than that, and if you have to kind of whittle it down to the, to certain ones I wasn't a fan of that one."
	Form a habit of putting an old empty meds packet in your purse, as reminder to collect your next prescription	"And then form a habit of putting an empty meds packet in your purse, I don't know how big people's purses are, but you know, by all means put it in your handbag or put it on a shelf by the back door, or but yeah, I just wasn't sure about saying to put it in your purse."
Prompts and cues	Keep your medication next to coffee/tea in kitchen cupboard to remind you to take it with your first cuppa.	"I think you have to be careful of that, because my, one lot of things I, something I have to take you can't take it with tea or coffee."
		New speaker: "I think all the store medications it says keep out of the reach of children, if you're sticking something on a worktop that's potentially within reach of a child, just need to be careful about giving directions like that I thought."
	Before taking the glass of water you may keep by your bed downstairs - stop and check if you have taken your medication that day	"It's kind of like that presumption that everyone goes upstairs with a glass of water, if you're taking, you know, you have got a glass of water so before you take it downstairs check that you've had your medication"
Self-monitoring of behaviour	At the end of each day, try ticking off whether you have taken your medication in a diary or calendar, to help you keep track	"I take mine on a morning, so by the time the end of the day comes with having chemo fog brain I couldn't remember whether I'd taken it or not. Well for me that was just a little bit is it worth putting in, you know, there are quite a few ladies that do suffer memory loss after they've had treatment, so I don't know, if you're doing something in the morning, trying to remember whether you've done it later on is just a bit…Yeah, not for me, but I mean some [laughs], with

Behaviour Change Technique	Message	Quote from focus group
		some people it might be alright for, but it did stand out that that one was a bit…"
	One way to help reduce forgetting to take your medication is to simply record each day if you took it or not.	"It's quite, 1) what's the point, remember your tablet, don't remember to write down you've forgotten it, so to me it's like kind of warped logic. But also it's quite negative, I think it should kind of be focusing on you are going to do this, forgetting is not an option, but don't… let's kind of go from a positive 100% point and sort of slide from that, not that oh you obviously will forget a few days, make sure you write it down and see if there's a link or whatever, so I just had a problem with that whole one to be honest"
	To monitor your meds you could try writing the first letter of each day next to each pill on your blister pack (M=Monday). This will track how you're doing	"I think number five is probably unachievable, so probably not worth the text message, I don't think there's space on your foil to get a, you know, to get a Sharpie and write the day of the week, and if anything that would be a good one to go back to the manufacturers of the medication, if they see it so often, that yeah it would be great if it could have days on the week just like the contraceptive pill does, but yeah, I'm not sure, I kind of think that would probably be a wasted text message because I can't imagine anybody would try and write the days of the week on the foil packet."

Appendix B.4 : Example SMS messages

BCT	Example Message
Restructuring the physical environment	Try putting your medication by something you do everyday e.g., your toothbrush. As long as you clean your teeth every day, you won't forget to take them!
Adding objects to the environment	Why not try buying yourself an attractive pillbox for your medication, to help you to remember to take it.
Habit formation	We suggest you always order your prescription in the same way (e.g., using an app) and in the same place (e.g., in your living room) so that it becomes a habit.
Prompts and cues	Try keeping your medication somewhere visible so that you are reminded to take the medication every day.
Action planning	As a suggestion, when you brush your teeth in the morning, follow it immediately by taking your medication.
Self-monitoring of behaviour	Making a note when you've taken your medication can help keep you on track. You could make a note in a calendar or diary, or use electronic notes or an app.

Behaviour change techniques (BCTs) are based on the behaviour change taxonomy (v1).

Appendix C : Study Three supplementary material

Appendix C.1 : Contextual scenario

All participants were presented with the following text prior to completing the baseline questionnaire. Participants were unable to move to the next page until 30 seconds had passed.

Some of you may have been diagnosed with breast cancer and may have had experience with adjuvant hormone therapy, a commonly prescribed treatment for breast cancer. Others will not have had experience of breast cancer, or these medications specifically. If you have not had experience of breast cancer and hormone therapy, please read the following scenario prior to beginning this survey. This explains the context in which hormone therapy would be prescribed as part of treatment for breast cancer. Please imagine you have been prescribed hormone therapy for breast cancer for the remainder of the survey.

Imagine you have received a diagnosis of oestrogen receptor-positive breast cancer, which is a specific type of breast cancer. The breast cancer has been found early which means it can be treated with the aim of curing it.

You have had surgery to remove the cancerous tumour, and have received radiotherapy and/or chemotherapy to get rid of any cancer cells that might have been left behind. This aims to reduce the chance that the cancer will return.

In the final appointment with your oncologist (the doctor that is coordinating your treatment plan), you have been told you will be prescribed a hormone therapy, and that you must take this medication (a small tablet) every day for the next 5 years, which could be increased to 10 years. You are told that this medication can reduce your risk of the breast cancer returning. You do not know much about this medication, but have heard from other women that it may cause some uncomfortable side-effects like hot flushes or joint pain. You are then discharged from the hospital, and are told to reorder your prescription via your GP. It is possible that you will experience some side-effects if you take the hormone therapy, but taking the hormone therapy can also reduce the chance that the cancer will come back.

Please note, you will only be able to proceed to the next page once 30 seconds has passed.

Appendix C.2 : R packages used for analysis

The following R packages were used;

- dplyr (v1.0.10) (1)
- summarytools (v1.0.1) (2)
- parameters (v0.18.2) (3)
- car (v3.1.0) (4)
- sjPlot (v2.8.12) (5)
- ggeffects (v1.1.3)(6)

1. Wickham H FR, Henry L, Müller K: dplyr: A Grammar of Data Manipulation. R package version 1.0.10. 2022.
2. Comtois D: summarytools: Tools to Quickly and Neatly Summarize Data. R package version 1.0.1. 2022.
3. Lüdecke D B-SM, Patil I, Makowski D: Extracting, Computing and Exploring the Parameters of Statistical Models using R. Journal of Open Source Software. 2020, 5:2445.
4. Fox J WS: An R Companion to Applied Regression. (Vol. 3rd). Thousand Oaks CA: Sage, 2019.
5. Lüdecke D: sjPlot: Data Visualization for Statistics in Social Science. R package version 2.8.12. 2022.
6. Lüdecke D: ggeffects: Tidy Data Frames of Marginal Effects from Regression Models. Journal of Open Source Software, 3:772.

