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Theory Guided Integrative Systematic Review of The Psychosocial Determinants Associated with Non-adherence to Adjuvant Hormonal Therapy Among Breast Cancer Population.

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Declaration Page

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where states otherwise by reference or acknowledgment, the work presented is entirely my own.

Signature

Date: 19 December 2018

Acknowledgement

I would like to express the deepest appreciation to my supervisors Professor David Weller and Dr. Christine Campbell of the Usher Institute at The University of Edinburgh. They consistently allowed this dissertation to be my own work but steered me in the right the direction when they thought I needed it.

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ABSTRACT

Background

Suboptimal adherence to 5 years adjuvant hormonal therapy (AHT) is prevalent among people with breast cancer. Non-adherence to prescribed AHT medication is linked to increased recurrence rates, lower survival rates and wasted healthcare resources. Targeting the modifiable psychosocial factors has been heralded as a means to improve the phenomenon of suboptimal medication-taking behaviour. This thesis aims to conduct a theory-guided integrative systematic review to identify (I) psychosocial factors that are associated with treatment initiation, adherence, persistence and premature discontinuation, (II) modifiable barriers and facilitators of medication-taking behaviour and (III) intervention strategies that can be used to target the psychosocial barriers.

Method

This integrative review follows PRISMA-P guidance and the review protocol was registered in PROSPERO (CRD42018102035). Systematic searches were conducted in 7 databases (MEDLINE, EMBASE, Web of Science Cochrane Library, CENTRAL, PsycINFO, PsycARTICLE and CINAHL). Only studies that addressed the following are eligible for inclusion: (I) examined associations between cognitive, behavioural, emotional, or social factors with non-initiation, non-adherence, non-persistence or discontinuation (II) published from 1998- 2018 papers and (III) study population that have clinically diagnosed breast cancer patient groups. Mixed Methods Appraisal Tool (version 2018) was used to access the quality of included evidence.

The Behaviour Change Wheel (BCW), made up of an inner layer of Theoretical Domains Framework (TDF), middle layer of Capabilities, Opportunities, Motivation and Behaviour (COM-B), and circled by a layer of intervention functions, was used to structure the design and analysis of the three research questions. TDF was used to frame the behavioural subgroup analysis, anchor the results, COM-B model and intervention functions were subsequently used to map the identified barriers with the intervention options and solution.

Result

Of the 1229 papers screened, 58 articles (43 quantitative studies, 13 qualitative studies and 2 mixed method studies) were included and analyzed. TDF collated the key psychosocial factors from the included studies into 11 domains (Knowledge; Skills; Beliefs about capabilities; Beliefs about Consequences; Reinforcement; Intention and goals, Memory, attention and decision process; Environmental contexts and resources; Social Influences; Emotion; and Behavioural regulation). In conformity with the TDF result, COM-B model has identified the psychological capabilities (knowledge of side effects, memory, decision making), reflective motivation (perceptions and expectations, behavioural barriers), automatic motivation (intention, negative emotion), physical opportunity (resources) and social opportunity (clinical support) as the modifiable components. Based on the collective findings of the TDF and COM-B model, 4 intervention functions (Education, Persuasion, Training, Enablement) were matched into the relative components.

Conclusion

This review is novel as it proposes a multilayer psychological understanding of nonadherence behaviour and provides a thorough overview of the behaviour change techniques that help to formulate future interventions. The cornerstone to improving optimal medication-taking behaviour is to educate patients on the knowledge of side effects seek to adjust the patients' psychological adaptation and provide communication skills training among healthcare providers. These results are pertinent to healthcare providers, researchers and stakeholders who are likely to initiate interventions.

Keywords: adjuvant hormonal therapy, adherence, discontinuation, initiation, persistence, psychosocial, review.

CHAPTER OVERVIEW

Chapter 1 introduces the Adjuvant Hormonal Therapy (AHT) and related research on medication taking behaviour (MTB). This chapter describes the research gap, research questions and study rationale that has been used as the foundation of this thesis.

Chapter 2 investigates the various types of psychosocial models and explains the rationale for the chosen models. The strength and interrelatedness of the chosen models are detailed.

In Chapter 3, the methodological steps undertaken to analyse three type of outcomes are detailed.

Chapter 4 reports the primary, secondary and tertiary outcomes separately. Thematic matrix and tables were used to summarize the research findings.

Chapter 5 presents the key findings and describes the implications drawn from the results. The identified research questions in chapter 1 are examined in a broader context of the research literature.

Chapter 6 consolidates all the key information extracted from the above chapters and presents a succinct summary of the overall findings.

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LIST OF ABBREVIATIONS

AHT: Adjuvant Hormonal Therapy

AET: Adjuvant Endocrine Therapy

AI: Aromatase inhibitors

BCW: Behaviour Change Wheel

COM-B model: Capability, Opportunity and Motivation Behaviour model

ER: Estrogen hormone receptor

LHRH: Luteinizing hormone-releasing hormone agonists

MTB: Medication Taking Behaviours

PR: Progesterone hormone receptor

TAM: Tamoxifen

TDF: Theoretical Domains Framework

CHAPTER 1: INTRODUCTION

1.1 Adjuvant Hormone Therapy and Treatment Efficacy

Breast cancer is a hormonally related disease that impacts 1 in 8 women and 1 in 870 men during their lifetime (1). 40-99% of breast cancer tumours are hormone receptor positive (HR+), meaning the growth of tumour cells is fueled by the estrogen hormone receptor (ER) or progesterone hormone receptor (PR) (2–7). Estrogen and progesterone are natural hormones produced by the body for sexual development and other body functions. A blood test is usually performed at diagnosis to determine whether the breast tumour is responsive to these hormones. The positive result, meaning the breast cancer tumour is reactive to the hormone receptor, is indicated by HR+ (responsive to ER or PR or both) in the clinical pathology report.

Adjuvant hormonal therapy (AHT), also known as adjuvant endocrine therapy (AET), is an integral treatment for all HR+ breast cancer patients. AHT increases the survival rate among HR+ breast cancer population by reducing the risk of recurrence and prevent the development of secondary breast cancer (8,9). The treatment entails oral consumption of hormonal agents such as Tamoxifen (TAM), Aromatase inhibitors (AI) or Luteinizing hormone-releasing hormone agonists (LHRH). The main function of these hormonal agents is to halt the exertion of hormonal activity or downgrade hormonal effect and consequently suppress the growth of hormone-responsive cancer cells (10). The deactivated tumour will shrink in size and hence prevent the spread of disease.

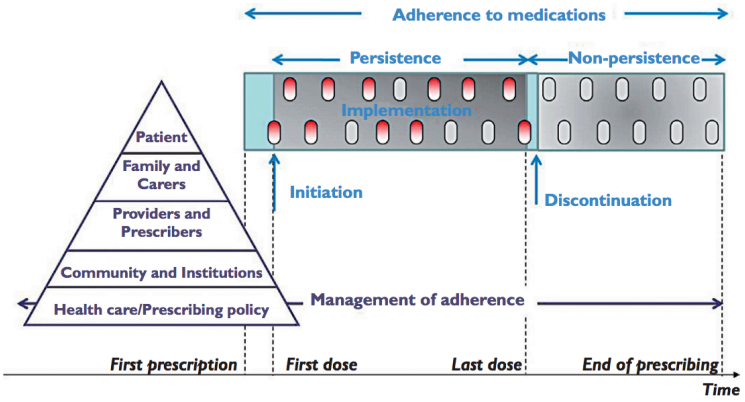
The therapeutic efficacy of AHT has been proven in a series of randomized controlled trials and cohort studies. Tamoxifen is recommended as first-line therapy and is proven to effectively reduce recurrence by 27% for 1-year adherence, 33% for 3-year adherence and 47% for 5 year-adherence (11,12). AI or LHRH antagonist is the alternative drug options best fitted for postmenopausal women. As demonstrated in randomized trials coupled with 3 to 7 years follow up, these hormonal agents are effective in reducing the risk of developing contralateral breast cancer by 65% and 50% (13,14). In summary, taking AHT for the full term has been shown to give therapeutic benefit in reducing the incidence of breast cancer for at least 20 years (15).

1.2 Terminology of Adherence to Medications

The standard AHT treatment entails daily oral consumption of hormonal agents for 5 to 10 years upon the completion of primary systemic therapy. The World Health Organisation (WHO) defines adherence as the extent to which patient behaviour is in concordance to the agreed recommendation from the healthcare provider (16). In response to the burgeoning research on medication adherence, a team of international experts refined the taxonomy for evaluating adherence to medication (17). The proposed taxonomy of "adherence to medication" composed of three continuum process, which is initiation, implementation and discontinuation. Figure 1.2 presents a visual overview of the process of adherence (blue) and management of adherence (purple) (17).

Medication-taking behaviour (MTB) starts when a patient takes the first dose of medicine at the prescribed start date. MTB continues in the implementation stage, which is defined as the degree to which a patient's actual dosing corresponds to the prescribed dosing regimen (17,18). Persistence encompasses the duration of time where patients are on track of the medication plan from the period of imitation to the discontinuation of therapy (17,19). Discontinuation is the final stage of the therapy, where patients have completed the whole set of the medication regimen (17). Non-adherence to medications can thus arise in the form of non-initiation, non-persistence or premature discontinuation of the treatment. To achieve the best use of the medication, the management of adherence emphasises the supporting roles of healthcare policy, community and institution, healthcare provider, family and carers and patients that may impact the process of adherence (17).

Figure 1.2: Adherence to medications and management of adherence(17).



1.3 Prevalence of Non-adherence and Associated Impacts

Many studies have reported that breast cancer patients face challenges in the management of adherence. The Northern California breast cancer cohort reported that 21% of patients did not initiate the treatment and of the 79% AHT user, one fourth either discontinued or were nonadherent (20). Findings from the analysis of consolidated data from 26 studies estimated the adherence rate of 79.6% at the first year of treatment would drop to 68.3% by the end of 5 years, with the persistence rate ranging from 13.6% at 1 year to 40.9% at 5 years (21). A review study on adherence levels also reported that 20% patients take less medication than prescribed at 1-year; increases to 32% in the subsequent year and eventually 32-73% of patients discontinued by the end of 5 years of treatment (22). As shown in meta-regression analysis of non-persistence in 17 trials, for tamoxifen, 5 year non-persistence was 47.2% (95% confidence interval, CI, 41.1%-53.5%) compared with 31.0% (95% CI, 25.9%- 37.5%) for aromatase inhibitors (21). The cohort study of 8769 early stage FBC shown for tamoxifen, an average of 24% nonadherence and 21% discontinuation whereas for AI, an average of 12% nonadherence and 45% discontinuation were noted (23). In summary, less than 50% of the patients have been reported to finish AHT as prescribed by the end of 5 years course of therapy in a variety type of nonadherence (23–25).

Compared with the risk of the general population for developing a first primary cancer, female and male breast cancer patients are respectively at 2-6 times and 30-90 times higher risk of developing a second primary contralateral breast cancer (26–28). Lack of adherence to the treatment plan is associated with lower survival rate and expose patients to a higher risk of developing new or recurrent breast cancers (24,29,30). A Scottish cohort of 2,080 patients found tamoxifen adherence <80% which was associated with increased mortality (HR, 1.100; 95% CI, 1.001– 1.21) among early stage breast cancer women (24).

Suboptimal adherence compromises optimal treatment benefits, causing significant deteriorations in health outcomes and higher statistic of secondary breast cancer population (24,29,30). Hospital manpower devoted to patients with recurrence and the expenses of the wasted medication incur soaring healthcare costs estimated to be as much as £30 million each year in the UK (31). Investment from stakeholders, clinical or pharmaceutical research into the refinement and development of new drugs would fail to deliver accountable outcomes due to incomplete adherence data. The impact of nonadherence on healthcare institute, clinical or pharmaceutical research and stakeholders are expected to increase given the incidence of breast cancer is increasing worldwide. Up to date, a gold-standard adherence intervention remains elusive in spite of the magnitude of medication nonadherence. WHO has called for concerted a research effort into formulating interventions solutions (32).

1.4 Challenges of Medication Management

1.4.1 Modifiable and non-modifiable factors

Long-term medication adherence is a dynamic, complex and multidimensional behavioural phenomenon. Current research and review studies into the long-term cancer medication have related nonadherence to five mainstream factors : (I) patient-related factors (e.g. age, demographic, race, financial status), (II) therapy-related factors (e.g. treatment beliefs, onset of side effects, polypharmacy, knowledge), (III) condition-related factors (e.g. cancer recurrence, tumor characteristics, hormone receptor status), (IV) health system factors (e.g. waiting time, time allocated for visits) and (V) socioeconomic factors (e.g. health care insurances, culture) as the correlates of medication-taking

behaviour (MTB) (22,33–35). Although the combination of these factors provides an overview MTB, almost all of the reported factors are out of patient's control and not easily modified in the home environment. Developing intervention to amend these nonmodifiable factors would be impractical and expensive to implement in practice (36). On the other hand, the patient's psychological perception, behavioural mechanism and social influences that may have greater potential to be altered through interventions are less investigated. Consequently, only a few interventions have been developed to improve AHT adherence (22), limiting the possibility of paradigm shifts in the way we manage suboptimal MTB among breast cancer patients.

Modifying medication adherence behaviour requires tracing back to the dynamic interaction of the underlying psychosocial factors (37). A growing body of empirical research has reported that understudied psychological factors (how a patient thinks, their feelings, moods, beliefs, cognitive construct), and social functioning (availability of social support, relationship with family and friends, environmental stressor, quality of social relationships) have stronger, proximal and modifiable influence on patients adherence behaviour (coping skills, behavioural regulation) (38). For instance, greater concerns about the treatment, and lower perceived necessity and self-efficacy were reported as the risk factor of intentional nonadherence of AHT (39,40). Anecdotal evidence suggests that illness and medication perceptions, such as necessity beliefs on the treatment, are predictive of adherence in other illnesses (41,42) and have been successfully modified via psychosocial interventions (43,44).

1.4.2 Lack of evidence and theoretical-based reviews

During an early stage of this dissertation research question formation, a brief scoping review was conducted to broadly investigate what is known in the research topic of interest. The term of the "psychosocial factor associated with AHT treatment management" was used to search for relevant reviews published in PubMed. The search has identified four of the most relevant reviews, among which only 1 review used the integration of psychological framework (45), 1 review researched exclusively on adherence and persistence behaviour (46), 3 reviews limit evidence search in two or less databases (46–

48) and 3 reviews include either qualitative or quantitative evidence only (45,46,48). (Table 1.3.2)

Table 1.4.2: Related systematic reviews

Author, Year	Aim	Framework used	MTB	Database, year limit	Data synthesis	Number of studies included, (type of study)	Key findings
Lin C, 2017	To review psychosocial motivators and barriers of breast cancer oral anti-cancer medication (chemotherapy, hormone therapy, immunotherapy) adherence.	-	A, P, D	Pubmed, 2016	Narrative synthesis	21 (3 qualitative, 18 quantitative studies)	• Adherence is associated with patient-provider relationship and views on medication.
Mausbach BT, 2015	To analyze the effects of depression on non-adherence to adjuvant endocrine therapy (AET) in women with breast cancer	-	A,D,P	MEDLINE and PsycINFO, 2015	Meta-analysis	9 (qualitative studies)	• Adherence is associated with depressive symptoms
Cahir C, 2015	To identify the modifiable determinants of adjuvant hormonal therapy medication taking behaviour (MTB) in women with stage I-III breast cancer in clinical practice settings.	Theoretical Domains Framework	A, P, I	PubMed, EMBASE, PsycINFO , and CINAHL, 2014	Meta-analysis	42 (quantitative studies)	• Persistence is associated with treatment side-effects, follow-up care and number of medication.
Van Liew, 2014	To evaluate the associations between psychosocial factors and breast cancer survivors' adherence to adjuvant hormone therapy.	-	A, P	PsycINFO and PubMed 2014.	Narrative synthesis	14 (quantitative studies)	• Adherence and persistence were associated with interpersonal factors,intrapersonal factors. • Adherence do not associate with depression and quality of life.
MTB: I= initiation, A=Adherence, P=persistence, D=Discontinuation							

The United Kingdom's Medical Research Council endorses developing intervention within a framework, model or theory for a theory-based and evidence-based intervention which has been predicted to have a higher success rate (49). Pertaining to the topic of interest, embedding psychological theory into intervention formation processes enables the identification of the mechanism of behaviour change in a methodical manner and aid the evidence transfer into another context (50). The only theory-guided systematic review identified was pioneered by Cahir in 2014 (45). His review aims to identify modifiable determinants of MTB among stage 1 to 4 breast cancer patients, underpinned with Theoretical Domains Framework (51). In contrast with the study aim, the main conclusion of his review focus on the influences of the non-modifiable factor, such as treatment side

effects, follow up care with an oncologist and a greater number of prescription medication on persistence behaviour (51). Cahir's study did not explore the psychological aspect in-depth, including beliefs about consequences, intentions, social identity, emotion and knowledge effect on medication-taking behaviour (51). The findings of the review were also limited by narrow evidence searches in 4 databases to only include observational studies published until 2014; qualitative studies and studies with discontinuation measures were not examined, and some important studies were omitted due to heterogeneity measures.

The inadequacy of the database searches was the common limitation among the listed previous reviews (Table 1.4.2). Systematic reviewing should be a meticulous research method and hence to maximize the review value, inclusions of a broad range of evidence, systematic and transparent analytic process are often encouraged. When performing the literature search in a systematic review, a minimum of five databases is usually advisable to guarantee the optimal retrieval of relevant and updated papers (52). All the included reviews limit evidence search in a maximum of four databases (45–48) and the latest review only include evidence that is published in PubMed (47).

In addition, contradictory and fragmented findings were found in between reviews that use different synthesis method. For example, a meta-analysis review reported that adherence is associated with depressive symptoms as opposed to a narrative review that concludes depression have no impact on adherence (46,48). None of these reviews evaluates psychosocial factors across the full spectrum of MTB ranging from initiation, implementation and discontinuation in a single report. The full picture of the potential magnitude of psychosocial influences and its synergy across treatment initiation, implementation and discontinuation were tends not reported. Lack of consensus and coherent report of findings therefore limit knowledge translation. In order to formulate an effective intervention design, this thesis aims to conduct a comprehensive review that includes broad coverage of behaviour type, in-depth search for up to date evidence and apply a theory-guided understanding of the nature of the behaviour.

1.5 Research Questions

The implications of nonadherence and its association with the individual, clinical and economic consequences have raised important questions about what psychosocial factors should be targeted by treatment management interventions. This thesis sought to build upon and address limitations in the previous reviews by employing a theory-guided integrative systematic review of the psychosocial determinants associated with 5 years AHT medication-taking behaviour with a view to directing the focus of future evidence and theory-based interventions.

This thesis aims to answer three types of research questions:

1. What are the psychosocial factors that relate to treatment initiation, adherence, persistence and premature discontinuation?
2. What psychosocial factors are modifiable and need to be changed in order to optimize the medication-taking behaviour?
3. What are the intervention strategies that can be used to target the identified psychosocial barriers?

CHAPTER 2: PSYCHOSOCIAL MODELS

2.1 Background

Pursuant to the medical dictionary, the term “psychosocial” relates to the interrelation of individual psychological thoughts, social or interpersonal aspects and behaviours (53). In the quest for understanding psychosocial determinants on health behaviour, various guises of theories and models have burgeoned to explain relationships between psychosocial variables and particular behaviour of interest. Psychological and social factors that influence the mechanism of behaviour have been investigated using the umbrella terms of Motivation Theory, Action Theory and Organization Theory. Examples of psychological theories and their brief descriptions, leading research and illustrative diagrams are explained as follows.

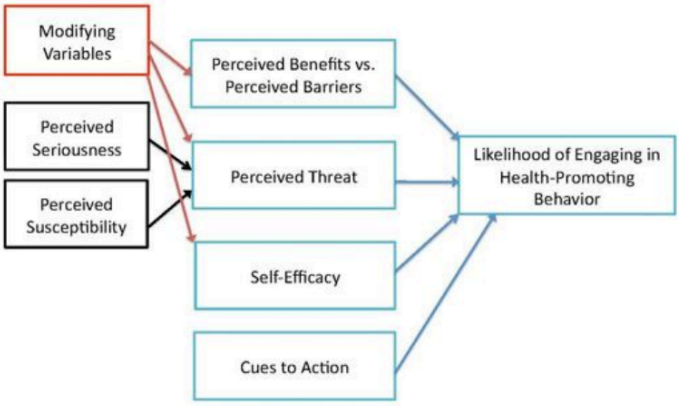
2.1.1 Motivation Theory

Motivation theory revolves around the influence of inner cognitive processes such as goal-directedness, intention, beliefs and attitudes as the core components that stimulate, eradicate or orients individuals to carry out certain kinds of behaviours (54). The general rule of motivation theories is that behaviour is modifiable on an individual level provided that attitudes, expectations and beliefs are understood and adapted (55). Examples of motivation theory include *Goal Theory, Cognitive Adaptation Theory and Intrinsic Motivation Theories* (56).

The most investigated motivation theories in understanding patient compliance behaviour have concentrated on the Health Belief Model (57). As shown in Figure 2.1.1, this model postulates that health-related behaviour is driven by a set of six cognitive variables, namely (I) perceptions about susceptibility (one’s risk perception of getting a condition), (II) perceived severity (one’s evaluation of the severity associated with the condition), (III) perceived benefits (one’s belief in effectiveness of taking a particular action to offset the treat or condition), (IV) perceived barriers (one’s negative aspects related to following the course of action), (V) cues to action (external prompt to motivate the action e.g. symptom) and (VI) self-efficacy (confidence in one’s confidence to execute a given action) (57).

Using medication intake as an example, this model assumed that individuals would adhere to the medication plan if only they perceive themselves at risk and are at threat of serious repercussions. The Health Belief Model has been widely utilized in adherence studies such as diabetes (58), HIV (59), and antipsychotic medication (60).

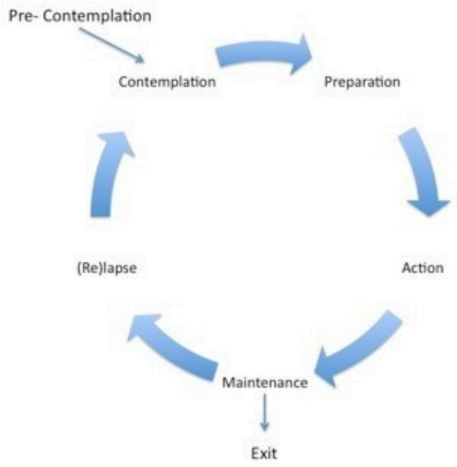
Figure 2.1.1: Health Beliefs Model (57)



2.1.2 Action Theory

Action theory proposes the voluntarist perspective and proposes that individuals have a choice on the presentation of their behaviour (61). This school of theory seeks to primarily explain the personal cognitive empowerment or goals of behaviour that are intrinsic to steering or sustaining behaviour (62). Influential work draws on the *Transtheoretical model*, also known as the *five stages of change model* frame behaviour, which conceptualized behaviour changes in 5 stages (63). It starts with an individual that has no intention to change behaviour (precontemplation stage) until they feel ambivalence (contemplation stage) which motivates them to take the initial steps (preparation stages) and eventually to make apparent and sustained behaviour changes (action stages and maintenance stages) (63). This model is useful for public health research as it tailors intervention specifically to address people at various stages of the decision-making process. Other choices of action theory include *Theory of Reasoned Action, Empowerment Theory,* and *Locus of Control Theory* (64,65).

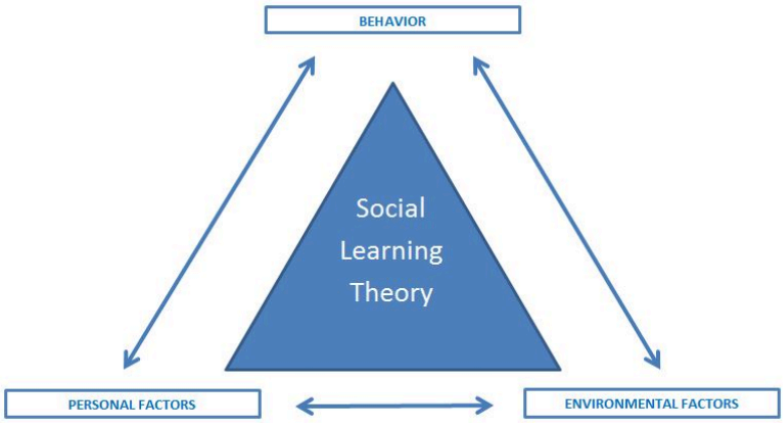
Figure 2.1.2: Transtheoretical Model (63)



2.1.3 Organisation Theory

Organization theories center on the assumption that behaviour is contagious and influenced by the social, organizations or communities groups (66). The leading work on Bandura's *Social Learning Theory,* which was later named as *Social Cognitive Theory* considers behaviour as a result of the social process (67,68). In Figure 2.1.3, the theory is mapped out into the complex interplay of personal factors and environmental factors on behaviour (67,68). Personal factors are the internal perception of individual self-control and self-efficacy to execute a certain behaviour. Environmental factors include the opinion of surrounding culture or social network that may affect an individual perception and behaviour. Social Cognitive Theory is relevant to health communication for designing and implementing comprehensive behaviour change programs by explaining how people acquire and maintain certain behavioural patterns (68). Other examples of organization theory includes *Group Theory, Modelling Theory, and Diffusion of Innovation Theory* (69,70).

Figure 2.1.3: Social learning theory (67,68)



2.2 Selection of Behaviour Change Models

As aforementioned, there are many behaviours change theories that have some degree of relevancy to long-term behavioural changes, such as medication adherence behaviour. Selectively choosing the best fit model in the wide array of potentially relevant theories is challenging as most of the health behavioural models share an amalgamation of concepts, approaches or constructs. For example, despite the terminology differences, Health Belief Model (perceived behavioural control) and Theory of Planned Behaviour (perceived barriers) both evaluate people's competency to perform target behaviour under the presence of barriers (71). Overlapping constructs of self-efficacy can also be found between the Health Belief Model and Social Cognitive Model. For this reason, adopting a single theory in implementation research is at risk of using a narrow approach and potentially underrepresenting some other key factors.

2.2.1 Theoretical Domains Framework (TDF)

In an effort to unify psychosocial perspectives, a broad spectrum of 14 motivation theories, 11 action theories and 8 organisation theories were integrated into a salient framework, named the Theoretical Domains Framework (TDF) (72,73). TDF was designed to be overarching, parsimonious and applicable to all behaviour. This revolutionized theory-informed approach in behaviour implementation research was developed as a result of the collaboration work among three groups of 18 health psychology theorists, 16 health

services researchers and 30 health psychologists. They underwent six phases to integrate the relevant theoretical constructs that have been developed and eventually reached the consensus of the original of 12 key theoretical constructs for use in the implementation of evidence-based practice (72). TDF underwent rigorous validation test by an independent group of experts using a card sorting task, a three-step validation approach, a cross-sectional study, an interdisciplinary evaluation, backward validation exercises and pilot interviews and to incorporate all the important areas refined into 14 domains (73).

14 domains of TDF encompass influences or sources of psychological factor (beliefs about abilities, beliefs about consequences, knowledge), behavioural factors (behavioural regulation, intention, goals) and social factors (social influence, environmental contexts) to provide a granular understanding description of the nature of the behaviour (Table 2.2.1).

Figure 2.2.1: TDF domains and constructs (72,73)

Domain (definition[1])	Constructs
1. Knowledge (An awareness of the existence of something)	Knowledge (including knowledge of condition /scientific rationale) Procedural knowledge Knowledge of task environment
2. Skills (An ability or proficiency acquired through practice)	Skills Skills development Competence Ability Interpersonal skills Practice Skill assessment
3. Social/Professional Role and Identity (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	Professional identity Professional role Social identity Identity Professional boundaries Professional confidence Group identity Leadership Organisational commitment
4. Beliefs about Capabilities (Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)	Self-confidence Perceived competence Self-efficacy Perceived behavioural control Beliefs Self-esteem Empowerment Professional confidence
5. Optimism (The confidence that things will happen for the best or that desired goals will be attained)	Optimism Pessimism Unrealistic optimism Identity
6. Beliefs about Consequences (Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)	Beliefs Outcome expectancies Characteristics of outcome expectancies Anticipated regret Consequents
7. Reinforcement (Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)	Rewards (proximal / distal, valued / not valued, probable / improbable) Incentives Punishment Consequents Reinforcement Contingencies Sanctions

Figure 2.2.1: TDF domains and constructs (continued)

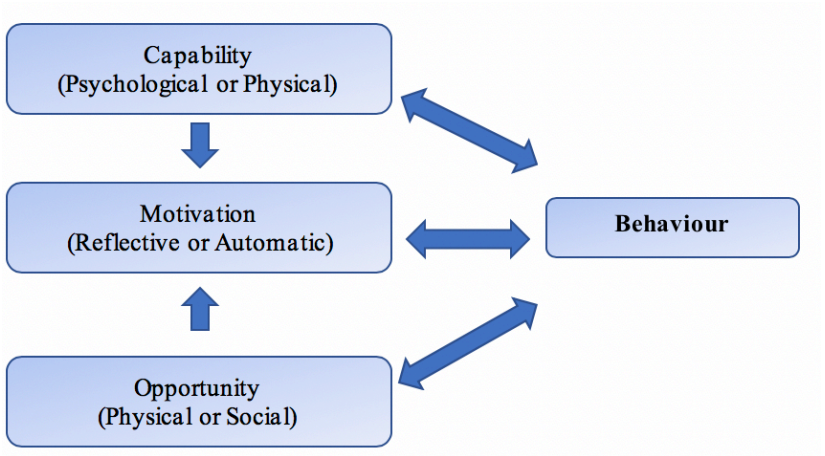
8. Intentions (A conscious decision to perform a behaviour or a resolve to act in a certain way)	Stability of intentions Stages of change model Transtheoretical model and stages of change
9. Goals (Mental representations of outcomes or end states that an individual wants to achieve)	Goals (distal / proximal) Goal priority Goal / target setting Goals (autonomous / controlled) Action planning Implementation intention
10. Memory, Attention and Decision Processes (The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)	Memory Attention Attention control Decision making Cognitive overload / tiredness
11. Environmental Context and Resources (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	Environmental stressors Resources / material resources Organisational culture /climate Salient events / critical incidents Person x environment interaction Barriers and facilitators
12. Social influences (Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)	Social pressure Social norms Group conformity Social comparisons Group norms Social support Power Intergroup conflict Alienation Group identity Modelling
13. Emotion (A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)	Fear Anxiety Affect Stress Depression Positive / negative affect Burn-out
14. Behavioural Regulation (Anything aimed at managing or changing objectively observed or measured actions)	Self-monitoring Breaking habit Action planning

The holistic approach of TDF reduces the risk of omitting key areas yet presents a standard framework and common language for use in multi-disciplinary health research teams. TDF has been applied primarily in healthcare settings to elucidate and describe the difficulties of implementing intervention relating to dementia treatment management (74), family-based intervention in schizophrenia (75) and electronic medication management systems in hospitals (76). Implementation trials have adapted TDF to identify predictive factors of blood transfusions in Canada and UK (77), evaluate the effectiveness of theory-informed behavioural change interventions (78) and the evidence-based guidelines for acute low back pain (79,80). Diagnostic studies using TDF as the theoretical basis include the uptake of tobacco use prevention and cessation counselling in dental practices (81), the Accelerated Chest pain Risk Evaluation (ACRE) implementation project (82), perceived barriers and facilitators to physical activity among stroke survivors (83), and medication adherence in stroke survivors (84).

2.2.2 Capability, Opportunity and Motivation Behaviour (COM-B model)

COM-B model is a psychological model for explaining the mechanism of human behaviour (85). This model hypothesises that human behaviour (B) results from the interplay between capability (C), opportunity (O) and motivation (M) (85). Each of these three main components (C, O, M) are divided into two subcomponents to allow a precise description of the relationship between behaviour and determinants. Figure 2.2.2 present the dynamic of the COM-B model.

Figure 2.2.2: COM-B model (85)



The capability is conceived as the individual's physical and psychological ability to perform a behaviour (86). The psychological capability is the ability of an individual to engage in the necessary thought processes whereas physical capability is based on whether an individual possesses certain skills or knowledge to carry out certain behaviour (86). Opportunity is evaluated on the external physical factors and social factors that prompt the behaviour (86). Physical opportunity is provided by the environment whereas the social opportunity is defined by the cultural milieu that facilitates or impedes the way an individual perceives the behaviour. The motivation of behaviour is determined by the combination of the reflective and automotive brain process (86). The reflective process is referred to as an individual consciously evaluating rational thoughts, making analytical decision making or knowing the intention whereas the automotive process is referred to habitual process or emotion responding that subconsciously energize the behaviour (86).

Overall, COM-B model is based on the premise that in order to enact a behaviour (B), the individual must be physically and psychologically capable (C), given sufficient social and physical opportunity, and be consciously motivated (M) (87) (Figure 2.2.2). The behaviour is unlikely to occur if there are deficits in any of the components. This model was commonly used as a starting point of the intervention development by first understanding why a person engages in certain of behaviour in order to know how to choose specific intervention to address the components that influence the performance of behaviour (88).

COM-B model is the simplified model of TDF, which both have a fitting scope of coverage on the determinants of behaviour (Table 2.2.2). TDF focuses on sourcing the influential psychosocial factors on behaviour in a broader coverage whereas COM-B model is specified in orienting what needs to be changed in favour of behaviour of interest (89). The utility of these two models is not limited to health behaviours but also proven useful in the development and initial validation of the determinants of physical activity questionnaire (90) and provide a coding framework that facilitates data analysis (91–93). A plethora of research has evinced the value and multifunctional of TDF and COM-B model in data collection, problem identification (79,80,84,87,94–97), behavioural analysis

(81–83), theorising pathways of change, and guiding design of evidence-based interventions (72,74–76,78,98).