Appendix C.3 : Engagement with the information leaflet

Experimental Condition	Median time spent on information leaflet page (range), in minutes
Condition 1	3.22 (3.0−7.93)
Condition 2	3.20 (3.02−10.42)
Condition 3	3.32 (3.02−7.80)
Condition 4	3.35 (3.02−10.33)
Condition 5	3.23 (3.02−10.87)
Condition 6	3.12 (3.02−10.18)
Condition 7	3.52 (3.02−12.25)
Condition 8	3.40 (3.02−11.47)
Condition 9	3.15 (3.02−13.93)
Condition 10	3.33 (3.02−42.48)
Condition 11	3.18 (3.03−8.08)
Condition 12	3.58 (3.02−37.37)
Condition 13	3.22 (3.02−7.18)
Condition 14	3.23 (3.02−10.27)
Condition 15	3.18 (3.00−7.20)
Condition 16	3.10 (3.02−29.28)
Condition 17	3.18 (3.02−6.73)
Condition 18	3.28 (3.02−11.30)
Condition 19	3.43 (3.02−9.32)
Condition 20	3.43 (3.02−9.32)
Condition 21	3.27 (3.02−15.05)
Condition 22	3.40 (3.03−16.80)
Condition 23	3.35 (3.02−9.40)
Condition 24	3.33 (3.02−10.88)
Condition 25	3.33 (3.03−10.15)
Condition 26	3.22 (3.02−13.05)
Condition 27	3.37 (3.03−10.93)
Condition 28	3.33 (3.02−16.52)
Condition 29	3.18 (3.02−6.18)
Condition 30	3.20 (3.02−8.58)
Condition 31	3.12 (3.02−6.33)
Condition 32	3.17 (3.02−8.25)

Appendix C.4 : Sensitivity analyses

Appendix C.4.1 : Sensitivity regression analysis of the primary analysis removing speed responders

		Beta	β (90% CI)	t	*p*
	Intercept	2.405		23.023	**< 0.001**
Main effects	Diagrams (D)	0.063	0.011 (−0.018, 0.040)	0.601	0.548
	Benefits (B)	−0.019	−0.003 (−0.032, 0.026)	−0.182	0.856
	Side-effects (SE)	−0.014	−0.002 (−0.031, 0.027)	−0.138	0.890
	Concerns (C)	−0.036	−0.006 (−0.035, 0.023)	−0.346	0.729
	Patient (P)	0.402	0.068 (0.039, 0.097)	3.852	**< 0.001**
Interactions	D × B	0.261	0.044 (0.015, 0.073)	2.495	**0.013**
	D × SE	−0.183	−0.031 (−0.060, −0.002)	−1.755	**0.079**
	B × SE	−0.097	−0.016 (−0.045, 0.013)	−0.929	0.353
	D × C	0.079	0.013 (−0.016, 0.042)	0.759	0.448
	B × C	−0.044	−0.007 (−0.036, 0.022)	−0.422	0.673
	SE × C	−0.094	−0.016 (−0.045, 0.013)	−0.904	0.366
	D × P	0.148	0.025 (−0.004, 0.054)	1.415	0.157
	B × P	0.026	0.004 (−0.025, 0.033)	0.247	0.805
	SE × P	−0.129	−0.022 (−0.051, 0.007)	−1.233	0.218
	C × P	−0.049	−0.008 (−0.037, 0.021)	−0.465	0.642
	D × B × SE	−0.070	−0.012 (−0.041, 0.017)	−0.670	0.503
	D × B × C	−0.037	−0.006 (−0.035, 0.023)	−0.357	0.721
	D × SE × C	0.120	0.020 (−0.009, 0.049)	1.148	0.251
	B × SE × C	0.032	0.005 (−0.024, 0.034)	0.310	0.757
	D × B × P	0.063	0.011 (−0.018, 0.040)	0.608	0.543
	D × SE × P	0.121	0.021 (−0.008, 0.050)	1.164	0.244
	B × SE × P	0.069	0.012 (−0.017, 0.041)	0.660	0.510
	D × C × P	0.170	0.029 (0.000, 0.058)	1.632	0.103
	B × C × P	0.002	< 0.001 (−0.029, 0.029)	0.019	0.985
	SE × C × P	0.006	< 0.001 (−0.028, 0.030)	0.054	0.957
	D × B × SE × C	−0.197	−0.033 (−0.062, −0.004)	−1.892	**0.059**
	D × B × SE × P	−0.082	−0.014 (−0.043, 0.015)	−0.794	0.427
	D × B × C × P	−0.170	−0.029 (−0.058, 0.000)	−1.624	0.105
	D × SE × C × P	0.070	0.012 (−0.017, 0.041)	0.670	0.503
	B × SE × C × P	0.108	0.018 (−0.011, 0.047)	1.029	0.304
	D × B × SE × C × P	0.140	0.024 (−0.005, 0.053)	1.338	0.181
Covariates	Baseline BMQ	0.792	0.744 (0.715, 0.773)	41.686	**< 0.001**
	Age	< 0.001	−0.002 (−0.032, 0.027)	-0.120	0.905

Note. Bold text indicates statistical significance ($p < 0.1$)
n = 1,450
Speed responders were classified participants who completed the survey in less than a third of the median time taken, or who answered the same response across all pretest or posttest BMQ-AET questionnaires.
Key: BMQ = Beliefs about medicines questionnaire.

Appendix C.4.2 : Demographics of participants split by presence of breast cancer diagnosis