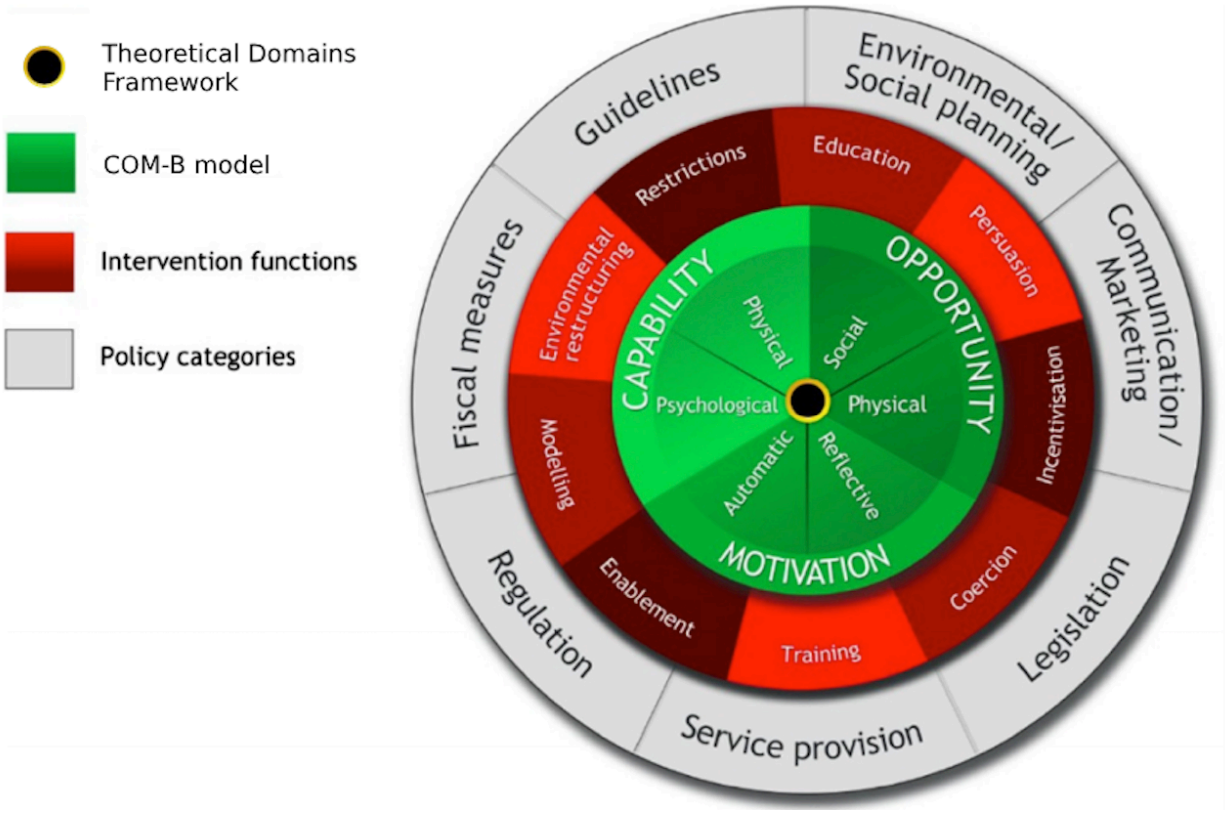
Table 2.2.2 : TDF domains definitions and corresponding COM-B model(85)

TDF domain	Definition of TDF domain	Corresponding COM-B model construct
Knowledge	An awareness of the existence of an entity or concept e.g. knowledge of a health condition	**Capability**
Skills	An ability or proficiency acquired though practice e.g. interpersonal skills	
Memory attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives e.g. decision making	
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions e.g. self-monitoring	
Social/professional role and identity	A set of behaviours and displayed personal qualities of an individual in a social or work setting e.g. social or professional identity	**Motivation**
Beliefs about capabilities	Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use e.g. self-efficacy	
Optimism	The confidence that things will happen for the best or that desired goals will be attained e.g. unrealistic optimism	
Beliefs about consequences	Acceptance of the truth, reality or validity about outcomes of a behaviour in a given situation e.g. outcome expectancies	
Intentions	A conscious decision to perform a behaviour or resolve to act in a certain way e.g. stability of interventions	
Goals	Mental representations of outcomes or end states that an individual wants to achieve e.g. action planning	
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus e.g. incentives	
Emotions	A complex reaction pattern, involving experiential, behaviour and psychological elements, by which the individuals attempts to deal with a personally significant matter or event e.g. fear	
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour e.g. resources/material resources	**Opportunity**
Social influences	Interpersonal processes that can cause individuals to change their thoughts, feelings and behaviours e.g. social norms	

2.2.3 Behaviour Change Wheel (BCW)

The Behaviour Change Wheel (BCW) represents a hub of coordinated toolkit sets for intervention design that is encircled by layers of TDF, COM-B model, interventions functions and policy categories (76,86). It incorporates a step by step approach in designing behaviour change intervention functions that cater to the mechanism and technique to amend target behaviour (76,86,99). Figure 2.2.3 embodied the inter-relationship and linkage of these models.

Figure 2.2.3: Behaviour Change Model (100)



TDF represents the central tenet of the wheel, which provides the starting point of identifying the key behaviour in a broad exploration of potential factors. The findings of TDF may be condensed into three core components of COM-B model to build a cumulative theoretical understanding of behaviour. The third layer of BCW involves intervention development spreading out into nine intervention function, which were deducted from a synthesis of 19 frameworks of behavioural-intervention strategies (86). These nine intervention functions provide a match of suggestions that were used to address deficits in behaviour mechanism of action relative to COM-B model components (89,101). The outer layer of the wheel identifies seven modes of policy categories that can use to optimize the delivery of the intervention functions (76). Table 2.2.3 listed the definition of intervention functions and policy categories.

Table 2.2.3: Intervention function and policy category definitions (76,86)

	Definition
Intervention function	
Education	Increasing knowledge or understanding
Persuasion	Using communication to induce positive or negative feelings or stimulate action
Incentivization	Creating an expectation of reward
Coercion	Creating an expectation of punishment or cost
Training	Imparting skills
Restriction	Using rules to reduce the opportunity to engage in the target behaviour (or to increase the target behaviour by reducing the opportunity to engage in competing behaviours)
Environmental restructuring	Changing the physical or social context
Modelling	Providing an example for people to aspire to or imitate
Enablement	Increasing means/reducing barriers to increase capability (beyond education and training) or opportunity (beyond environmental restructuring)
Policy categories	
Communication/marketing	Using print, electronic, telephonic, or broadcast media
Guidelines	Creating documents that recommend or mandate practice. This includes all changes to service provision
Fiscal measures	Using the tax system to reduce or increase the financial cost
Regulation	Establishing rules or principles of behaviour or practice
Legislation	Making or changing laws
Environmental/social planning	Designing and/or controlling the physical or social environment
Service provision	Delivering a service

Collectively, multilayers of BCW are rich in constructs and it gives prominence to the behaviour needs assessment as well as guiding evidence-based behavioural intervention. By basing implementation interventions on a theoretical approach, the mechanism of action and sources of the problem can be targeted effectively with the right fit of the intervention strategies (78,99,102). BCW has been applied effectively in the context of modification health behaviour such as reducing sedentary behaviour at work (103), improving medication management in multimorbidity (104), reducing alcohol consumption (105) and promote long-term use of hearing aids in adult auditory rehabilitation (106).

2.4 Research Aim

The aim of this thesis is to conduct a theory-guided integrative review of the psychosocial determinants associated with AHT medication-taking behaviour among breast cancer patients. Multilayer of the BCW was chosen as the theoretical framework of this thesis as TDF function to trace the root of behaviour; COM-B model defines what needs to be amended in favour of target behaviour and the intervention functions guide the selection of intervention design with the right behaviour change techniques.

Synchronized with the three of the research questions aforementioned in section 1.5, this thesis underpins TDF, COM-B model and intervention function respectively to (1) understand treatment management behaviour (primary outcome) (2) identify target and mechanism of changes and (secondary outcome) (3) identify intervention and implementation options (tertiary outcome).

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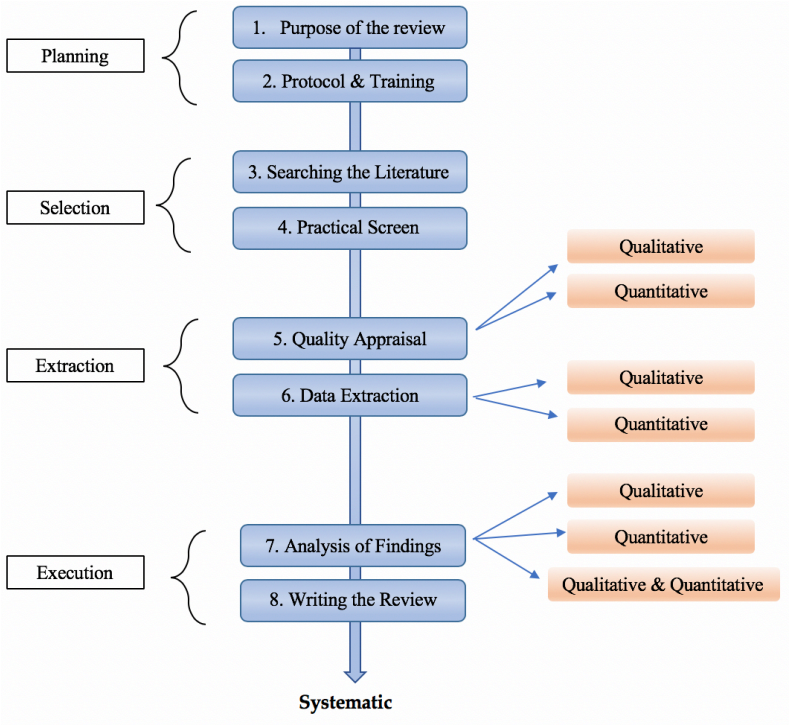
CHAPTER 3: METHODOLOGY

1.1 Integrative Reviews

Systematic review evidence is at the heart of guiding policy decision making and developing evidence-based interventions (107). The systematic review adheres to a predesigned protocol to explicitly and rigorously consolidate research-based knowledge related to a specific research question (108). The process of generating a systematic review follows eight mandatory steps, which involves (I) defining the purpose of the review, (II) formulating a review protocol, (III) searching for literature on database, (IV) screening for the eligible studies, (V) appraising study bias using validated quality assessment tool, (VI) systematically extracting the applicable information, (VII) synthesising the extracted data using qualitative method, quantitative method or both and (VIII) reporting the result in detail (Figure 3.1) (109). These steps are essential to ensure the summary of research evidence generated is reliable, meticulous and reproducible to inform decision making.

Figure 3.1: Complementary steps of standard systematic review (109)



There are various types of systematic review designs catered to the specific purposes of the review (110). Integrative review (also known as the mixed-method review) aggregates vary types of data (e.g. quantitative, qualitative, experimental or non-experimental) into a sizeable chunk of evidence relevant to the scholarly reviewer, the policymakers and the healthcare practitioners (111,112). Theory-based systematic reviews apply an explanatory approach that allows a better understanding of the causal mechanism in the data and identifies the research gaps and needs using the theoretical model, theory or framework (113). Pertaining to the research topic, this thesis uses a combination of theory-guided and integrative reviews to present a full picture on the topic of interest and maximize the utility and impact of the review.

Specifically, this integrative review was designed to be (I) inclusive of diverse methodologies, (II) theory-guided and (III) apply three stages of recursive framework analysis (TDF, COM-B model and intervention function) to synthesize three types of outcomes. Following the complementary steps of the standard systematic review (Figure 3.1) and a predesigned review protocol (detail in section 3.2- section 3.7), this review details the analysis steps to strengthen the validity, transparency, applicability of the findings.

3.2 Review Protocol

3.2.1 Protocol guidelines

The protocol of this review was registered prospectively with PROSPERO, an international health research database specifically for reviews registration on March 2018 (registration number: CRD42018102035). The key components of this review protocol were structured in accordance with the interventional and observational studies recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (114). The eligibility criteria of the review were framed using PICOT (Population, Exposure, Comparison, Outcomes and Timeframe) format (115,116). To gauge the consistent and robust reporting of this review, the PRISMA P checklist was used and reported in Appendix A.

3.3 Eligibility Criteria

3.3.1 Study design

We included any empirical study that examined at least one correlation between a psychosocial variable and adjuvant hormonal therapy medication-compliance behaviour. The empirical quantitative research design was not limited to comparative cohort studies, cross-sectional survey, observational studies and case-control studies. For qualitative research that employed a focus group study, ethnography study or interviews are eligible for inclusion. Mixed method studies were reviewed for its eligibility on separate components. All identified published, unpublished, and grey literature written in English was searched and reviewed against the inclusion criteria. No restriction on the ethnicity of the study population or geographical region was imposed in both reviews.

We excluded epidemiological, clinical, cost-effectiveness, quality of life, or preferences studies, or survival analysis studies that did not investigate psychosocial factors and adherence behaviour. We excluded studies that were not based on original data, reviews, books, editorial, commentary studies, conference abstract or study protocol.

3.3.2 Participants

This review included clinically diagnosed breast cancer populations of any type or stage. Studies that included high-risk populations but without a clear clinically diagnosed result were not eligible. Eligible study populations had to be HR+ (either ER-positive or PR-positive), have prescribed and initiated adjuvant hormonal therapy upon completion of primary systemic therapy. No restriction on the age, race, gender or demographic characteristics of the study population was imposed.

3.3.3. Exposures

Psychosocial factors that affect the level of medication compliance was the primary interest of this systematic review. We also reviewed intervention studies that had a comparative control group and the psychosocial aspects of patient medication compliance behaviour.

This review recategorized psychosocial factors into four main domains: (I) cognitive inclusive of knowledge, medication beliefs and related cognitive constructs; (II) emotional distress and well-being; and (III) behavioural skills and coping (IV) social or interpersonal inclusive of social support, patient-oncologist relationship and provider interaction (117). All studies that apply psychosocial theory, a clear definition of the theory and at least one of the aforementioned variables were considered eligible for inclusion.

3.3.4 Comparators

No restriction on the comparison group was imposed.

3.3.5 Outcomes measure

MTB was evaluated using initiation, adherence, persistence and discontinuation as the outcome measures. Medication initiation is defined as when the patient takes the first dose of prescribed medication (17). Medication adherence refers to the extent to which the patient follows the provider's recommendation with respect to dosage, timing, duration, and frequency of medication taking (18). Medication persistence refers to the extent to which the patient continues the recommended treatment over the prescribed length of time (19). Medication discontinuation implies that a patient has terminated AHT medication as evidenced by not refilling a prescription (118). Due to there being no gold standard of MTB measure, MTB measurements using either objective measure measurements (e.g., pill count, medication refill data), via a validated self-reported instrument, or alternatively a clear explanation of the alternative measurement that was provided are eligible for inclusion.

3.3.6 Timeframe

The review exclusively assesses medication adherence behaviours of the standard 5 years AHT prescription among HR+ breast cancer population. Studies that examine medication adherence behaviours of extended AHT prescription to more than 5 years were not included.

3.4 Information Sources

Papers published from the year of introduction of AHT into clinical use, 1998, until March 2018 were searched in 7 databases: MEDLINE (OVID interface), EMBASE (OVID interface), Web of Science (WOS), Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL, Wiley interface), PsycINFO (OVID interface), PsycARTICLE (OVID interface) and Cumulative Index for Nursing and Allied Health Literature (CINAHL) (10).

The MEDLINE and WOS were selected for its wide coverage of medicine, pre-clinical sciences, social sciences and humanities research. The PsycINFO, PsycArticles and CINAHL database covers medical and academic literature in the field of psychological aspect and its related disciplines including medicine, nursing, allied health, sociology, pharmacology and other areas (119). EMBASE and CENTRAL database indexes drug trials inclusive randomized and quasi-randomized controlled clinical trials (120). To ensure the all relevant studies were included, reference lists of included articles were reviewed to retrieve additional relevant articles that were not captured in the search result from the database.

3.4.1 Search strategy

Literature search strategies were developed using medical subject headings (MESH) keywords and index terms that used to describe the relevant article. Search strings of all the groups were combined by using Boolean operators (OR, AND, NOT), truncator (*) and wildcard (?) for maximum yield of search. A pilot search using MEDLINE as a trial was executed in consultation with my supervisor (DW), co-supervisor (CC) and academic support librarian (MD) from the University of Edinburgh. After the MEDLINE search strategy is finalized, the search syntax on subject headings, abstract and titles were revised to reflect database-specific guideline. The search string used is included in Appendix B.

3.4.2 Data Management and Reliability Management

Search results from the databases were exported from the web and organized using Endnote. In line with the systematic review method guidelines, two reviewers (HO and CC) were independently involved in the process of data screening, data selection, data extraction, quality assessment and data synthesis to minimize error and avoid bias. Discrepancies between the two reviewers were discussed and synchronized along the steps.

3.4.3 Data screening and collection process

All duplicates were removed before moving to the selection stages and reviewed by two independent reviewers. In the initial selection phase, titles and abstracts were reviewed and papers were retrieved if eligible. In the second selection stage, full texts of the selected papers were scrutinized against predefined inclusion criteria. Any disagreement regarding the article selection was resolved through discussion. The screening and selection process was illustrated using PRISMA flowchart (121).

3.4.4 Methods to obtain full-text articles and missing information

The full text of the eligible research articles was searched using Endnote and an open access paper was downloaded from online. Five email attempts were sent to the lead author to obtain missing information and request for full texts.

3.5 Quality Assessment

Given that our sample included qualitative, quantitative, and mixed methods studies, all studies selected for retrieval were assessed for methodological quality using the Mixed Method Appraisal Tool (MMAT) version 2018 (122). Algorithm and MMAT user manual that was used to assist the appraisal procedure was included in Appendix C.