Demographics	**Total sample (*n* = 1,603*)***	**Women reporting breast cancer diagnosis (*n* = 79)**	**Women not reporting breast cancer diagnosis (*n* = 1,524)**
Age, mean (SD, range)	47.93 (16.29, 18–83)	51.62 (17.36, 18–79)	47.74 (16.22, 18–83)
Marital Status (%)			
Single	398 (24.8)	10 (12.7)	388 (25.5)
Married	749 (46.7)	55 (69.6)	694 (45.5)
Cohabiting/ living with a partner	244 (15.2)	4 (5.1)	240 (15.8)
Divorced/ separated	159 (9.9)	9 (11.4)	150 (9.8)
Widowed	53 (3.3)	1 (1.3)	52 (3.4)
Education (%)			
GCSE/O-Level/ CSE	374 (23.3)	17 (21.5)	357 (23.4)
Vocational Qualifications (NVQ1+2)	142 (8.9)	8 (10.1)	134 (8.8)
A-Level	269 (16.8)	12 (15.2)	257 (16.9)
Higher educational qualifications (below degree)	190 (11.9)	9 (11.4)	181 (11.9)
Degree level education	547 (34.1)	24 (30.4)	523 (34.3)
Still Studying	9 (0.6)	0 (0.0)	9 (0.6)
Other	18 (1.1)	2 (2.5)	16 (1.0)
No formal qualifications	54 (3.4)	7 (8.9)	47 (3.1)
Ethnicity (%)			
Asian or Asian British	78 (4.9)	3 (3.8)	75 (4.9)
Black or Black British (African)	16 (1.0)	1 (1.3)	15 (1.0)
Black or Black British (Caribbean)	10 (0.6)	2 (2.5)	8 (0.5)
Mixed	27 (1.7)	2 (2.5)	25 (1.6)
Chinese	6 (0.4)	0 (0.0)	6 (0.4)
White British	1424 (88.8)	71 (89.9)	1353 (88.8)
Other	36 (2.3)	0 (0.0)	36 (2.4)
Do not wish to answer	6 (0.4)	0 (0.0)	6 (0.4)
Menopausal status (%)			
Premenopausal	697 (43.5)	31 (39.2)	666 (43.7)
Postmenopausal	684 (42.7)	45 (57.0)	639 (41.9)
Unsure	222 (13.9)	3 (3.8)	219 (14.4)

Appendix C.4.3 : Comparison between baseline and follow-up BMQ scores between women with and without breast cancer

	Baseline					Follow-up				
	BC, mean (SD)	**No BC, mean (SD)**	***t* (95% CI)**	**df**	***p***	**BC, mean (SD)**	**No BC, mean (SD)**	***t* (95% CI)**	**df**	***p***
Necessity[a]	18.92 (4.27)	17.94 (4.27)	1.99 (0.01, 1.95)	1601	**0.047**	19.11 (4.23)	18.72 (4.20)	0.82 (−0.55, 1.35)	1601	0.411
Concerns[a]	16.73 (5.07)	16.46 (3.90)	0.48 (−0.87, 1.43)	82.86*	0.632	16.57 (4.95)	16.42 (4.06)	0.26 (−0.98, 1.27)	83.55*	0.794
Differential[b]	2.19 (5.93)	1.49 (5.33)	1.14 (−0.51, 1.92)	1601	0.259	2.54 (5.75)	2.29 (5.72)	0.38 (−1.04, 1.54)	1601	0.704

Note. [a]Possible range: 5-25

[b]Possible range: -20 to +20

BC = participants reporting a diagnosis of breast cancer, *n* = 79

No BC = participants not reporting a diagnosis of breast cancer, *n* = 1, 524

* Indicates equal variances not assumed

Bold text indicates statistical significance ($p < 0.05$)

Appendix C.4.4 : Sensitivity analysis of the primary analysis removing women with breast cancer

		Beta	β (90% CI)	t	*p*
	Intercept	2.338		23.318	**< 0.001**
Main	Diagrams (D)	0.067	0.012 (−0.017, 0.041)	0.672	0.502
effects	Benefits (B)	−0.066	−0.011 (−0.040, 0.017)	−0.654	0.514
	Side-effects (SE)	0.064	0.011 (−0.018, 0.040)	0.638	0.523
	Concerns (C)	−0.030	−0.005 (−0.034, 0.024)	−0.303	0.762
	Patient (P)	0.373	0.065 (0.036, 0.094)	3.723	**< 0.001**
Interactions	D × B	0.290	0.051 (0.022, 0.080)	2.892	**0.004**
	D × SE	−0.171	−0.030 (−0.059, −0.001)	−1.704	**0.089**
	B × SE	−0.115	−0.020 (−0.049, 0.009)	−1.145	0.252
	D × C	0.020	0.003 (−0.025, 0.032)	0.196	0.845
	B × C	−0.075	−0.013 (−0.042, 0.016)	−0.749	0.454
	SE × C	−0.091	−0.016 (−0.045, 0.013)	−0.908	0.364
	D × P	0.127	0.022 (−0.007, 0.051)	1.268	0.205
	B × P	0.015	0.003 (−0.026, 0.031)	0.145	0.884
	SE × P	−0.124	−0.022 (−0.051, 0.007)	−1.241	0.215
	C × P	−0.060	−0.010 (−0.039, 0.018)	−0.595	0.552
	D × B × SE	−0.032	−0.006 (−0.034, 0.023)	−0.318	0.751
	D × B × C	−0.069	−0.012 (−0.041, 0.017)	−0.690	0.490
	D × SE × C	0.128	0.022 (−0.006, 0.051)	1.281	0.200
	B × SE × C	0.038	0.007 (−0.022, 0.036)	0.382	0.703
	D × B × P	0.072	0.013 (−0.016, 0.042)	0.720	0.471
	D × SE × P	0.132	0.023 (−0.006, 0.052)	1.316	0.189
	B × SE × P	0.057	0.010 (−0.019, 0.039)	0.566	0.571
	D × C × P	0.196	0.034 (0.005, 0.063)	1.955	**0.051**
	B × C × P	0.502	0.009 (−0.020, 0.038)	0.500	0.617
	SE × C × P	−0.001	< 0.001 (−0.029, 0.029)	−0.012	0.990
	D × B × SE × C	−0.209	−0.037 (−0.065, −0.008)	−2.083	**0.037**
	D × B × SE × P	−0.088	−0.015 (−0.044, 0.013)	−0.882	0.378
	D × B × C × P	−0.152	−0.027 (−0.056, 0.002)	−1.508	0.132
	D × SE × C × P	0.050	0.009 (−0.020, 0.038)	0.502	0.616
	B × SE × C × P	0.104	0.018 (−0.011, 0.047)	1.038	0.299
	D × B × SE × C × P	0.111	0.019 (−0.010, 0.048)	1.101	0.271
Covariates	Baseline BMQ	0.783	0.730 (0.701, 0.759)	41.228	**< 0.001**
	Age	0.004	0.011 (−0.019, 0.040)	0.601	0.548

Note. Bold text indicates statistical significance ($p < 0.1$)

Anyone who answered yes to having breast cancer was removed from analysis (n = 79)

Key: BMQ = Beliefs about medicines questionnaire.

n = 1,524

Appendix D : Study Four supplementary material

Appendix D.1 : Individual RAP sheet

SMS Component	Notes	Quotes
Fidelity of receipt (receiving messages, understanding of messages)		
Barriers to receipt		
Opt out and reasons		
Fidelity of enactment (using suggestions from messages)		
Barriers to enactment		
Affective attitude-likes		
Affective attitude-dislikes		
Burden		
Coherence		
Perceived effectiveness		
Improvements		
Miscellaneous		

Information Leaflet	Notes	Quotes
Fidelity of receipt (receiving, reading, understanding)		
Barriers to receipt		

Fidelity of enactment (using suggestions)		
Barriers to enactment		
Affective attitude-likes		
Affective attitude-dislikes		
Burden		
Coherence		
Perceived effectiveness		
Improvements		
Miscellaneous		

ACT	Notes	Quotes
Fidelity of receipt (attending sessions, understanding)		
Barriers to receipt		
Fidelity of enactment (using skills)		
Barriers to enactment		
Affective attitude-likes		
Affective attitude-dislikes		
Burden		
Coherence		
Perceived effectiveness		

Relationship with therapist		
Improvements		
Miscellaneous		

Website	Notes	Quotes
Fidelity of receipt (using website, understanding)		
Barriers to receipt		
Fidelity of enactment (using strategies)		
Barriers to enactment		
Affective attitude-likes		
Affective attitude-dislikes		
Burden		
Coherence		
Perceived effectiveness		
Improvements		
Miscellaneous		

Appendix D.2 : Withdrawals from SMS and ACT components

Condition	SMS withdrawal	ACT withdrawal	Time of ACT withdrawal	Reason(s) for withdrawal
1 (SMS, Leaflet, ACT, Web)	Y	Y	Before any ACT sessions	• Discontinuation of ACT due to eligibility violation and had preference for ACT • Does not need help remembering to take medication • Too many SMS messages • Does not like SMS intervention
1 (SMS, Leaflet, ACT, Web)	Y	Y	After ACT session 1	• Does not like the ACT intervention • Changed mind about trial involvement • Computer literacy
1 (SMS, Leaflet, ACT, Web)	Y	Y	After ACT session 1	• Clinical decision
1 (SMS, Leaflet, ACT, Web)	N	Y	After ACT session 4	• Bereavement
2 (SMS, Leaflet)	Y	N/A	N/A	• No reason given
3 (SMS, ACT)	Y	Y	After ACT session 2	• Does not have the time to give to the intervention; not the right time. • Involvement too much as back at work on a phased return.
3 (SMS, ACT)	Y	N	N/A	• Does not need help remembering to take medication
4 (SMS, Web)	Y	N/A	N/A	• Had enough of SMS and questionnaires
4 (SMS, Web)	N/A	N/A	N/A	• Changed mind about trial involvement • Does not feel the study is having any impact on her
5 (Leaflet, ACT)	N/A	Y	After ACT session 1	• Personal issues unrelated to health
5 (Leaflet, ACT)	N/A	Y	After ACT session 2	• No reason given
7 (ACT, Web)	N/A	Y	After ACT session 2	• Changed mind about trial involvement

Key: SMS = Short message service. ACT = Acceptance and commitment therapy. Web = Website component.

Appendix D.3 : Additional acceptability items for ACT component

Appendix D.3.1 : Additional acceptability items, overall and by site

Acceptability item	Overall, n = 19	Nottingham, n = 2	Gateshead, n = 4	King's Lynn, n = 5	Woolwich, n = 5	Whiston, n = 3
Usefulness of ACT components, n (%)						
Therapist support sessions						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somewhat	3 (15.8)	0 (0.0)	1 (25.0)	1 (20.0)	0 (0.0)	1 (33.3)
Very	14 (73.7)	0 (0.0)	3 (75.0)	4 (80.0)	5 (100)	2 (66.7)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Participant manual						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somewhat	4 (21.1)	0 (0.0)	1 (25.0)	1 (20.0)	1 (20.0)	1 (33.3)
Very	13 (68.4)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	2 (66.7)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Home practice exercises						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	2 (10.5)	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)
Somewhat	2 (10.5)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (33.3)
Very	13 (68.4)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	2 (66.7)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Audio files						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	2 (10.5)	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)
Somewhat	2 (10.5)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)
Very	13 (68.4)	0 (0.0)	3 (75.0)	4 (80.0)	3 (60.0)	3 (100.0)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Introductory session						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	2 (10.5)	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)
Somewhat	2 (10.5)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)
Very	13 (68.4)	0 (0.0)	3 (75.0)	3 (60.0)	4 (80.0)	3 (100.0)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Session 2						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Somewhat	1 (5.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Very	14 (73.7)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	3 (100.0)
Missing	2 (10.5)	1 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Session 3						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)

Acceptability item	Overall, n = 19	Nottingham, n = 2	Gateshead, n = 4	King's Lynn, n = 5	Woolwich, n = 5	Whiston, n = 3
Somewhat	1 (5.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Very	14 (73.7)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	3 (100.0)
Missing	2 (10.5)	1 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Session 4						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Somewhat	1 (5.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Very	14 (73.7)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	3 (100.0)
Missing	2 (10.5)	1 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Closing session						
Not at all	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A little	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somewhat	2 (10.5)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)
Very	14 (73.7)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	3 (100.0)
Missing	2 (10.5)	1 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phone/video sessions						
Phone	12 (63.2)	1 (50.0)	3 (75.0)	2 (40.0)	4 (80.0)	2 (66.7)
Video	6 (31.6)	0 (0.0)	1 (25.0)	3 (60.0)	1 (20.0)	1 (33.3)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acceptability of phone/video sessions						
Completely unacceptable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unacceptable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No opinion	1 (5.3)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acceptable	4 (21.1)	0 (0.0)	1 (25.0)	1 (20.0)	1 (20.0)	1 (33.3)
Completely acceptable	13 (68.4)	0 (0.0)	3 (75.0)	4 (80.0)	4 (80.0)	2 (66.7)
Missing	1 (5.26)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note. Only data from participants who completed the acceptability questionnaires are included.
Key: ACT = Acceptance and commitment therapy.