MMAT is a comprehensive and validated appraisal tool that was specifically designed for the methodological appraisal stage of systematic mixed studies review. Unlike other appraisal tool is designed exclusively for either quantitative or qualitative studies, MMAT

provides a set of quality criteria checklist items that cater to different type of empirical study design (123). MMAT was developed in 2006 based on constructionist theory and thematic analysis of 17 critical appraisal tool and it has undertaken a series of efficiency, validity and reliability test in 2011 (124). The current 2018 version refined the content criteria based on the joint result of the literature review, feedback from MMAT users and international expert consensus meetings (125). MMAT has been used in more than 100 explanatory, effectiveness mixed studies systematic reviews ranging from HIV studies, physical health, mental health, dementia and etc. (123,126–130).

The present version (2018) abandoned score-based ratings and endorsed use of the checklist to provide a detailed presentation of each criterion instead. It contains two eligibility screening questions and a set of four methodological quality criteria corresponding to 5 categories of studies (qualitative, quantitative randomized controlled trials, quantitative non-randomized, quantitative descriptive and mixed methods studies). All non-empirical studies were first be excluded from the appraisal stage if they answer 'No' or 'Can't tell' to one or both eligibility screening questions. Methodology quality of the feasible studies were be ranked using five item design-specific criteria in each category (125). Each category is subjected to assess quality related to reporting of the context (e.g. is there an adequate description of the approach, rationale, methods or sample used), risk of bias (e.g. is the risk of nonresponse bias low) and appropriateness of the study methods (e.g., were data collection methods reflects the research question). Each item was rated on a categorical scale (yes, no, and cannot tell), and the number of items rated "yes" was counted to provide an overall score. There is no defined cutoff study quality score and all articles were included independent of their quality.

3.6 Data Extraction

Quantitative studies such as clinical trials or observational studies, generally employ statistical inference to explain the significance of the relationships between and among a set of study variables (112). The data and findings were reported numerically in the form of effect size, significant level, odd ratios, means and etc. Qualitative reports explore a specific topic in depth through interviews or focus group (112). These types of studies usually report findings in a thematic, narrative form or in a theoretical construct or context, both of which are less informative in term of numbers. Mixed method research merges both types of research design into a single study or series of studies and reports a combination of numerical data non-numerical data (131).

To gain a holistic sense of available data, 20 papers were randomly selected from included studies and read in full prior to the beginning of data extraction. The key concepts, succinct summaries of findings, potential interest and significance, as well as any impressions, thoughts, and ideas in light of our research question were discussed between reviewers. These papers were used as an initial calibration exercise and the findings were extracted into a customized pilot template created using Microsoft Excel 2007 as instructed in Cochrane Collaboration guidelines (132).

The draft extraction template contains multi-page extraction sheets to extract study information separately for ease of retrieval and reference. Characteristic of the study such as author, publication year, database, location and quality assessment score were extracted into Sheet I. Sheet II contain extracted PICO information including study design, type of study, study populations, sample size, the location of the study, sampling method, settings and statistical information. The outcomes extracted are the type of MTB, MTB measure, the definition of the MTB, psychosocial measures, validity of the questionnaire, method of score calculation and the reported results. Other information such as study limitation, suggested strategy and the main conclusion was extracted into Sheet III. Appendix D details the full data extraction elements.

From the results of the pilot extraction test, we have identified that (I) selected papers are suitable to be used in tandem due to the homogenous nature of the study and (II) most of

the qualitative studies are not quantifiable and hence the conversion of data is needed. Two form of Bayesian conversion approaches are available for integrated synthesis; (I) convert qualitative data into numerical form and analyzed with meta-analysis or (II) codified quantitative data into themes and interpret with qualitative synthesis (133,134). We favour the latter method as most of the eligible qualitative studies did not present numerical data.

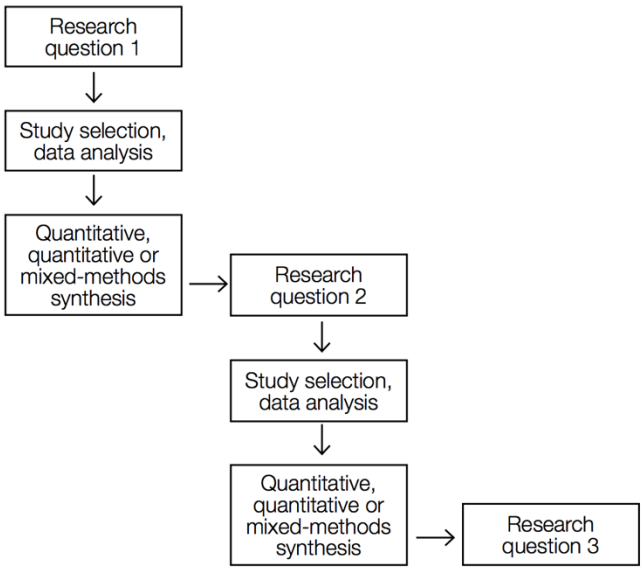
The extraction template was then revised to separate the extraction in 2 major ways: the characteristic of study and the study's main findings for ease of data analysis. For the characteristic of the study, we extracted information followed by PICO guidelines to include demographic details, study details (Author, year, study location), study type, MTB group, outcome definition and measure. For the psychosocial findings, significant findings reported in the quantitative study or quantitative components of mixed method study were abstracted and transformed into simplified findings. Qualitative findings were extracted in the form of theme as reported in the original study to preserve the context. The direction of study effect was indicated by + (positively related), - (negatively related) and X (no effect).

3.7 Data Synthesis and Outcome Prioritisations

3.7.1 Integrative review methodology

In an integrative review, the aggregated data can be synthesized using segregated methodologies, integrated methodologies or contingent methodologies (135). Segregated methodologies synthesized qualitative and quantitative data separately prior to mixed method synthesis; integrated methodologies combined both types of data into single mixed method synthesis whereas contingent methodologies involve two or more syntheses conducted sequentially (135). The contingent methodology was chosen in this review to sequentially generate three types of outcomes specific to answer three types of research questions. (Figure 3.7.1).

Figure 3.7.1: Contingent methodology (135)



3.7.2 Analysis

The “best fit” framework analysis is a form of theory-based qualitative synthesis, which uniquely utilizes a priori identification framework, model or theory to systematically aggregate, configure and synthesis data (136). This method is akin to thematic analysis and realist synthesis, but it allows more than one identified model or theory to be employ parallelly in the data synthesis (137). This approach begins by reviewers in choosing a best fit conceptual model and use it as the foundation to code, index and map the data in a form of the thematic matrix (137,138). The initial coding against the predefined model formed a draft of the framework and allows further amendments or addition of new factors to be incorporated as they emerge from the data (78,79,139–141).

This review accommodates framework analysis because compared to other more exclusively interpretative forms of qualitative synthesis, this approach offered a flexible, transparent, systematic and pragmatic process. It provides strength in explicitly describing the process that guides the systematic analysis of data from the development of descriptive to structures disparate idea in a methodical manner (142). This ensures transparency and traceability of the data transfer from the original conceptual framework

to the final product (78,79,139–141). Additionally, its synthesised data is pertinent to research questions that use the charting technique, which straightforwardly presents a visual recognition of patterns and enhance transparency of the coding process (138).

3.7.3 Research outcomes

Following the contingent methodologies, three main outcomes were recursively synthesized using framework analysis guided with a cohesive conceptual model of TDF, COM-B model and intervention function. Framework analysis involves a fivefold process (I) familiarization with the data, (II) identify the framework "best fit" to each research questions, (III) systematically indexes or reduces or pulls together the data into the predefined framework (IV) construct a map or chart for each key dimensions (V) interprets explanatory conclusions clustered around themes (136,138). Each research question repeats the framework analysis customary steps using the respective identified model. The synthetic product is expressed in the form of a thematic matrix or chart using selected theoretical constructs or domains (100). A demarcation of the three main analytic steps is illustrated as follows.

Step 1: Code psychosocial related findings into 14 of TDF domains

Primary outcome: Subgroup analysis of behaviour group

The first step of the analysis is to systematically summarize psychosocial findings associated with non-initiation, non-adherence, non-persistence and premature discontinuation into TDF relevant domains. All the identified psychosocial determinants findings associated with each type of behaviour group were thematically coded, assembled and mapped into the most appropriate domains (73,139,143). This review follows the original definition of the 14 TDF domains, which was derived from the American Psychological Associations' Dictionary of Psychology (Figure 3.7.3). A set of data extraction templates were created using Excel spreadsheet with the rows to represent study cases, columns to represent 14 TDF domains and "cells" of summarized data. Colour coding was used to differentiate the types of behaviour group. The magnitude of influences within the strata was indicated as "positive", "negative" or "no effect" on the

associated behaviour. The end product formed a matrix, which allowed a visual representation of the key domains. Constant comparison technique was used to review the data within and between the behaviour group and the findings were summarize narratively (144).

Table 3.7.3: Definition of TDF (73,139,143)

Theoretical Domains Framework domains	Definition
Knowledge	An awareness of the existence of something [knowledge (including knowledge of condition/scientific rationale), procedural knowledge, knowledge of task environment].
Cognitive and interpersonal skills	An ability of or proficiency acquired through practice [interpersonal skills]
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions [self-monitoring, breaking habit, action planning].
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives [memory, attention, attention control, decision making, cognitive overload/tiredness].
Physical skills	An ability of or proficiency acquired through practice [skills, skills development, competence, ability, practice, skill assessment].
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour [environmental stressors, resources/material resources, organisational culture/climate, salient events/critical incidents, person x environment interaction, barriers and facilitators].
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feeling, or behaviours [social pressure, social norms, group conformity, social comparisons, groups norms, social support, power, intergroup conflict, alienation, group identity, modelling].
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting [professional identity, professional role, social identity, identity, professional boundaries, professional confidence, group identify, leadership, organisational commitment].
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use [self-confident, perceived competence, self-efficacy, perceived behavioural control, beliefs, self-esteem, empowerment, professional confidence].
Optimism	The confidence that things will happen for the best or that desired goals will be attained [optimism, pessimism, unrealistic optimism, identity].
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way [stability of intentions, stages of change model, transtheoretical model and stages of change].
Goals	Mental representations of outcomes or end states that an individual wants to achieve [goals (distal/proximal), goal priority, goal/ target setting, goals (autonomous/controlled), action planning, implementation intention].
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation [beliefs, outcome expectancies, characteristics of outcome expectancies, anticipated regret, consequents].
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus [rewards (proximal/distal, valued/not values, probable/improbable), incentives, punishment, consequents, reinforcement, contingencies, sanctions].
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event].

Step 2: Index the TDF preliminary findings into the COM-B model

Secondary outcome: Identification of barriers and facilitator of capabilities, opportunities and motivation.

The second step is to identify what psychosocial factors need to be changed using the COM-B model. To prepare the data for subsequent retrieval and exploration, findings from the primary outcome were summarized and transformed into a statement that represents the significant themes. The results of the primary synthesis were matched with relative components of COMB-model to distil barriers and facilitators that need to be addressed. Data within the theme were matched, assign, sifted and sorted in accordance with relative Capabilities (psychological and physical), Opportunities (physical and social) and

Motivation (reflective and automatic) components of COM-B model (Table 2.2.2). The end product of this phase assembles an overall finding into a thematic matrix with the citation of the contributing studies was indicated alongside.

Step 3: Map COM-B model findings with relevant intervention functions

Tertiary outcome: Link relevant intervention function using intervention functions

Analysis at this stage moved the description of the data to a bigger picture of intervention formation. The aim of the tertiary outcome is to link the sources of the problem with the relevant intervention function. In a similar fashion, the barriers identified in the secondary outcomes were used as a signpost to match the mechanism of action to the relevant intervention functions. The result was presented in the form of a schematic diagram and summarized using narrative synthesis. The result was supplemented by narrative referring to the included studies that advocate the similar recommendation on the future intervention.

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CHAPTER 4: RESULTS

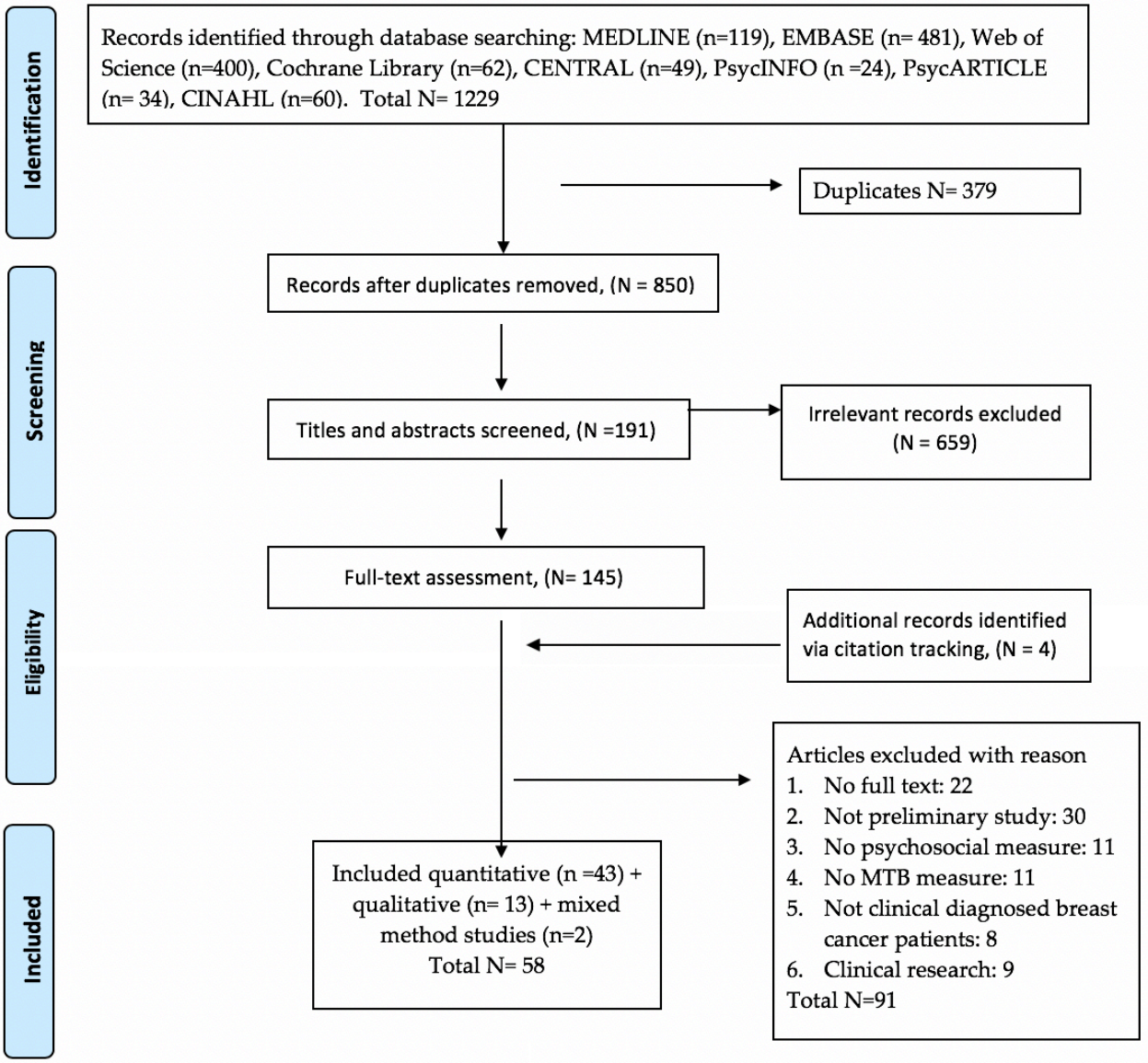
4.1 Study Validity

To minimize selection bias and interpretative bias, two reviewers (HO and CC) were independently involved in the data selection process. Meetings were held to resolve the discrepancy, uncertainties and analytic decisions. The title and abstract of papers were screened and 80% of the papers were mutually selected by both of the reviewers. This indicates that both the reviewers have a good agreement regarding which papers were deemed relevant and should be retained for analysis. The discrepancy of the remaining 20% of the papers was discussed and a full consensus was reached before moving on to the following stages. Based on the consensus pool of eligible papers, the lead reviewer (HO) conducted the data extraction, quality assessment and coding procedure. In accordance with the "rule of thumb", the result of each procedure was verified by second reviewers (CC), who did an agreement check on 10% randomly selected papers (145). All the results were in full agreement.

4.2 Study Retrieval

The database search captured a total of 1229 records inclusive of 379 duplicates. After removing the duplicates, the titles and abstracts of 850 articles were checked for relevance, of which 659 ineligible records were removed. The distilled 191 potential papers were examined against the inclusion criteria in full text. Exclusion of 91 papers was made for the following reasons: no full text available (N=22), not primary study (N=30), no psychosocial measure (N=11), no medication-taking behaviour measure (N=11), population are not clinically diagnosed breast cancer patients (N=8) and clinical research (N=9). Citation tracking of the 145 papers identified additional of 4 papers, summing the total number of eligible articles to 58. Final selection includes 43 quantitative studies, 13 qualitative studies and 2 mixed method studies. The PRISMA flow diagram depicts the multi-step study selection process (Table 4.2).

Table 4.2: PRISMA flow diagram



4.3 Characteristic of Included Studies

The following tables describe the pool of data extracted from included studies stratified by MTB measure. The characteristic of studies that examine single MTB were organized in the order of initiation (Table 4.3A), adherence (Table 4.3B), persistence (Table 4.3C), and discontinuation (Table 4.3D). Table 4.3E provides an overview of the characteristic of studies that investigate combined MTB measure. Table 4.3F listed the acronym used in Table 4.3 A – Table 4.3D. The full reference list of included papers in this review was indicated by "[reference number]" and listed separately in Reference II (page 134-137).