Appendix D.4 : Quotes to illustrate qualitative findings

Appendix D.4.1 : Qualitative findings regarding acceptability of the SMS intervention component

TFA Domain	Key findings	Illustrative quote(s)
Affective attitude	• Most women liked the messages and the variety.	"I think it's a really good idea, yeah. Um I think the messages that are contained in them are quite helpful, useful and informative really and I think as opposed to, I, I envisaged that they would just be reminders where the extra information that they contained I thought was, um, was quite useful." *(≤ 50, C4[SMS, Web])*
	• A minority felt some messages were common sense, or out of place.	"Some I thought, well, well yeah that's really common sense…I think there was one about taking your medication on holiday and making sure you had it in your handbag…to me that's common sense." *(≥ 70, C4[SMS, Web])*
Burden	• Overall messages were low burden, and not intrusive.	"Uh, I thought the frequency was fine, cos it's only a message…a text message is is easy to either look at or ignore, isn't it?...So I, I, I didn't find it too intrusive." *(51−69, C3[SMS, ACT])*
	• Two participants felt daily messages were too frequent.	"I think when I was getting them like daily, there was points where I kind of would check my phone and go oh it's just that, because [laughs] I felt they were a bit too frequent." *(≤ 50, C3[SMS, ACT])*
	• Some participants may have opted out if not within trial setting.	"Had I not been within the trial, had, had this been kind of like real life [laughs] if that makes sense, um, but, I may well have done [opted out]… I figured that you know I was in the trial, and therefore I wanted to see what all the messages, because they were clearly different, how they changed and what the messages were like." *(51−69, C2[SMS, IL])*
Coherence	• Most women understood the messages were about building routines.	"They would be useful because at the start it's about, it's about getting, um, routines in place… and once you've got your routines in place, then things become easier and, and you're more likely to do that [take AET]." *(51−69, C2[SMS, IL])*
	• Some women felt the messages were a prompt.	"I guess to prompt, to prompt you to take them and suggest ways, an immediate way to suggest ways of how to help you to remind you to, to take them, um, and I suppose a way of sending you tips about things." *(≤ 50, C3[SMS, ACT])*

TFA Domain	Key findings	Illustrative quote(s)
	• Some felt the messages emphasised the importance of taking AET.	"The reminder made me kind of talk to myself and say look you've got to take it, it's for your own good so just take it." *(≥ 70, C2[SMS, IL])*
	• One participant felt the messages were a form of social support.	"So my understanding of the trial, rightly or wrongly, was that it kind of just a sort of a friendly voice really, just to, sort of a gentle, a gentle support, a gentle we're still here for you and there is still somebody." *(51–69, C2[SMS, IL])*
Perceived Effectiveness	• Most women felt they had routines to take AET, but messages would be effective for those that didn't.	"I think if you, if you need a bit of help organising, I thought they would be very useful…they were just kind of coming from different angles… I can imagine that some women might just think ooh yeah that will work for me and try it, um because there was quite a few different ideas I think." *(51–69, C1[SMS, IL, ACT, Web])*
	• Some women felt personalising the timing of the messages would make them more helpful.	"Maybe if there had been one midday option, then you know that would've been nearer to the time that I take it... you know if you have like an 8am or a 6pm option." *(< 50, C4[SMS, Web])*

Key: SMS = Short message service. 'C' = Condition, e.g., C1 = Condition 1. Web = Website component. IL = Information leaflet component. ACT = Acceptance and commitment therapy component. AET = Adjuvant endocrine therapy. ≤ 50 = aged 50 or below. 51–69 = aged 51 to 69. ≥ 70 = aged 70 or above.

Appendix D.4.2 : Qualitative findings regarding the acceptability of the information leaflet component

TFA Domain	Key findings	Illustrative quote(s)
Affective attitude	• Several aspects of the leaflet were liked, including the quotes from other women, and information about side-effects.	"I think quotes from other women, I think that's, that is a good idea. I think that's something, you know, that you can relate to." *(51–69, C6[IL, Web])* "The side-effects table, I just thought that was just like really useful knowing that, that those things are side-effects of the drugs that I'm taking. Um and I suppose it was just kind of reinforcing that what I was experiencing wasn't different from what other people experienced." *(51–69, C1[SMS, IL, ACT, Web])*
	• One participant felt they already knew the information, but liked having it written down.	"I do think it's important to reinforce it and have it written down, so you've got that if you need to look back…for me I did a lot of research and reading around it anyway." *(51–69, C2[SMS, IL])*
Burden	• Concise and easy to read, without "medical jargon".	"It was easy to read, it wasn't written in complicated medical jargon so I understood what I was reading. And it wasn't a load of information bombarded at you. It was, it was concise, it was all I needed to know was in there." *(≥ 70, C2[SMS, IL])*
Coherence	• Most women understood the leaflet was aiming to provide information about AET.	"I feel like it, you were you were trying to support women to have, have the right information so they'd keep taking the tablets…I think the message was this is kind of how they work, this is what other people have to deal with, there are side-effects but it's so important that you keep taking, taking them." *(51–69, C1[SMS, IL, ACT, Web])*
Perceived Effectiveness	• Some women reported being able to go back to the leaflet and re-read it to remind themselves of the benefits was helpful to remind them why they are taking AET.	"The usefulness of it for me is that I can always go back to it and read it over again to reassure myself that I'm doing the right thing." *(≥ 70, C2[SMS, IL])* "There's a whole page with, you know what the benefits of taking it, and um it's very clear, you know, it can reduce it to come back and it can reduce your risk of dying from it. And if nothing else, it's that page that just makes me think, OK, I can cope with the side-effects because I'm going to do everything possible to stop it coming back. I think that's, I think that's your message." *(51–69, C1[SMS, IL, ACT, Web])*

Key: SMS = Short message service. 'C' = Condition, e.g., C1 = Condition 1. Web = Website component. IL = Information leaflet component. ACT = Acceptance and commitment therapy component. AET = Adjuvant endocrine therapy. ≤ 50 = aged 50 or below. 51–69 = aged 51 to 69. ≥ 70 = aged 70 or above.

Appendix D.4.3 : Qualitative findings regarding the acceptability of the ACT intervention component

TFA Domain	Key findings	Illustrative quote(s)
Affective attitude	• Participants liked the practical, skills focus.	"Practical stuff, I think. So, you know, it wasn't kind of really like in-depth kind of therapy, it was more about, OK, you know, these things are going on, let's think about positive ways that you can deal with some of this stuff… I thought that was really good." *(51−69, C1[SMS, IL, ACT, Web])*
	• A number of ACT skills were liked, with participants providing several explicit examples of how they have applied the skills to their lives.	"There was an audio where you had to imagine like a stream running past and like put your thoughts on a leaf and let them float past… I'm struggling with like menopausal symptoms, things like anxiety palpitations, hot flushes, and trying to kind of find ways to sort of breathe, take a moment out, just calm myself, like re-centre…so that's an easy one for me now, that really stuck with me and I can like visualise and think about my thoughts." *(≤ 50, C3[SMS, ACT])* "I was talking a lot about wanting to do something, but because I, I don't have the energy for work I, I wanted to do you know, something like volunteering where I only go if I feel up to it. And on Saturday I did a full days volunteering at, um, our local rugby club, you know and Oh my God like it just it's like a new lease of life to be able to go out and spend the day out. My confidence was up to talk to people, you know." *(≤50, C7[ACT, Web])*
	• Support sessions from the therapist were liked by all participants overall.	"She was lovely, um, and, you know I got, I felt as though we got on well together and we, you know, we could chat, or I could chat easily to her…I didn't feel as though I couldn't say anything, or I was guarded at all, I was, you know, quite comfortable talking to her." *(51−69, C3[SMS, ACT])*
	• Most participants felt the timing of the sessions were good, as other support had ceased. One participant felt they were not ready for the sessions.	"After I'd finished the radiotherapy there was nothing for a long time and that felt, that felt hard to cope; how do I know the cancer has gone…I mean yes I have phone calls to phone people but it was just that I should be feeling happy about the fact that it's all over, but having the sessions with the psychologist helped me to cope with that, and get over it, and not feel as dependent on needing to go to the hospital all the time." *(51−69, C5[IL, ACT])*

TFA Domain	Key findings	Illustrative quote(s)
		"Just the opportunity to talk was the most helpful thing. Um, and I could see where it could go with like the, the mindfulness and acceptance that way, I could, I could see where it could go, um, I felt for me it was all too raw still." *(51−69, C7[ACT, Web])*
	• One participant felt some pressure to talk in the sessions to fill the time.	"She listened really well, but I didn't feel like I got too much from her back. I felt like I was the one that had to do, so I felt a little bit sort of anxious that I had to keep talking, if you know what I mean." *(51−69, C3[SMS, ACT])*
Burden	• Liked the online delivery and flexibility of sessions- made it easier to attend.	"If I hadn't of been, if it hadn't of been virtual, I probably would have missed three sessions…because I wasn't well enough to do, to get out." *(≤ 50, C7[ACT, Web])*
	• Weekly sessions too close together- need more time to practice skills.	"I felt like I didn't have much time to sort of do the booklet and work on it before I was having a review...Two to three weeks [between sessions] I would have, I would have felt better. I would have felt like I'd worked on it more and probably could have asked more questions." *(51−69, C3[SMS, ACT])*
	• Therapy was physically and emotionally challenging- having sessions in the morning and then going back to work was difficult.	"The second I start talking about how I feel and my emotions I get very tearful, and, um, I then sort of have to talk and think about things that I, I really suppress a lot of the time, and then I get this physical reaction to it with the tears, um, and so I would get the, the end of the session and I feel like I've been steam-rollered basically, um, and, and it takes me a while to, sort of, get my equilibrium back. Um, and I think the, the, challenge for me was the timing of the sessions, often the only time slot I could have, um, would be in the mornings and then having to then put myself back together and go to work was quite difficult." *(51−69, C7[ACT, Web])*
Coherence	• Overall understanding that ACT was teaching skills and coping mechanisms.	"It's giving you those skills to cope because there's, there's such a lot going on, and I think until you go, like I didn't even realise myself how, how much I'd still be dealing with now, um so I suppose it kind of arms you with the skills for what else might come along, you know, come your way while you're going along this journey if you like." *(≤ 50, C3[SMS, ACT])*

TFA Domain	Key findings	Illustrative quote(s)
	• Some participants were initially unsure about how ACT would help them.	"Well, in the beginning, it was, the first two sessions, it was kind of, um, hard to get my head around it. Do you know, I didn't really see a plan for it or what it was doing. But then by the third one, I felt that it was doing very, you know, I could understand it more, and I was figuring it out, um, I found it very good from then on in." *(≤ 50, C7[ACT, Web])*
Perceived Effectiveness	Multiple experiences were shared regarding perceived effectiveness: • How ACT had helped take AET • Reduced psychological distress • Helpful to return to work • Helped to cope with side-effects of AET	• "I was gonna pack it in [taking AET] and, um this [ACT] sorta gave me the positivity um, so that when I did speak to my, um, doctor when she rang the the cancer doctor, the oncologist, um, I was going to ask her to take me off it, but I decided to give it another chance and that happened about the same time as starting this." *(51−69, C7[ACT, Web])* • "I found them very, very therapeutic, especially mentally. I think that that's helped my mental health 100%. You know, it really has, it really has helped that side of it." *(51−69, C7[ACT, Web])* • "I think as well going through those, some of those strategies and thinking, you know, make you think what's important and what's not, with going back to work, it sort of helped to know, I was a bit like well I'm not gonna stress about this anymore." *(51−69, C3[SMS, ACT])* • "I got such a lot out of it, um, I was able to relax more, my sleeping came back… I sorted my hot flushes without taking drugs." *(51−69, C5[IL, ACT])*

Key: SMS = Short message service. 'C' = Condition, e.g., C1 = Condition 1. Web = Website component. IL = Information leaflet component. ACT = Acceptance and commitment therapy component. AET = Adjuvant endocrine therapy. ≤ 50 = aged 50 or below. 51−69 = aged 51 to 69. ≥ 70 = aged 70 or above.

Appendix D.4.4 : Qualitative findings regarding the acceptability of the website intervention component

TFA Domain	Key findings	Illustrative quote(s)
Affective attitude	• Some women felt it was beneficial to see videos of other women.	"It's actually so beneficial when you're watching other people who have gone through it, um, when you're just starting, it really, really helps." *(51−69, C7[ACT, Web])*
	• However, one participant felt the videos were too stereotypical.	"More relatable age, more relatable people to me as well, you know I'm not typical grey haired 50-60 year old, that's awful but you know what I mean." *(≤ 50, C4[SMS, Web])*
	• One participant felt the website was not aesthetically pleasing.	"It seemed quite, not overly user friendly and a little bit clunky, I don't think it's attractive aesthetically…It's all very boxy…not soft, or not approachable really." *(≤ 50, C4[SMS, Web])*
	• A few participants found the information too general and vague in places.	"I accessed it because I was experiencing joint pain, bone pain...the information about bone pain was that vague that I came away thinking well it didn't really answer my question you know what I mean, it, it, it's informative but not enough. It's too vague." *(≤ 50, C4[SMS, Web])*
	• Some women liked the honesty of the evidence ratings for the side-effect management strategies, but others did not feel this was helpful.	"I mean I liked the fact that it gave the evidence. You know, I'm. I kind of like working on sort of facts. It kind of work, it worked for me. It wasn't a great revelation, but it was like, you know, some of these things are worth trying, they might not help. But you know, there's no particular evidence, but you never know." *(51−69, C1[SMS, IL, ACT, Web])* "I mean it's almost saying right there's the suggestions however there's no evidence. It's just like taking and giving on one hand and then saying well there's no evidence for this...if there's no evidence to it it's almost like well it shouldn't even be there then." *(≤ 50, C4[SMS, Web])*
Burden	• The website modality was acceptable.	"I liked it being online, I think you know for, um, certainly people, most people these days, um, you know, are familiar with accessing websites and navigating around them now." *(51−69, C6[IL, Web])*
Coherence	• Participants generally understood the website was to provide side-effect self-management strategies.	"They can dig into things that would help them manage side-effects, that's useful." *(51−69, C6[IL, Web])*