Table 4.3A: Studies with initiation measure

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[1] Heisig SR,2016, Germany	**Cross-sectional**	To identify correlates of pre-treatment expectations.	166	**Initiation** ·Self-report	· **Questionnaire** (BMQ, BIPQ, EORTC-QLQ 30) · **Scale** (HADS, NCB)	(-) Negative necessity–concern, perceived lower treatment efficacy, no knowledge of tumor receptor status, , negative expectation, higher medication harmfulness beliefs ,negative treatment pre-appraisal and higher concern on quailty of life.
[2] Beryl LL, 2017, USA	**Longitudinal semistructured interview** (57, 97,167 days post-diagnosis and at the end of primary treatment)	To map the decision-making process, patterns of uncertainty and decisional change for treatment initiation	35	**Initiation** ·Self-report	·**Self-report**	(-) High uncertainty and physical or psychological concerns affect decisional resolve
[3] Stu¨ber T, 2017 Germany	**Prospective multi-centre cohort**	To analyze factors that influence patients' and physicians' decisions against treatment initiation.	759	**Initiation** ·Self-report	· **Questionnaire** (EORTC QLQ-C30) ·**Self-report**	(-)Fear of ET. (X) Psychiatric comorbidity ,poor QOL, and education ,were not associated with the decision.
[4] Neugut AI, 2012, USA	**Prospective cohort** (4–8,12–24 weeks)	To investigate the impact of psychosocial factors and patient perceptions regarding decision-making on non-initiation of HT.	1,050	**Initiation** Electronic pharmacy, prescription fill, medical records data, self report	· **Questionnaire** (MOS-SS) · **Scale** (communication, decision making)	(-)Negative beliefs about treatment efficacy, perceived higher difficulty in treatment decision (+) high quality of patient/physician communication (X) demographic factors
[5] Khan LK, 2007 USA	**Prospective cohort**	To examine key components of patient-centered care and rates of ongoing Tamoxifen.	881	**Initiation** Medical record data, survey	· **Questionnaire** (PCCI)	(-) Less support than needed, less than wanted role in decision-making , absence of doctor input, patients not informed side effects in advance. (X) demographic, cancer characteristics

Table 4.3B: Studies with adherence measure

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[6]Grunfeld EA, 2005, UK	**Survey**	To investigate treatment perceptions, side effects experienced and how these related to adherence behaviour.	110	**Adherence** MARS-5	• **Questionnaire** (WHQ,BMQ)	(-) Experienced higher side effect, forget, change of routine, lower perceived treatment benefit (X) self monitor strategy , emotional and physical wellbeing, severity of vasomotor symptom (+) Positive beliefs on the treatment efficacy
[7] Liu Y, 2013 USA	**Statewide survey** (6,18,36 months)	To investigate impact of patient-provider communication on adherence.	303	**Adherence** Medical records	• **Questionnaire** (CAHPS) • **Scale** (MAS)	(-) Having at least one comorbid condition, no health insurance, experience side effect. (+) Patient centered communication, perceived self-efficacy in patient-physician interaction (X) discussion on why AHT is needed
[8] Brier MJ, 2018, USA	**Prospective cohort**	To examine how arthralgia-associated aging perceptions predict non-adherence	509	**Adherence** Medical charts	• **Scale** (PASS, HADS)	(-) Ageing perceptions, depressive symptoms
[9] Brier MJ, 2017 USA	**Mixed method**	To explore interpersonal factors and adherence.	25 (interview); 240 (cross-sectional)	**Adherence** Self-Report	• **Self-report** • **Scale** (SIRRS,HADS)	(+) Emotionally nurturing support (X) Physical affection, Tangible support , Information support made no contributions to support satisfaction
[10] Brier MJ, 2017 USA	**Prospective cohort**	To evaluate the relationship between health beliefs, risk perception on adherence	437	**Adherence** Oncology progress notes, medical charts	• **Scale** (HBMABC)	(-) Perceived greater barriers (financial barriers, side-effects, difficulty getting) to treatment (X) perceived susceptibility to cancer recurrence and perceived benefits of AIs
[11] Bright EE, 2016 USA	**Online cross sectional survey** (2 weeks)	To test barrier x facilitator interaction with adherence in 3 domains (cognitive, affective, behavioral)	1,371	**Adherence** Adapted MMAS-8	• **Questionnaire** (WAISCF) •**Self-report**	(-) Experienced behavioral barrier (+) self coping strategies (eg cognitive self-talk) (X) interpersonal variable
[12] Bright EE , 2018, USA	**Longitudinal analytic study** (initiation, 1, 4 month after initiation)	To test a model of contributors to objective adherence.	130	**Adherence** MEMS	• **Questionnaire** (COPE, ISEL, CES-D)	(+) Greater social support at prescription initiation was associated with lower depressive symptoms. (X) Use of avoidance-oriented coping was not statistically significantly related to depressive symptom
[13] Nestoriuc Y, 2016 Germany	**Prospective cohort** (5 weeks post-surgery, 3, 24 months of post-AHT)	To determine the modifiable role of patient expectations on adherence to AHT	111	**Adherence** Pre-validated patient self-report score	• **Questionnaire** (EORTC/QLQ-C30) • **Scale** (HADS)	(-) Patients with moderate or severe side-effect expectations at baseline experienced higher side-effects at follow up
[14] Wickersham K, 2012, USA	**In-depth semistructured interviews**	To describe the AHT medication-taking experiences	12	**Adherence** MEMS	• **Self-report**	(X) Experienced side effect. (-) Forgetfulness (+) Necessity belief in treatment. Routine training. Self-monitor strategy (eg. store medication at obvious place)
[15] Wuensch P, 2015 Germany	**Survey**	To examine the influence of treatment experiences, communication, knowledge on adherence	281	**Adherence** Online structured questionnaire	•**Self-report**	(-) Lack of information, physicians did not react on reported side effects. (-) Did not received detailed answers to questions

Table 4.3B: Studies with adherence measure (continued)

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[16] Brett J, 2018 UK	**Cross-sectional survey** (2–4 years post diagnosis)	To investigate factors associated with non-adherence	292	**Adherence** MARS-5 and self-report	• **Questionnaire** (BMQ)	Intentional: (-) side effects ,greater concerns about AET and a lower perceived necessity to take AET Unintentional :(-) younger age ,post-secondary education and paid employment. (X) side effects
[17] Brett J, 2018 UK	**Semistructured interview**	To explore factors that influence adherence	32	**Adherence** Self-report	•**Self-report**	(+) Receive timely and relevant information. Self-monitor strtegy. Supportive social relationships. Commitment to their family. (-)Burden of side effects, feeling unsupported, concerns about long-term effect of AHT, value quality of life over length of life, low risk of perception
[18] Arriola K, 2014 USA	**Cross sectional**	To test the hypothesis that patient beliefs about medication mediate the relationship between frequency of physician communication and adherence	200	**Adherence** MARS, self-report and medical chart abstraction.	• **Questionnaire** (BMQ)	(+) Frequent physician communication that shapes what patients believe about AET importance may be associated with (-) frequent physician communication that shapes patient concerns about side effects.
[19] Moon Z, 2017 England	**Cross-sectional questionnaire**	To explore relationship between CSM and TPB components on intentional and unintentional non-adherence	777	**Adherence** MARS	• **Questionnaire** (MSPSS,IPQ-BCS, BMQ) • **Scale** (HADS) • **Theory** (TPB,CSM)	Intentional :(-) Side-effect intensity, distress , low social support (+) Higher levels of perceived behavioural control and intention Unintentional: (+)stronger beliefs in the risk of recurrence and stronger beliefs on recurrence, higher levels of perceived behavioural control
[20] Moon Z, 2017 England	**Semi-structured interviews**	To understand treatment experiences and factors associated with non-adherence.	32	**Adherence** self-report	• **Theory** (GT)	(+) Necessity beliefs outweighed concerns, self develop coping strategy (-) Conflicting beliefs around the harms and benefits of tamoxifen, depression, lack of comprehensive information ,lack of support, lack of validation with side effects
[21] Lin J, 2017 USA	**Cross sectional analytic**	To assess association between associated side effects and adherence.	100	**Adherence** MMAS-4	• **Questionnaire** (PRA, BMQ)	(X) no association between current adherence and report of side effects. (-) difficulty asking providers for more information were more likely to report side effects.
[22] Kimmick G, 2015 USA	**Prospective, cross-sectional**	To explore how symptoms and psychosocial factors are related to intentional and unintentional non-adherence	112	**Adherence** MMAS	• **Questionnaire** (BMQ, PEPPI) • **Scale** (SEAMS)	Intentional: (-) presence of symptoms and lower self-efficacy for physician communication. Intentional and non-intentional: (-) having more concerns about taking one's medications (+) higher self-efficacy for taking medication.
[23] Karmakar M, 2017 USA	**Cross sectional survey**	To examine the relationships among the PMT constructs; and predictors of adherence	145	**Adherence** MMAS-8	•**Theory** (PMT)	(+) High self-efficacy, motivation, response efficacy and coping appraisal (-) Response Cost (X) Threat Appraisal
[24] Lee JY, 2018 South Korea	**Cross-sectional analytic study**	To identify reasons for AET adherence	210	**Adherence** MMAS-8	• **Questionnaire** (BMQ, FoP-Q-SF) • **Scale** (GSE, CES-D)	(+) lower depression level, higher necessity beliefs , high self-efficacy and lower concerns beliefs.

Table 4.3B: Studies with adherence measure (continued)

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[25] Markovitz LC, 2017 USA	**Survey**	To test depression and non-adherence.	133	**Adherence** MGLS	• **Questionnaire** • **Scale** (CES-D, PMS, MHLC)	(Neutral) Depression mediated the relation between physical symptoms, cognitive symptoms, social support, and adherence to medication.
[26] Bender CM, 2014 USA	**Cross sectional**	To assess the interaction between patient and illness or treatment factors and non-adherence	91	**Adherence** MEMS, medication bottle cap, dosing history	• **Questionnaire** (BMQ, ISEL) • **Scale** (BDI-II, PoMS)	(-) Pre-therapy levels of depressive symptoms and anxiety, as well as poorer pre-therapy physical functioning. Perceptions of financial hardship, symptoms, disease stage, and more complex medication regimens intensified the effect of negative mood on adherence over time.
[27] Wouters H, 2014, Netherlands	**Cross sectional questionnaire**	To examine associations between patient experiences and perceptions on non-adherence.	241	**Adherence** MMAS-5	• **Questionnaire** (TMI) •**Scale** (MUUSE)	Unintentional: (-) experience of practical problems and low perceived self-efficacy. Intentional: (-) Number of side effects experienced and perceived self-efficacy with regard to learning about medication. Overall: (-) doubted the efficacy of endocrine therapy, worried about side effect, practical barriers
[28] Heisig S, 2015 Germany	**Interventional single cohort** (Pre and post-intervention)	To analyze the effects of a structured treatment information on patients' satisfaction, knowledge, and adherence.	137	**Adherence** Validated self-assessment questionnaire	• **Scale** (IMS)	(+) Enhanced information (verbal and written information on the mechanisms of AET, its benefits, and possible side effects that was presented by trained professionals.) (+) Higher satisfaction, better learning, and higher comprehension of information.
[29] Harrow A, 2015, Scotland	**Semistructured interview**	To examine women's experiences, beliefs and influence of health professionals on adherence.	30	**Adherence** Self-report	•**Self-report**	(+) Perceived necessity, belief in efficacy ,trust in doctor, self-discipline (-) forget, less follow up, few opportunity to discuss impact of side effect. (x) side effect did not always cause women to stop taking their medication, or to seek advice
[30] Wells KJ ,2016 , USA	**Cross-sectional interviews**	To evaluate the barriers and facilitators to taking medications	25	**Adherence** Self-report	•**Self-report**	(+) Develop routine, ease of access to medication, reduction of medication cost, negative consequences associated with not taking the medication, reminder from friends/family. (-)Side effects, trouble remembering to take medication, faith and belief in God
[31] Pellegrini I , 2010, France	**Semi-structured interviews**	To determine contribution of patients' perceptions of the treatment and experience of side-effects on adherence.	34	**Adherence** Self-report	• **Theory** (GT)	(-) dislike of taking drugs, lack of definite answer, etiology of the changes in their menopausal status, symptoms leads to psychosocial discrimination (-) distress, ambivalence and tension
[32] Iacorossi L, 2016, Rome	**Semistructured interviews.**	To explore the patients' experiences of adherence and their perceptions of the challenges they face on adherence.	27	**Adherence** Self-report	•**Self-report**	(-) Fear of drugs, fear of side effects, forget (+) consider adherence in terms of duty (ie, duty to totally correspond to the doctor's advice) or habit (previously acquired behavior), patient-centrerd approach, functional strategy

Table 4.3B: Studies with adherence measure (continued)

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[33] Humphries B , 2018, Canada	**Focus groups and individual interviews**	To identify patient's attitudinal, normative, and control beliefs regarding AHT adherence	34 (focus group), 9 (Interviews)	**Adherence** Self-report	·**Theory** (TPB)	Attitudinal beliefs; (+) beliefs in treatment efficacy. (-)side effect, reminder of cancer treatment is not over. Normative beliefs: (+)social support, (-) social label Control beliefs: (+) self monitor strategy, seek additional information, (-)unexpected side effect, having unanswered questions).
[34] Walker HE, 2016, USA	**Prospective cohort** (Twice a year for the initial 3 years and annually thereafter until end of study	To describe association between treatment symptoms, perceptions, and emotions on adherence.	106	**Adherence** MMAS-5	· **Scale** (necessity perception, emotion, concern)	(+) Necessity beliefs, higher financial status, more positive emotions toward ET. (X) Symptom attribution
[35] Atkins L, 2006, UK	**Prevalence study**	To investigate the factors associated with non-adherence	131	**Adherence** Self-Report	· **Questionnaire** (MHLOC)	(-) Disliked taking their medication, forget, low 'internal' and 'powerful others' dimensions of health locus of control. (X) Degree of interference in daily life from tablet taking or problems attending clinic
[36] Bluethmann SM, 2017 USA	**Mixed-methods**	To build on survey results to qualitatively explore survivors' experiences with prescribed AHT	452 (survey) 30 (Interview)	**Adherence** Self-Report	· **Theory** (GT)	(+) Strong tolerance of side effects and perseverance. Some sought advice from their oncology team (-) More difficulty managing side effects and perceived fewer benefits when side effects were bothersome.

Table 4.3C: Studies with persistence measure

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[37] Brauer, 2016, USA	**Semistructured interviews**	To understand decision making regarding persistence.	27	**Persistence** Self-report	· **Theory** (GT) ·**Self-report**	(-) Less contact with their oncology team, concerns of adverse effects impact quality of life and ability to carry out social roles. Lack of professional support when adverse effects were present (+) Informal support networks, self-management
[38] Yu KD, 2012, China	**Non RCT, prospective, multicenter, controlled, observational study** (1 year)	To evaluate the efficacy of a patient support program in improving patients' persistence to adjuvant AI medication	262. (Control group), 241 (experimen -tal group)	**Persistence** Prescription refills records and number of tablets remaining	· **Questionnaire** (PCCQ)	(-) Lower patient-provider relationship , doctor sometimes or never spends time (X) Patient support program (educational support material and a follow-up reminder service)
[39] Hershman DL, 2016 USA	**Prospective cohort study** (6 months intervals for the first 2 years, annually thereafter until end of study)	To determine the associations between psychosocial factors and non-persistence.	523	**Persistence** Electronic pharmacy record	· **Questionnaire** (MOS- SS) TSQM, FACT-G) · **Scale** (IPC, IES)	(+) Better quality of life, treatment satisfaction, positive attitudes. (X) Social support, patient-physician communication (-) Intrusive, avoidant thoughts

Table 4.3D: Studies with discontinuation measure

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[40] Fink AK, 2004 USA	**Longitudinal cohort** (3, 6,15, 27months post-surgery)	To investigate the predictor factors and the role of beliefs on treatment discontinuation	597	**Discontinuation** Self report and pharmacy records	· **Questionnaire** (CARES-SF, , MHI-5, MOSS) ·**Self-report**	(-) Neutral or negative beliefs about the value of tamoxifen, patients with positive nodes. (X) Side effects, were not associated with tamoxifen discontinuance
[41] Bluethmann SM, 2017 USA	**Secondary analysis of longitudinal cohort** (6 ,12 months post-baseline, and then annually thereafter for up to 7 years.)	To investigate effects of cognitive function and time to discontinuation.	1280	**Discontinuation** Medical records and self-report	· **Questionnaire** (EORTC QLQ-C30)	(-) Lower cognitive function are more likely discontinue at the treatment midpoint, but not related to discontinuation in the other period.
[42] Cluze C, 2012 France	**Prospective cohort** (10, 16, 28 months post-diagnosis)	To estimate the incidence of tamoxifen interruption and its correlates.	196	**Discontinuation** Medical record , pharmacy refill data	· **Scale** (WHOQOL-BREF,CES-D)	(-) poor social support,lack of understandable information about treatment, no longer fearing cancer relapse, no opportunity to ask questions and symptoms experiences.

Table 4.3E: Studies with mixed MTB measure

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[43] Pinheiro LC, 2017 USA	**Two cohorts** (median of 25.1 months post-diagnosis)	To determine if health-related quality of life subgroups were associated with underuse.	953 (Initiation group); 1114 (Adherence group)	**Initiation and adherence** Medical records, survey, modified MGLS	· **Questionnaire** (HRQOL, FACT-B, FACIT-SP)	Initiation: (X) health related quality of life Adherence: (-) poor health related quality of life
[44] Friese, 2016, USA	**Prospective cohort** (9 months and 4 years post-diagnosis)	To examine factors associated with treatment initiation and persistence	743	**Initiation and persistence** Self-report	· **Scale** (medication beliefs, emotion)	Initiation: (+) worry about recurrence (-) inadequate information about therapy Persistence: (+) took two or medications weekly Both: (-)doctor left it up to the patient , concerns about side effects, reported a general dislike of medication
[45] Livaudais JC, 2012 USA	**Telephone interview survey**	To explore patient factors, treatment factors and physician-patient communication factors associated with the use and discontinuation of AHT	744	**Initiation, Discontinuation** Self-report	·**Self-report**	Initiation: (-) Less discussion with provider , (+)Follow up with oncologist Continuation:(-) side effects, family history, high education Both: (+) high strength of physician recommendation
[46] Hadji P, 2013 German	**Randomized controlled trial** (Pre-treatment,12, 24 months post-treatment)	To investigate whether the provision of education material leads to an improvement in patient compliance and persistence	4484	**Adherence and persistence** Self-report, prescription record	· **Scale** (patient attitude and behaviour)	(X)Addition of education materials to standard therapy did not significantly affect compliance and persistence.
[47] Stanton , 2014 USA	**Online cross sectional survey** (2 weeks)	To identify potential contributors to nonadherence and nonpersistence	1465	**Adherence and Persistence** MMAS-8	· **Questionnaire** (WAISCF) · **Scale** (HADS) · **Framework** (NCF)	Adherence: (-) lower financial status, a prior switch in endocrine therapies, poorer relationship with the oncologist and lower perceived need , more negative emotions Persistence: (X) financial status , (-) negative emotions like depression, lower positive emotion

Table 4.3E: Studies with mixed MTB measure (continued)

Author, Year, Location	Study type (follow up)	Study aim	Sample size	MTB measure	Psychosocial measure	Psychosocial findings (- negative effect, + positive effect, X no effect on MTB)
[48] Bhatta SS, 2013 Chicago	**Mail-in survey** (2 years)	To examine factors associated with adherence and persistence to AHT	197	**Adherence and Persistence** Chart review	• **Scale**	Both: (+) Perceived importance of AHT and the high value placed on their doctor's opinion about the importance of AHT
[49] Huiart L, 2013 France	**Cohort** (Every 10 month for 2 years)	To describe adherence and persistence with AHT along with their determinants.	382	**Adherence and Persistence and Initiation** MPR, pharmacy refills, medical records and self-report	• **Questionnaire** • **Scale** (ADL, IADL, GDS-15)	Adherence: (-) forget Persistence: (X) cancer characteristic Discontinuation: (-) use of complementary or alternative medicine ,suffering from comorbidities (+) polypharmacy
[50] Huiart L, 2012, France	**Cohort** (10 month after diagnosis)	To describe discontinuation and non-compliance with Tamoxifen treatment	288	**Adherence, Persistence, Discontinuation** MPR	• **Questionnaire** (WHOQOL-BREF) • **Scale** (CES-D)	Continuation: (-) low social support, Adherence: (-) younger age
[51] Verbruggi e M, 2017, Belgium	**Semi-structured interviews**	To examine the process of non-adherence and non-persistence by researching influencing factors and their interrelatedness	31	**Adherence and Persistence** Self-report	• **Theory** (GT)	(-) poorly informed possible impact, expectation and perception of AHT, little social support from family, social expectations (+) peer support, support and reassurance from healthcare provider, self-management
[52] Cahir C, 2015, Ireland	**Semi-structured interviews**	To source modifiable influences on medication-taking behaviour	31	**Adherence Persistence** Self-report	• **Theory** (TDF)	Both: (+) belief in necessity and treatment efficacy , set treatment as high-priority, abilities to cope side effects and managing medication Adherence: (-) no routine, forgetting and environmental stressors , inadequate medication management techniques Persistence: (-) value quality of life, temporal self-regulation), non-necessity and distrust of medication
[53] Lash T, 2006, USA	**Cohort** (3, 6, 15, 27, 39, 51, 63 months post-surgery)	To identify predictors of non-adherence.	462	**Adherence and Discontinuation** medical records	• **Questionnaire** (MOS-SS, CARES-SF) • **Scale** (DBS)	Continuation: (+) positive views, (-)polypharmacy , side effect Adherence: (+) perceived benefits outweighed risks
[54] Pan Yq, 2018 Germany	**Prospectieve cohort** (3 months- 2years)	To identify modifable factors that predict long-term adherence to AHT.	116	**Adherence and Discontinuation** Self-report and a validated single item	• **Questionnaire** (EORTC QLQ-C30, BMQ) • **Scale** (HADS)	Adherence:(+) lower side-effect severity, higher necessity–concern beliefs, lower anxiety and depression, lower expected side-effect severity Discontinuation: (-) worries about potential side effect and actual experienced side effect
[55] Quinn EM, 2016 Ireland	**Cross-sectional anonymous survey**	To assess modifiable factors associated with suboptimal adherence.	261	**Adherence and Discontinuation** Validated medication adherence score	• **Questionnaire** (social support)	Adherence: (-) young, employed, side effects , perceived themselves to have low levels of emotional support and source information from the internet
[56] Hadji P, 2013, Germany	**Retrospective database analysis** (3 months -3 years)	To identify determinants of non-persistence	12,412	**Persistence and Discontinuation** Prescription record	• **Medical database**	Continuation :(+) use of other treatments, presence of the co-morbidities like diabetes ,depression, (-) patients treated in general practitioner practice Persistence: (+) patients treated in general practitioner practice
[57] Freedman RA, 2017 , USA	**In-depth telephone interviews**	To explore reasons for incompletion of and whether knowledge may have influenced treatment management.	18	**Initiation, Adherence, Discontinuation** Self-report and medical records	•**Self-report**	Adherence: (-) forget. Continuation: (-) concern about side effect , transportation issue
[58] Kroenke CH, 2018 USA	**Prospective cohort** (2, 8 months post-diagnosis)	To explore associations between personal and clinical social support and non-adherence to AHT	3382	**Initiation, Adherence, Discontinuation** MPR and outpatient pharmacy records	• **Questionnaire** (MOS-SS) • **Scale** (CES-D, IPC)	All: (-) low personal support

Table 4.3F: Acronym used in Table 4.3A – Table 4.3 E

Table Column	Acronym	Full sentence
MTB measure	MARS	Medicatio Adherence rating Scale
	MARS-5	Medication Adherence rating Scale-5 items
	MMAS-4	Morisky Medication Adherence Scale-4 items
	MMAS-8	Morisky Medication Adherence Scale-8 items
	MEMS	Medication Event Monitoring System
	MGLS	Morisky, Green, and Levine's medication Adherence Scale
	MPR	Medication Possession Ratio
Psychosocial measure	ADL	Activities of Daily Living scale
	BDI-II	Beck Depression Inventory–II
	BIPQ	Brief Illness Perception Questionnaire
	BMQ	Beliefs about Medicines Questionnaire
	CAHPS	Consumer Assessment of Healthcare Providers and Systems
	CARES-SF	Cancer Rehabilitation Evaluations System – Short-Form
	CES-D	Centers for Epidemio- logic Studies Depression scale
	COPE	Coping and Emotional Approach Coping
	CSM	Common Sense Model of Illness Representations
	DBS	Decisional Balance Scale
	EORTC-QLQ 30	European Organization for Research and Treatment of Cancer
	FACT-G	Functional Assessment of Cancer Therapy: General
	FACIT-SP	Functional Assessment for Chronic Illness Therapy for Spiritual Well-Being
	FACT-B	Functional Assessment of Cancer Therapy for Breast Cancer
	FoP-Q-SF	Fear of Progression Questionnaire
	GDS-15	Geriatric Depression Scale-15 question
	GSE	General self-efficacy scale
	GT	Grounded Theory
	HADS	Hospitality Anxiety and Depression Scale
	HBMABC	Health Beliefs and Medication Adherence in Breast Cancer scale
	IADL	Instrumental Activities of Daily Living scale
	IES	Impact of Events Scale
	IPQ-BCS	Illness Perceptions Questionnaire for Breast Cancer Survivors
	IPC	Interpersonal Processes of Care scale
	IMS	Information about Medicines Scale
	ISEL	Interpersonal Support Evaluation List
	MAS	Marin Acculturation Scale

Table 4.3C: Acronym used in Table 4.3A and Table 4.3B (continued)

Table Column	Acronym	Full sentence
Psychosocial measure	MOSS	Medical Outcomes Study Short Form
	MOS-SS	Medical Outcomes Study Social Support Survey
	MUUSE	Medication Use and Understanding Self-efficacy scale
	MHI-5	five-item Mental Health Index
	MHLC	Multidimensional Health Locus of Control
	MSPSS	Multidimensional Scale of Perceived Social Support
	NCB	Nesseity concern balance scale
	NCF	Necessity-concerns framework
	PASS	Penn Arthralgia Aging Scale
	PCCI	Patient-Centered Care Item
	PEPPI	Perceived Efficacy in Patient-Physician Interactions
	POMS	Profile of Mood States tension-anxiety subscale
	PCCQ	Patient centered care question- naire
	PRA	Patient Reactions Assessment
	PMS	Profile of Mood States)
	PMT	Protection Motivation Theory
	SEAMS	Self-Efficacy for Appropriate Medication Use Scale
	SIRRS	Support in intimate relationships rating scale
	TDF	Theoretical Domains Framework
	TMI	Tailored Medicine Inventory
	TPB	Theory of planned behaviour
	TSQM	Treatment Satisfaction Questionnaire for Medication
	WAISCF	working alliance inventory short client form
	WHOQOL-BREF	World Health Organisation Quality of Life-BREF
	WHQ	Women's Health Questionnaire

Study location, year of publication, main authors

A large number of studies were conducted in the USA (n=32), followed by Europe (n=17), United Kingdom (N=7), and 2 studies were undertaken in Asia. Within the year limit from 1998 until 2018, 8 studies were published in 2018, 14 studies in 2017, 10 studies in 2016, 5 studies in 2015, 4 studies in 2014, 5 studies in 2013, 6 studies in 2012 and 2 studies in the year 2006. 1 study was published each in 2010, 2007, 2005, 2004. No study was published in the year 1998-2003, 2009, 2008 and 2011.

The lead researcher in the topic of interest are Brier MJ [7-9], Heisig SR [1,28], Bright EE [11,12], Brett J [16,17], Moon Z [19,20], Bluethman SM [36, 41], Hadji P [46,56] and Huairt L [49,50], who published more than one papers, among which, four sets of studies were published by the same author in the same year, which are Bluethman SM [36, 41], Moon Z [19,20], Hadji P [46,56] and Brier MJ [8-9]. As the study design, sample size and study aim were different, no study was merged, and all were included as an individual study for analysis.

Study type

The included studies constituted of 43 quantitative studies, 13 qualitative studies and 2 mixed method studies. The main bulk of quantitative studies (N=19) employed a cohort design, 14 studies used cross-sectional design, and a minority of 7 are survey studies. Randomised controlled trials (RCT) were not explicitly excluded from the search strategy but only one RCT identified was considered relevant to the review question [46]. A quarter of qualitative studies conducted Grounded theory guided interview and the rest uses qualitative description methodology. Of the 2 of the mixed method studies, Brier MJ study is grey literature published in the form of PhD dissertation [9].

Study population

All the populations that were studied include female breast cancer population who are the eligible candidates for adjuvant hormone therapy. Few studies further restrict the study population to explore low-income group [7], ethnic minority group [45] postmenopausal

breast cancer population [10,14,38,40,41,46,49,56], medically and historically underserved breast cancer survivors [30], young age group [34,42], invasive breast cancer stage [44], and patients with ductal carcinoma in situ who have been prescribed with AHT [45,54]. Only one study included both female and male breast cancer population [55]. We purposely included a string of male breast cancer syntax in the database search but none of the scoped research focused on male breast cancer on the issue of psychosocial factors and treatment management. Some of the studies that include male breast cancer did not fit the inclusion criteria of this review as they focused on factors associated with delayed diagnosis, adherence and survivorship studies and the prevalence of adherence rate (146,147).

Type of MTB measures

Concerning the operationalization of studies that examine one type of MTB, 5 studies measure treatment initiation [1-5], 31 studies measure treatment adherence [6-36], 3 studies measure treatment persistence [37-39] and 3 studies measure premature discontinuation [40-42]. 16 studies evaluated MTB with combined measure [43-58]. The numerous and inconsistent type of MTB measurement was distinguished into three main types. The most common type is the objective measure, where a validated scale such as Medication Adherence Rating Scale (MARS), Medication Event Monitoring System (MEMS), Morisky, Green, and Levine's Medication Adherence Scale (MGLS), Morisky Medication Adherence Scale (MMAS), or Medication Possession Ratio (MPR) [6,11,12,14,21-27,34,47,50]. Alternatively, medical record, medical charts or prescription refill record was used as a proxy of objective MTB measure [7,8,10,13,15,38-42,48,53,56]. The second largest pool is the subjective measure, where MTB data was provided by patient's self-report via survey, questionnaire or interviews [9,15,17,20,28-33,35-37,44,45,51]. The third type is the mixed measure, which both of the subjective measure and objective measure were used concomitantly [4,5,16,18,40-41,43,46,49,54,57]. A handful of studies do not specify the definition of MTB [1-3, 52]. As there is currently no gold standard for measuring MTB, all the studies were included regardless of the type of MTB measure applied.

Type of psychosocial measures

Psychosocial factors of the included studies were measured and reported to varying degrees of specificity. The type of psychosocial measure used includes validated questionnaire, Likert scale items, psychological theory or patient's self-report that based survey or interview responses. Table 4.3F present an exhaustive list of the validated questionnaire and scales that were used to measure the psychological, social, behaviour aspect of MTB. Eight studies underpinned theory such as Grounded theory, Theory of Planned Behaviour, Protection Motivation Theory, Theoretical Domains Framework to guide the understanding of the factors that modulate MTB [19,20,23,31,33,36,37,52]. One study extracts medical records to examine the diagnosis of depression [56].

Heterogeneity Measure

The included studies were highly heterogeneous in terms of variation in the definition of outcome and study measure. It is, therefore, inappropriate to conduct a meta-analysis to determine the effect sizes between the data using a statistical approach(148). Given the heterogeneousness of the data, qualitative synthesis was chosen over quantitative synthesis in this review.

4.4 Quality Assessment

MMAT was used to evaluate the quality rating of 5 main categories of study designs, (I). Qualitative studies (Table 4.4A), (II). Quantitative randomized controlled trials (Table 4.4B), (III) Quantitative nonrandomized (Table 4.4C), (IV) Quantitative descriptive (Table 4.4D) and (V) Mixed methods studies (Table 4.4E). A checklist of 5 design-specific criteria was used to evaluate the quality rating of a study based on criteria rather than assigning an overall score (Appendix B). All the included studies passed the screening questions (S1 and S2). Most of the included studies scored favourably on the MMAT study quality checklist, with four studies report missing more than 2 components [15,35]. In accordance with the guideline of MMAT, no threshold of quality score was used as the yardstick to exclude papers with a low methodological quality score (122).

Table 4.4A: Quality assessment of qualitative studies

Study number	Author	Year	MMAT study category	MMAT criteria 1	MMAT criteria 2	MMAT criteria 3	MMAT criteria 4	MMAT criteria 5
17	Brett J	2018	1D	Y	Y	Y	Y	Y
30	Wells KJ	2016	1D	Y	Y	Y	Y	Y
33	Humphries B	2018	1D	Y	Y	Y	Y	Y
37	Brauer	2016	1D	Y	Y	Y	Y	Y
2	Beryl LL,	2017	1F	Y	Y	Y	Y	Y
14	Wickersham K	2012	1F	Y	Y	Y	Y	Y
20	Moon Z	2017	1F	Y	Y	Y	Y	Y
29	Harrow A	2014	1F	Y	Y	Y	Y	Y
31	Pellegrini I	2010	1F	Y	Y	Y	Y	N
32	Iacorossi L	2016	1F	Y	Y	Y	Y	Y
51	Verbruggie M	2017	1F	Y	Y	Y	Y	Y
52	Cahir C	2015	1F	Y	Y	Y	Y	Y
57	Freedman RA	2017	1F	Y	Y	Y	Y	Y

MMAT study category: 1D= Grounded theory ; 1F= Qualitative description

MMAT criteria 1: Is the qualitative approach appropriate to answer the research question?

MMAT criteria 2: Are the qualitative data collection methods adequate to address the research question?

MMAT criteria 3: Are the findings adequately derived from the data?

MMAT criteria 4: Is the interpretation of results sufficiently substantiated by data?

MMAT criteria 5: Is there coherence between qualitative data sources, collection, analysis and interpretation?