TFA Domain	Key findings	Illustrative quote(s)
Perceived Effectiveness	• Some women acknowledged the website would be helpful for those who haven't researched coping strategies. • Some women felt the website didn't teach them anything new.	"It was all things that made sense, um, were logical and you know, I can imagine that if you weren't the sort of person that would've thought of all those things already, it would've been very helpful." *(51−69, C7[ACT, Web])* "Nothing was really surprising. And nothing's really light bulb moment… It, it was an interesting read, but I don't think it massively changed things for me." *(51−69, C1[SMS, IL, ACT, Web])*

Key: SMS = Short message service. 'C' = Condition, e.g., C1 = Condition 1. Web = Website component. IL = Information leaflet component. ACT = Acceptance and commitment therapy component. AET = Adjuvant endocrine therapy. ≤ 50 = aged 50 or below. 51−69 = aged 51 to 69. ≥ 70 = aged 70 or above.

Appendix D.5 : Triangulation

Appendix D.5.1 : SMS triangulation

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Affective attitude	Most women felt the messages were a good idea and found the content interesting and informative.	The majority of women (55%) liked or strongly liked the messages. A substantial proportion had no opinion (40%), and 5% disliked the messages.	Partial agreement	Partial agreement	Partial agreement
Affective attitude	A minority felt some messages were too much like common sense or out of place.	The majority of women (55%) liked or strongly liked the messages. A substantial proportion had no opinion (40%), and 5% disliked the messages.	Partial agreement	Partial agreement	Partial agreement
Burden	Overall low burden, and not intrusive.	Most participants (85%) felt it took no effort or a little effort to engage with the SMS messages. Some participants (15%) had no opinion, but no participants felt it too a lot or a huge amount of effort to engage with the SMS messages.	Agreement	Agreement	Agreement
Burden	Overall low burden, and not intrusive.	Most (90%) participants felt the frequency was completely acceptable or acceptable. A minority (5%) of participants thought the frequency was unacceptable.	Partial agreement	Partial agreement	Partial agreement

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Burden	Two participants felt daily messages were too frequent.	Most participants (85%) felt it took no effort or a little effort to engage with the SMS messages. Some participants (15%) had no opinion, but no participants felt it too a lot or a huge amount of effort to engage with the SMS messages.	Silence	Silence	Silence
Burden	Two participants felt daily messages were too frequent.	Most (90%) participants felt the frequency was completely acceptable or acceptable. A minority (5%) of participants thought the frequency was unacceptable.	Agreement	Agreement	Agreement
Burden	Some participants may have opted out if not within trial setting.	Most participants (85%) felt it took no effort or a little effort to engage with the SMS messages. Some participants (15%) had no opinion, but no participants felt it too a lot or a huge amount of effort to engage with the SMS messages.	Silence	Dissonance	Silence
Burden	Some participants may have opted out if not within trial setting.	Most (90%) participants felt the frequency was completely acceptable or acceptable. A minority (5%) of participants thought the frequency was unacceptable.	Silence	Partial agreement	Partial agreement

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Coherence	The majority of women understood the messages were about building routines of taking medication.	Most (65%) of participants agreed or strongly agreed that it was clear how the SMS messages would help them to take their medication. A quarter (25%) had no opinion, and 10% disagreed that it was clear how the SMS messages would help them to take their medication.	Agreement	Agreement	Agreement
Coherence	Some women felt the messages were a prompt to take medication.	Most (65%) of participants agreed or strongly agreed that it was clear how the SMS messages would help them to take their medication. A quarter (25%) had no opinion, and 10% disagreed that it was clear how the SMS messages would help them to take their medication.	Partial agreement	Partial agreement	Partial agreement
Coherence	Some felt the messages emphasised the importance of taking medication.	Most (65%) of participants agreed or strongly agreed that it was clear how the SMS messages would help them to take their medication. A quarter (25%) had no opinion, and 10% disagreed that it was clear how the SMS messages would help them to take their medication.	Partial agreement	Partial agreement	Partial agreement

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Coherence	One participant felt the messages were a form of social support.	Most (65%) of participants agreed or strongly agreed that it was clear how the SMS messages would help them to take their medication. A quarter (25%) had no opinion, and 10% disagreed that it was clear how the SMS messages would help them to take their medication.	Partial agreement	Partial agreement	Partial agreement
Perceived effectiveness	Most women felt they had routines to take AET, but that the messages would be effective for those that didn't.	Some women (35%) agreed or strongly agreed that the messages would help them to take their AET. The same number of women had no opinion (35%). Some women (30%) disagreed or strongly disagreed that the messages would help them to take their medication.	Partial agreement	Dissonance	Partial agreement
Perceived effectiveness	Some women felt personalising the timing of the messages would make them more beneficial.	Some women (35%) agreed or strongly agreed that the messages would help them to take their AET. The same number of women had no opinion (35%). 30% of participants disagreed or strongly disagreed that the messages would help them to take their medication.	Silence	Partial agreement	Silence

Key: SMS = Short message service. TFA = Theoretical framework of acceptability. AET = Adjuvant endocrine therapy.