MMAT criteria 1-5: Y=Yes ; N= No

Grounded theory and qualitative description are the two main research approach used in the qualitative studies of this review. All the study uses appropriate qualitative approach and data collection methods to answer the research question and the findings were interpreted and supported by the data collected. Almost all the study present clear links between data sources, collection, analysis and interpretation expect study [31] which do not discuss the grounded approach in the result interpretation.

Table 4.4B: Quality assessment of quantitative randomized controlled trials

Study number	Author	Year	MMAT study category	MMAT criteria 1	MMAT criteria 2	MMAT criteria 3	MMAT criteria 4	MMAT criteria 5
46	Hadji P	2013	2	Y	Y	Y	CT	Y
MMAT study category: 2=Randomized controlled clinical trial								
MMAT criteria 1: Is randomization appropriately performed?								
MMAT criteria 2: Are the groups comparable at baseline?								
MMAT criteria 3: Are there complete outcome data?								
MMAT criteria 4: Are outcome assessors blinded to the intervention provided?								
MMAT criteria 5: Did the participants adhere to the assigned intervention?								
MMAT criteria 1-5: Y=Yes ; CT=Cant tell								

The only quantitative randomized controlled trial was conducted by Hadji P in 2013. The study performed appropriate randomization, used comparable groups at baseline, have more than 80% of complete data less than 20% of dropout rate at assigned intervention. However, the study does not present clear information on how they withheld the aim of the study to eliminate response bias (MMAT criteria 4).

Table 4.4C: Quality assessment of quantitative nonrandomized studies

Study number	Author	Year	MMAT study category	MMAT criteria 1	MMAT criteria 2	MMAT criteria 3	MMAT criteria 4	MMAT criteria 5
38	Yu KD	2012	3A	Y	Y	Y	Y	Y
3	Stu¨ber T,	2017	3B	Y	Y	Y	Y	Y
4	Neugut AI,	2012	3B	Y	Y	Y	Y	Y
5	Khan LK	2007	3B	Y	Y	N	Y	Y
8	Brier MJ	2017	3B	Y	Y	Y	Y	Y
10	Brier MJ	2017	3B	Y	Y	Y	Y	Y
13	Nestoriuc Y	2016	3B	Y	Y	Y	Y	Y
28	Heisig S	2015	3B	Y	Y	N	Y	Y
39	Hershman DL	2016	3B	Y	Y	Y	Y	Y
40	Fink AK	2004	3B	Y	Y	CT	Y	Y
41	Bluethmann SM	2017	3B	Y	Y	Y	Y	Y
42	Cluze C	2012	3B	Y	Y	Y	Y	Y
43	Pinheiro LC	2017	3B	Y	Y	N	Y	Y
44	Friese	2016	3B	Y	Y	N	Y	Y
49	Huiart L	2013	3B	Y	Y	CT	N	Y
50	Huiart L	2012	3B	Y	Y	Y	N	Y
53	Lash T	2006	3B	Y	Y	N	N	Y
54	Pan Yq	2018	3B	Y	Y	Y	Y	Y
58	Kroenke CH	2018	3B	Y	Y	N	Y	Y
12	Bright EE	2018	3C	Y	Y	N	Y	Y
1	Heisig SR	2016	3D	Y	Y	CT	Y	Y
11	Bright EE	2016	3D	Y	Y	Y	Y	Y
16	Brett J	2018	3D	Y	Y	N	Y	Y
18	Arriola K	2014	3D	Y	Y	N	Y	Y
19	Moon Z	2017	3D	Y	Y	N	Y	Y
21	Lin J	2017	3D	Y	Y	Y	Y	Y
22	Kimmick G	2015	3D	Y	Y	Y	Y	Y
23	Karmakar M	2017	3D	Y	Y	Y	Y	Y
24	Lee JY	2018	3D	Y	Y	N	Y	Y
26	Bender CM	2014	3D	Y	Y	CT	Y	Y
27	Wouters H	2014	3D	Y	Y	N	Y	Y
47	Stanton	2014	3D	Y	Y	N	Y	Y
55	Quinn EM	2016	3D	Y	Y	Y	N	Y

MMAT study category: 3A= Non-randomized controlled trials; 3B=Cohort study; 3C= Case-control study; 3D= Cross-sectional analytic study

MMAT criteria 1: Are the participants representative of the target population?

MMAT criteria 2: Are measurements appropriate regarding both the outcome and intervention (or exposure)?

MMAT criteria 3: Are there complete outcome data?

MMAT criteria 4: Are the confounders accounted for in the design and analysis?

MMAT criteria 5: During the study period, is the intervention administered (or exposure occurred) as intended?

MMAT criteria 1-5: Y=Yes ; N=No ; CT=Cant tell

Of the 33 quantitative non-randomized studies, 1 trial study used non-random method of allocation [38], 1 performed case-control study [12], 18 cohort studies were included [3-5,8,10,13,28,39-44,49,50,5354,58] , and 13 cross-analytic studies were used as the design [1,11,16,18,19,21-27,47,55]. All of these studies' population are representative of AHT breast cancer population (MMAT criteria 1), the study variables were clearly defined and accurately measured (MMAT criteria 2) and no deviation of the response to intervention were found (MMAT criteria 5). There are plenty of studies which struggled to retain more than 80% of the data [5,28,43,44,53,58,12,16,18,19,24,27,47] and 4 studies do not report the respond rate [40,47,1,26] (MMAT criteria 3). In the MMAT criteria 4, the issue of confounder was not discussed in the design nor the analysis in Quinn EM, Huairt L and Lash T study [49,50,53,55].

Table 4.4D: Quality assessment of quantitative descriptive studies

Study number	Author	Year	MMAT study category	MMAT criteria 1	MMAT criteria 2	MMAT criteria 3	MMAT criteria 4	MMAT criteria 5
35	Atkins L	2006	4A	Y	Y	Y	N	Y
56	Hadji P	2013	4A	Y	Y	Y	Y	Y
6	Grunfeld EA	2005	4B	N	Y	Y	N	Y
7	Liu Y	2013	4B	Y	Y	Y	N	Y
15	Wuensch P	2015	4B	Y	Y	N	N	CT
25	Markovitz LC	2017	4B	N	Y	Y	N	Y
34	Walker	2016	4B	Y	Y	Y	N	Y
45	Livaudais JC	2012	4B	Y	Y	Y	Y	Y
48	Bhatta SS	2013	4B	Y	Y	Y	N	Y
MMAT study category: 4A= Incidence or prevalence study without comparison group; 4B=Survey								
MMAT criteria 1: Is the sampling strategy relevant to address the research question?								
MMAT criteria 2: Is the sample representative of the target population?								
MMAT criteria 3: Are the measurements appropriate?								
MMAT criteria 4: Is the risk of nonresponse bias low?								
MMAT criteria 5: Is the statistical analysis appropriate to answer the research question?								
MMAT criteria 1-5: Y=Yes ; N=No ; CT=Cant tell								

One of the two incidence studies [56] scores perfectly on all the five MMAT criteria. The response rate of Atkins study was less than 80% [56]. The rest of the seven surveys studies fulfil more than three quality criteria except Wuensch P study [15]. Assessing the studies by criteria components, Grunfeld EA and Markovitz LC studies do not provide a justification of the sampling strategy [6,25]; all studies samples are representative of the

target population [6,7,15,25,34,45,48]; Wuensh P study used measurement that has not been tested for its reliability or validity [15]; and the statistical analysis method of the Wuensh P study can't be judged for its appropriateness as it was not presented clearly in the method session [15]. A high number of studies (N=6) lost points in criteria 4 due to having less than 80% of the response rate [6,7,15,25,34,48].

Table 4.4E: Quality assessment of mixed method studies

Study number	Author	Year	MMAT study category	MMAT criteria 1	MMAT criteria 2	MMAT criteria 3	MMAT criteria 4	MMAT criteria 5
9	Brier MJ	2017	5A	Y	Y	Y	Y	Y
36	Bluethmann SM	2017	5B	Y	Y	Y	N	Y
MMAT study category: 5A: Convergent design 5B = Sequential explanatory design								
MMAT criteria 1: Is there an adequate rationale for using a mixed methods design to address the research question?								
MMAT criteria 2: Are the different components of the study effectively integrated to answer the research question?								
MMAT criteria 3: Are the outputs of the integration of qualitative and quantitative components adequately interpreted?								
MMAT criteria 4: Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?								
MMAT criteria 5: Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?								
MMAT criteria 1-5: Y=Yes ; N=No ; CT=Cant tell								

Referring to mixed-method studies design, Brier MJ study combine qualitative and quantitative components to inform the study conclusion whereas Bluethmann SM study builds on survey results to qualitative explore breast cancer survivors' experience on AHT. Both the study present sufficient rationale for the chosen sequence research design (MMAT criteria 1), effectively integrated both the qualitative and quantitative components to address the research questions (MMAT criteria 2), adequately interpret both of the components (MMAT criteria 3) and adhere the quality criteria (MMAT criteria 5). Bluethman SM study received weak ratings in the MMAT criteria 4 as it shows a lack of comparison between the quantitative on the qualitative components of the findings.

4.5 Primary Outcome: Subgroup Analysis

Following the step illustrated in section 3.7.3, the extracted psychosocial findings were mapped conceptually and inductively onto the relevant TDF domains based on similarities. Table 4.5A presents the thematic matrix grid with a column comprising of TDF domains, and a row representing the study cases. The domains *intention* and *goals* were combined for its interrelatedness. Overall, 11 out of the 14 TDF domains were considered to have some relevancy across initiation, adherence, persistence and continuation measure. No findings were coded into *optimism* and *social/professional role and identity* domains. The top three of the most frequently occurring and salient domains were *social influences*, *beliefs about consequences*, *emotion.* The least reported domains were *skills*, *intention* and *goals* and *reinforcement*.

As shown in Table 4.5A, all the determinants within each domain present inconsistent or mixed finding. For the purpose of synthesizing the results, variables have been classified as having a positive effect (+), negative effect (-), no effect (X) or modulator effect (+/-). Colour coding were used to differentiate the type of behaviour groups.

Table 4.5A: Integration thematic matrix of behaviour group analysis

		TDF domains										
Authior, Year	**Study number**	**Knowledge**	**Skiils**	**Belief about capabilities**	**Beliefs about consequences**	**Reinforcement**	**Intentions and goals**	**Memory , Attention and decision process**	**Environmental contexts and resources**	**Social influences**	**Emotion**	**Behavioural regulation**
Heisig SR, 2016	*1*	-			-			-			-	
Beryl LL, 2017	*2*							-			-	
Stu¨ber T, 2017	*3*								X		-	
Neugut AI, 2012	*4*				-			-		-		
Khan LK, 2007	*5*	-						-		-		
Grunfeld EA, 2005	*6*				+/-			-	-		X	X
Liu Y, 2013	*7*	X		+					-	+		
Brier MJ, 2018	*8*				-						-	
Brier MJ, 2017	*9*	X								+/-		
Brier MJ, 2017	*10*			-	X				-			
Bright EE, 2016	*11*			-						X		+
Bright EE , 2018	*12*									+	+	X
Nestoriuc Y, 2016	*13*				-							
Wickersham K, 2012	*14*				+			-		+		+
Wuensch P, 2015	*15*	-								-		
Brett J, 2016	*16*				-						-	
Brett J, 2018	*17*	+			-		-			+/-	-	+
Arriola K, 2014	*18*				+					+/-		
Moon Z, 2017	*19*			+	+		+			-	-	
Moon Z, 2017	*20*	-			+/-		-			-	-	+
Lin J, 2017	*21*			-						-		
Kimmick G, 2015	*22*			+/-							-	
Karmakar M, 2017	*23*			+	X		+		-			+
Lee JY, 2018	*24*			+	+/-						+	
Markovitz LC, 2017	*25*										+/-	
Bender CM, 2014	*26*					-			-		-	
Wouters H, 2014	*27*			-	-						-	
Heisig S, 2015	*28*	+	+									
Harrow A, 2015	*29*		+		+			-		+/-		X
Wells KJ ,2016	*30*			-	+			-	+	+		+
Pellegrini I , 2010	*31*	-									-	
Iacorossi L, 2016	*32*		+				+	-		+	-	+
Humphries B , 2018	*33*				+/-	-		-		+/-	-	+/-
Walker HE, 2016	*34*				+				+		+	
Atkins L,2006	*35*			-				-	X	+	-	
Bluethmann SM,	*36*		+		-							
Brauer, 2016	*37*									+/-	-	+
Yu KD, 2012	*38*	X								-		
Hershman DL, 2016	*39*				+				+	X	-	
Fink AK, 2004	*40*				-							
Bluethmann SM,	*41*							-				
Cluze C, 2012	*42*	-								-	-	

Table 4.5A: Integration thematic matrix of behaviour group analysis (continue)

Author, Year	Study number	TDF domains: Knowledge	Skills	Belief about capabilities	Beliefs about consequences	Reinforcement	Intentions and goals	Memory, Attention and decision process	Environmental contexts and resources	Social influences	Emotion	Behavioural regulation
Pinheiro LC, 2017	43								- X			
Friese, 2016	44	-				+		-		- -	- -/+	
Livaudais JC, 2012	45									-		
Hadji P, 2013	46	X X										
Stanton , 2014	47				-				X -	-	- -	
Bhatta SS, 2013	48				+ +					+ +		
Huiart L, 2013	49					+		-				-
Huiart L, 2012	50									-		
Verbruggie M, 2017	51	- -								+ +		+ +
Cahir C, 2015,	52	-		+ +	+/- +/-		-	-	-			+ -
Lash T, 2006,	53				+ +	-						
Pan Yq, 2018	54				+						-/+	
Quinn EM, 2016	55									-		-
Hadji P, 2013	56					+				+/ -		
Freedman RA, 2017	57							-	-		-	
Kroenke CH, 2018	58									- - -		

Initiation	+	Negative effect
Adherence	-	Positive effect
Persistence	X	No effect
Continuation	+/-	Modulater

Domains associated with treatment initiation

Psychosocial factors associated with treatment initiation were stratified under domains of *knowledge* [1,5,44], *beliefs about consequences* [1,4], *memory attention and decision process* [1,2,4,5], *social influences* [4,5, 44,45,58] and *emotion* [1-3, 44]. The domain *environmental and resources* were examined in two studies, but no effects were reported [3,43].

The decision to execute long-term AHT treatment is difficult, complicated and involve multiple decisional states (*memory attention and decision)* [1,2, 4,5]. Patients tend to forego the treatment in the absence of information about side effects (*knowledge*), clinician inputs (*social influences*), negative beliefs (*beliefs about consequences*) and given isolated decision role [1,4,5,44]. Negative beliefs on treatment efficacy (i.e. doubts, harmfulness and high side effect expectations,) and having negative emotion like fear of treatment and concern that endocrine therapy disrupts life would have complicated the decision conflict [1-3,4]. The strength of physician recommendation modulates decision making whereas medication cost and health-related quality of life (*environmental and resources*) reported no relation to treatment initiation [3,43].

Domains associated with treatment adherence

31 studies reported adherence as the main findings in adherence studies [6-36], 11 studies reported as combined finding [43, 46, 47-49, 51-58]. The domains associated with adherence is as follow: *belief about the consequences, social influences*, *emotion, behavioural regulation beliefs about capabilities*, *knowledge, memory*, *environmental and resources, intention and goals*, *skills*, *and reinforcement*.

Central influences of adherence were reported in *belief about the consequences*, *social influences* and *emotion* domain. These three domains were reported to have the bidirectional effect on adherence behaviour. Having positive beliefs such as necessity beliefs (i.e. beliefs treatment as compulsory), beliefs in treatment efficacy (i.e., belief treatment is effective and beneficial), risk perception (i.e., taking pills helped to reduce the

risk of recurrence) drives adherence behaviour [6,14,18-20,24,29,30,33,34,48,52-54]. On the other hand, having negative beliefs such as doubts about the treatment and negative expectations which hinder adherence [8,13,16,17,20,24,27,33,36,47,52]. Only a minority of 2 studies reported threat appraisal, perceived susceptibility to cancer recurrence and perceived benefits do not associate with adherence [10,23]. Patients who receive emotional support from family members, as well as informational support from the healthcare provider, were more likely to adhere medication. [7,9,12,14,17,18,32,33,35] as opposed to patient who feels isolated and unsupported [15,17-21,33]. In the domain of *emotion*, high frequency of negative emotion such as depression, concern, worry, fear, distress and dislike of the drug were reported among non-adherers [8,16,17,19,20, 22, 25-27, 31-33,35,47,54].

Under the domain *belief about capabilities*, studies have documented positive influences of self-efficacy and confidence to cope with the side effect on adherence [7,19,22-24,52]. The barrier to belief about capabilities are the patients' perception of having limited behavioural control, experience a greater barrier to treatment and given low opportunity to communicate concerns with healthcare providers [10,11,21,27,35]. Combining 9 findings categorized under the domain *knowledge*, knowledge of treatment rationale, and information support [7,9, 46] have no impact on non-adherence but timely information and information on side effects have the beneficial effect on adherence [15,17,20,28,31,51].

Forgetfulness or trouble remembering *(memory*) [6,14,29,30,33,35,49,52,57] and financial hardship (*resources*) [6,7,10,23,26,43,47,52] causes nonadherence with medication routine. Two studies have reported that treatment complexity and the act of taking medication set as a reminder that the cancer is not over were found to reinforced negative mood (*reinforcement*) [26,33]. Patients' motivation was fueled by the intention to be cancer free (*intention and goals)* [19,23,32]. *Skills* that facilitate adherence includes learning skills, comprehension skills and self-discipline [28,29,32,36].