Appendix D.5.2 : Information leaflet triangulation

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Affective attitude	Several aspects of the leaflet were liked, including the quotes from other women, and information about side-effects.	Most participants (55%) liked or strongly liked the leaflet. The remainder of participants (45%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Affective attitude	One participant felt they already knew the information, but liked having the information written down.	Most participants (55%) liked or strongly liked the leaflet. The remainder of participants (45%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Burden	Many women felt the leaflet was concise and easy to read, without "medical jargon".	Most women (75%) felt it took no effort at all, or a little effort to read the leaflet. Some women (20%) had no opinion, and a minority (5%) felt it took a lot of effort to read the leaflet.	Agreement	Partial agreement	Partial agreement
Coherence	Most women understood the leaflet was aiming to provide information about AET.	Half of the women (50%) agreed that it was clear how the leaflet would help them to take their AET. Half of the women (50%) had no opinion.	Dissonance	Agreement	Partial agreement
Perceived effectiveness	Some women reported being able to go back to the leaflet and re-read it to remind themselves of the benefits was helpful to remind them why they are taking AET.	The majority (55%) of women had no opinion on whether the information leaflet would improve their adherence to AET. Some women (40%) agreed the leaflet would help them to take AET, and a minority (5%) strongly disagreed.	Partial agreement	Partial agreement	Partial agreement

Key: TFA = Theoretical framework of acceptability. AET = Adjuvant endocrine therapy

Appendix D.5.3 : ACT triangulation

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Affective attitude	Participants liked the practical, skills focus.	Most participants (84.2%) liked or strongly liked the ACT component. A minority (10.5%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Affective attitude	A number of ACT skills were liked and applied. Examples included using mindfulness to reduce hot flushes, and identifying values to get back to enjoyed activities such as volunteering.	Most participants (84.2%) liked or strongly liked the ACT component. A minority (10.5%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Affective attitude	Support sessions from the therapist were liked by all participants overall.	Most participants (84.2%) liked or strongly liked the ACT component. A minority (10.5%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Affective attitude	Most participants felt the timing of the sessions were good, as other support had ceased. One participant felt they were not ready for the sessions.	Most participants (84.2%) liked or strongly liked the ACT component. A minority (10.5%) had no opinion.	Partial agreement	Silence	Partial agreement
Affective attitude	One participant felt some pressure to talk in the sessions to fill the time.	Most participants (84.2%) liked or strongly liked the ACT component. A minority (10.5%) had no opinion.	Dissonance	Silence	Dissonance

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Burden	Most participants liked the online delivery and flexibility of sessions.	Most participants (57.9%) felt participating in the ACT component took no effort at all or a little effort. Some participants (31.6%) felt it took a lot of effort or a huge effort to participate. A minority (5.3%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Burden	Weekly sessions too close together- need more time to practice skills.	Most participants (57.9%) felt participating in the ACT component took no effort at all or a little effort. Some participants (31.6%) felt it took a lot of effort or a huge effort to participate. A minority (5.3%) had no opinion.	Partial agreement	Silence	Silence
Burden	Therapy is emotionally challenging- having sessions in the morning and then going back to work was difficult.	Most participants (57.9%) felt participating in the ACT component took no effort at all or a little effort. Some participants (31.6%) felt it took a lot of effort or a huge effort to participate. A minority (5.3%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Coherence	Overall understanding that ACT was teaching skills and coping mechanisms to move forwards.	Most participants (52.7%) agreed or strongly agreed that it was clear how the ACT sessions would help them take AET. Some participants (21.0%) had no	Partial agreement	Agreement	Agreement

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
		opinion, and a minority (21.1%) disagreed or strongly disagreed.			
Coherence	Some participants were unsure about how ACT would help them when beginning the intervention, but gained more understanding after attending a few sessions.	Most participants (52.7%) agreed or strongly agreed that it was clear how the ACT sessions would help them take AET. Some participants (21.0%) had no opinion, and a minority (21.1%) disagreed or strongly disagreed.	Partial agreement	Partial agreement	Partial agreement
Perceived effectiveness	Multiple experiences were shared regarding perceived effectiveness: • How ACT had helped take AET • Reduced psychological distress • Helpful to return to work • Helped to cope with side-effects of AET	Most participants (52.6%) agreed or strongly agreed that the ACT sessions were likely to improve their medication adherence. Some participants (31.6%) had no opinion and a minority of participants (10.6%) disagreed or strongly disagreed that the ACT sessions would help them to take their medication.	Partial agreement	Partial agreement	Partial agreement

Key: ACT = Acceptance and commitment therapy. TFA = Theoretical framework of acceptability. AET = Adjuvant endocrine therapy

Appendix D.5.4 : Website triangulation

TFA Domain	Qualitative	Quantitative	Coder 1	Coder 2	Final decision
Affective attitude	Some women felt it was beneficial to see videos of what other women are experiencing. However, one participant felt the videos were too stereotypical.	Most women (73.7%) liked or strongly liked the website. The remainder of women (26.3%) had no opinion.	Partial agreement	Partial agreement	Partial agreement
Affective attitude	One participant felt the website was not aesthetically pleasing.	Most women (73.7%) liked or strongly liked the website. The remainder of women (26.3%) had no opinion.	Dissonance	Partial agreement	Dissonance
Affective attitude	A few participants found the information too general and vague in places.	Most women (73.7%) liked or strongly liked the website. The remainder of women (26.3%) had no opinion.	Dissonance	Partial agreement	Dissonance
Affective attitude	Some women liked the honesty of the evidence ratings for the side-effect management strategies, but others did not feel this was helpful.	Most women (73.7%) liked or strongly liked the website. The remainder of women (26.3%) had no opinion.	Dissonance	Partial agreement	Dissonance
Burden	The website modality was acceptable.	Most women (73.7%) felt it took no effort at all or a little effort to use the website. The remainder (26.3%) had no opinion.	Silence	Silence	Silence

Coherence	Participants generally understood the website was to provide side-effect self-management strategies.	Most participants (52.6%) agreed or strongly agreed that it was clear how the website would help them to take their AET. A large proportion (42.1%) had no opinion, and a minority (5.3%) disagreed that it was clear how the website would help to take AET.	Agreement	Agreement	Agreement
Perceived effectiveness	Some women acknowledged the website would be helpful for those experiencing side-effects, who haven't researched coping strategies.	Some women (36.9%) agreed or strongly agreed that the website would help them to take AET. A large proportion (42.1%) had no opinion and some women (21.5%) disagreed that the website would help them to take their medication.	Partial agreement	Partial agreement	Partial agreement
Perceived effectiveness	Some women felt the website didn't teach them anything new.	Some women (36.9%) agreed or strongly agreed that the website would help them to take AET. A large proportion (42.1%) had no opinion and some women (21.5%) disagreed that the website would help them to take their medication.	Partial agreement	Partial agreement	Partial agreement

Key: TFA = Theoretical framework of acceptability. AET = Adjuvant endocrine therapy