Self-develop coping appraisal and medication management strategies (*Behavioural regulation)* like cognitive self-talk, establish a routine, ease of medication, pill box to

overcome memory barrier cognitive and side effects barriers and impact of side effect is well documented [11,14,17, 20, 23, 30,32,33,51,52,55].

Domains associated with treatment persistence

Persistence is associated with domain *social influences, emotion, behavioural regulation, beliefs about consequence* and *intention and goals.* Consistent findings reported that having negative emotion (*emotion*) such as concerns of adverse effects, intrusive thoughts and avoidance affect persistence intake of medication [37,39,44,47]. Medication management and developing the coping strategy (*behavioural regulation*) are important as 3 studies consistently showed that women relied on informal networks for support [37,51,52]. Patients who possess higher necessity beliefs and treatment satisfaction tend to display persistence intake of medication [39,48,52]. Having professional guidance on side effect, patient-provider relationship, mutual decision role, and frequent contact (*social influences*) with their oncology team boost persistence rate [37,38, 48, 51]. 2 out of 3 studies report provision of educational materials (*knowledge*) do not affect persistence, but poorly informed side effect does [38,46,51].

Domains associated with discontinuation of treatment

Findings of 12 studies of discontinuation report major relevance under *social influences*, e*motion*, *beliefs about consequences*, and *reinforcement*. The domain *knowledge, memory, attention and decision, environmental resources and behavioural regulation* was represented by one study each. Lack of understandable information about endocrine (*knowledge*) [42], more medication [44,48,55], lower cognitive function (*memory, attention and decision)* [41], logistic issue (*environmental resources)* [56] and use of complementary medicine (*behavioural regulation)* [49] are the reported barriers to full completion of prescribed treatment. Social and clinical support (*social influences*) and beliefs that the treatment is beneficial (*beliefs about consequences*) play a major role in preventing patients from discontinuing the treatment prematurely [42.45,49,55,57]. Having worries and concerns to no longer fear of cancer relapse were reported to causes premature discontinuation [42, 53,56].

4.6 Secondary Outcome: Identification of Barriers and Facilitators

On the basis of TDF findings, the data was aggregated, summarized and matched into corresponding COM-B model components. The COM-B model identifies barriers in psychological capabilities (knowledge of side effects, memory, decision making), reflective motivation (perceptions and expectations, behavioural barriers), automatic motivation (intention, negative emotion), physical opportunity (resources) and social opportunity (clinical support). Facilitators were highlighted in psychological capabilities (skills), physical capabilities (self-monitor), reflective motivation (necessity beliefs, self-efficacy), automatic motivation (goals and reinforcement) and social opportunity (social support). Table 4.6 present the representative statement of the domains.

Table 4.6 Indexed TDF findings and align with respective COM-B model

COM-B	TDF domains and key findings	Barrier/ Facilitator
CAPABILITY		
Psychological	**Knowledge, Memory**	
	Side effect information • Lack of side effect information, timely information and supportive treatment in case of side effect [1,5,15,20,31,42,44,51] • General education support materials have no effects. [7,9,38,36]	Barrier
	• **Memory** Forgetfulness [6,14, 29,30,32,35,41,49,52,57]	
	• **Decision making.** Decision difficulty, less than wanted role in decision making [1,2,4,5]	
	Skills	
	• **Skills** Learning skills, comprehension skills, self-discipline [28,29,32,36]	Facilitator
Physical	**Behavioral regulation**	
	Self-Monitor • Self-developed coping strategy [11,14,17,20,23,30,3233,37]	Facilitator

Table 4.6 Indexed TDF findings and align with respective COM-B model (continued)

COM-B	TDF domains and key findings	Barrier/ Facilitator
MOTIVATION		
Reflective	**Beliefs about consequences**	
	Perceptions and expectations • Doubts in treatment efficacy, low risk perception, negative treatment expectation [1,4,6,8,13,16,17,27,36] • Unmet expectation of patient-provider discussion and communication. Expect to be able to resume their normal lives [14,51,31,39]	Barrier
	Necessity beliefs • Beliefs treatment is necessary to prevent recurrence [19,20,24,29-31,33,34]	Facilitator
	Beliefs about capabilities	
	Self-efficacy • Self-efficacy in patient provider interaction, perceived behavioral control [7,19,23,24,44]	Facilitator
	Behavioral barrier • Difficulty asking for information, practical problem [10,11,21,22,27,35]	Barrier
Automatic	**Intention and goals**	
	Intention • Value quality of life over length of life [17,20,52]	Barrier
	Goals • Cancer free and commitment to family to stay healthy [23,35,52]	Facilitator
	Reinforcement	
	Stimuli • Strength of clinician recommendation and taking other medications [45,49]	Facilitator
	Emotion	
	Negative emotion • Concerns about side effect, depression, distress, fear, dislike of drugs, intrusive thoughts, avoidances [1-3,8,16,19,20,22,24-27,31-35,37,39,44,47,54,57]	Barrier
OPPORTUNITY		
Physical	**Environmental contexts and resources**	
	Resources • Financial resources, external stressor, logistics issues [7,23,26,30,34,47,52]	Barrier
Social	**Social Influences**	
	Clinical support • Lack of patient-centered communication, clinician input and attention on experienced side effect [4,5,7,15,19-21,29,37,3842,44,45,47]	Barrier
	Social support • Physical (eg reminder) and emotional support from family and friends [12,14,17,30,51]	Facilitator

Capability

The majority of patients have sufficient capabilities to develop self-monitor strategy when they encounter setback from the treatment such as side effect, limited time from practitioner or forgetfulness [11,14,17,20,23,30,3233,37]. Self-management allows them to exert some control over side effects, counter memory problems and reduce psychological distress. It also helps patients to establish a routine, which makes medication taking a habit and automatic response. The most cited strategies cited are cognitive self-talk, mediating, wearing thin clothes to reduce hot flashes and using medication reminder, which was found to be the significant predictors of adherence and motivation to persistence. Candidates of AHT also reported good comprehension of the treatment rationale and instruction to use [28,29,32,36] and it might explain why intervention studies that apply general education materials have no effects on adherence and persistence [7,9,38,36].

Barriers of psychological capabilities were reported in lack of knowledge on the side effect forgetfulness, and difficulty in decision making. Patients encounter unmet needs on information on side effects, supportive treatment in case of side effect, and timely information from healthcare providers which affect decision making and treatment management [1,2,4,5]. Knowing the possible side effect helps patients to prepare for what to expect, act rationally, increase commitment and allowing activation of a series of behavioural strategies to support adherence. On the other hand, lack of timely side effect information had meant a delay in attributing the side effects to AET and led to anxiety and concern about other conditions [1,5,15,20,31,42,44,51].

Opportunity

Patients lacking the physical opportunities to adhere may include those with difficulties accessing medicines due to environmental constraints, logistic issues such as difficulties getting to pharmacies, and financial constraint [7,23,26,30,34,47,52].

Social opportunities have a twofold effect on MTB. The social opportunity afforded by physically supporting and emotional support from family, friends and peers are important to keep patients on track of medication taking [12,14,17,30,51]. Studies have shown that patients priorities clinical support over social support as they have the "doctor knows best" attitude. Patients rely on healthcare provider judgment and would comply with instruction if they received enough care and attention [18,33,19,45,29,57]. The lack of patient-provider communication, clinician input on concerns and attention on experienced side effect were negatively associated with consistent medication intake [4,5,7,15,19-21,29,37,3842,44,45,47].

Motivation

In terms of reflective motivation, necessity beliefs and self-efficacy were reported as facilitators whereas perception and behavioural barriers were reported as barriers. Positive attitudes and beliefs that treatment is necessary or having the feeling of the drug ‘‘as a friend" were found to be the adherence motivators [19,20,24,29-31,33,34]. By contrast, women holding negative views, doubts in treatment efficacy, low-risk perception and negative expectations were associated to medication nonadherence and severity of experienced side effects [1,4,6,8,13,16,17,27,36]. Women who hold negative expectations about the side-effects of AET before treatment start experienced twice the side-effects than those with positive or low negative expectations. Higher side effects expectations were associated with lower expectations about the efficacy of endocrine therapy. In other example, cognitions about the experience of pain, as opposed to pain itself, was shown to drive nonadherence behaviour [8].

Reflective motivation was challenged when patients encounter difficulty in patient-provider interaction, perceived barriers in behavioural control [7,19,23,24,44]. Lower self- efficacy for taking one's medication was significantly related to both greater intentional and non-intentional non-adherent behaviour. Motivation also struggled when the expectation of clinical support and expectation to be able to resume normal lives were not met. Patients' automatic motivation was limited by having negative emotion, which have impartial impact across initiation, adherence, persistence and premature discontinuation [1-

3,8,16,19,20,22,24-27,31-35,37,39,44,47,54,57].Negative emotions were more frequently report as concerns about the impact, fear of side effect, fear of becoming dependent on drugs, anxiety, depression and dislike of drugs. Having more concerns AHT medication causes intrusive thoughts, avoidance and symptoms attribution. The thoughts process was highly stem stimulated by the strength of clinician recommendation and the goals to be healthy and cancer free for themselves and for their loved ones. [23,35,45,49,52]. These beliefs help them to overcome fear and counter side effects

4.7 Tertiary Outcome: Mapping Intervention Functions to Psychosocial Determinants

COM-B model analysis revealed behaviour changes would occur through modification of the amendable psychological capabilities, reflective motivation, automatic motivation, physical opportunity and social opportunity. Tracing back to the evidence, we have developed logical sequence to recommend taxonomy behaviour change techniques that best match with the mechanism of action. Table 4.7 illustrates that determinants-intervention linkage supplemented by the intervention suggestion identified through empirical studies.

Four behaviour change technique: Education, Persuasion, Training, Environmental restructuring and Enablement were directed into the respective COMB-model components. Table 4.7 present the matching between the COM-B model and intervention functions with the study recommendations listed in the intersecting cells.

Table 4.7. The matrix of links between COM-B and intervention functions

<table>
<tr><th rowspan="2">COMB-model</th><th colspan="4">Intervention functions</th></tr>
<tr><th>Education</th><th>Persuasion</th><th>Training</th><th>Enablement</th></tr>
<tr><td>Psychological capabilities</td><td>[1,3,4,15,17,28,30,51]</td><td rowspan="3"></td><td rowspan="3"></td><td>[47,30]</td></tr>
<tr><td>Physical opportunity</td><td rowspan="3"></td><td>[57]</td></tr>
<tr><td>Social opportunity</td><td colspan="2" rowspan="2">[12,17,28,33,36,51,53,56]
[1, 4,45,47,48,49,51]</td><td rowspan="2"></td></tr>
<tr><td>Automatic motivation</td></tr>
<tr><td>Reflective motivation</td><td>[20,24]</td><td colspan="2">[1,7,1518,21,22,23,25,26,29,30, 54]</td><td>[23,27, 43,54]</td></tr>
</table>

The result has shown that interventions function may be used to serve more than one determinant or precursor to behaviour. 10 studies suggested education as a mean to address psychological capabilities (knowledge) and reflective motivation (perception and expectation). 18 studies postulate a combination of persuasion and training are the potential solution to elicit automatic motivation (emotion), reflective motivation (self-efficacy, perceptions and expectations) and social opportunity (clinical support). Enablement was matched to counter psychological capabilities (forget) and Physical opportunity (environmental and resources), as suggested by 7 studies.

Education: Psychological capability (side effect knowledge); reflective motivation (beliefs, perception, expectancy)

Education is defined as increasing knowledge or understanding to alter behaviour may be utilized to intervene reflective motivation and psychological capability (76,86). Providing personalised information before the treatment, in which negative beliefs about the medication and expected side effect were discussed are needed to prepare patients for long-term medication commitment and avoid false expectation [1,15] In addition, being well informed on the negative effect helps patients adjust expectation [51]. This is echoed by 6 empirical studies that suggested education interventions should emphasize the benefit of treatment efficacy, provide timely information, provide information on supportive care in case of side effects would help patients to gauge the treatment expectation and enhance coping expectation [1,4,15,17,28,30,51]. One intervention trial has successfully demonstrated that including information about the mode of action and potential side effects of endocrine therapy into the clinical routine has been shown to foster patient autonomy and prevent early disruptions in adherence [28].

Persuasion and Training: social opportunity (clinical support), automatic motivation (emotion), reflective motivation (self-efficacy, perceptions and expectations)

Persuasion is defined as “using communication to induce positive or negative feelings or stimulate action” and training, defined as “imparting skills” are linked to automatic and reflective motivation as the key strategy for intervention (76,86). The empirical study supports the notion that physician recommendation and challenge in self-efficacy are the most important factors associated with treatment use and adherence. Many studies indicate adherence may be improved directly through improvement in clinician support such as joint decision role, provide supportive care on side effect management and recognition on experienced side effect [28 33,36,51,53,56]. This highlight that perceived therapy importance and doctor-patient communication on medication compliance represent modifiable variables which can improve overall cancer survival.

The healthcare provider is perceived as a credible source and has an influential role to communicate doubts and explain the confusion in order to promote adherence [7,18,33,19,20,29,57,33]. Medical oncologists should prompt the discussion on the side effect, elicit medication beliefs and positive treatment expectation during follow up. This is resonance in studies indicate adherence may be improved directly through improvement in clinician support such as joint decision role, provide supportive care on side effect management and recognition on experienced side effect [1,28 33,36,51,53,56].

Some evidence has suggested that negative emotions such as fear of treatment could be mitigated by doctors, as patients highly rely on healthcare provider judgment, and value the doctor's opinion [6,12,14,17,30,51]. To increase psychological capability in making the treatment decision, joint decision-making between patients and provider would increase psychological capability in making the decision to achieve higher initiation and greater adherence. Intervention should leverage on influential role of healthcare by encouraging persuasive language, patient-centered communication and improve patient-provider relationship [30,45,47,48,49,51]. Assessments and interventions that encompass the patient's medication beliefs, self-efficacy, and expectation are integral to motivate patients AET adherence [18,21,22,23,29,54]. Having balanced patient-provider relationship would encourage patients to reach out when they face difficulties [51]. Overall, this highlight that perceived therapy importance and doctor-patient communication on medication compliance represent modifiable variables which can improve overall cancer survival. Study has suggested that discussing benefits, addressing concerns of AET, and providing side-effect coping strategies are the promising option to improve adherence in clinical practice [54].

Enablement: Psychological capacity (memory) and (Physical opportunity: resources)

Enablement is defined as ‘increasing means or reducing barriers to increasing capability or opportunity” (76,86)**.** This intervention function may be utilized to serve psychological capabilities, physical opportunity, and reflective motivation. Barriers of psychological capacity reported are forgetfulness. Patients with memory impairment or who face difficulties with remembering the report that they have forgotten to take the pills due to a change of routine or busy days. The risk of forgetfulness might consequently lead to high risk of intentional non-adherence like altering one's dosage or taking less than the instructed dosage and discontinuing prematurely without informing doctors. [6,22]. Using mail-order pharmacies to fill prescriptions (Physical opportunity: resources) might be the options to eliminate time and transportation constraints [57].

CHAPTER 5: DISCUSSION

5.1 Summary of Review

This thesis aims to systematically collect, collate and map empirical research evidence to answer three types of research questions (RQ): RQ1: What are the psychosocial factors that relate to treatment initiation, adherence, persistence and premature discontinuation? RQ2: What psychosocial factors are amendable and need to be changed in order to optimize the medication-taking behaviour? RQ3: What are the best fit intervention strategies?

In the context of the present body of research (N=58), this theory-guided integrative review has elucidated chronic disease management in the case of 5 years AHT medication intake as a series of complex and interrelated behaviour modulated by psychosocial factors. Up to one-third of patients do not comply with their prescribed AHT medication regimen at some point of their treatment, either by non-initiation, non-adherence, non-persistence or by prematurely discontinuing AHT treatment within 5 years. This review presents the overall impact of psychosocial factors on the full spectrum of MTB and delves deep into sourcing the key modifiable psychosocial factors.

Underpinned by triad-level theoretical frameworks, this thesis has successfully identified linkages between sources of the problem and deduced options of intervention solutions based on the mechanism of action supplemented with suggestions extracted from empirical studies. Specifically, TDF has integrated the key psychosocial factors from included studies into 11 domains, from which the COM-B model has pinned the psychological capabilities, opportunities as the modifiable components. Based on the collective findings of TDF and COM-B model, 4 relevant intervention functions were linked to postulate viable options for interventions.

5.2 Research Question 1: *What are the psychosocial factors that relate to treatment initiation, adherence, persistence and premature discontinuation?*

Key findings

Behaviour analysis underpinned by TDF provides a coherent picture of psychosocial determinants associated with different types of medication-taking behaviour. Interestingly, this review pinpoints that self-discipline and self-efficacy *skills* were to uniquely act as the facilitator to adherence behaviour only. Having clear *intention and goals* to be cancer free and confidence in their ability to implement a medication regimen *(beliefs about the capabilities)* only reported to have an effect on adherence and persistence behaviour. Self-develop coping strategies (*behavioural regulation)* and external information *(environmental resources)* coherently affect adherence, persistence and premature discontinuation behaviour. Notably, even though 11 TDF determinants were considered to have some relevancy across medication-taking behaviour, only five domains: I. *knowledge,* II*. beliefs about consequences,* III. *memory, attention and decision process,* IV. *social influences and* V*. emotion* were shown to have overlap impact across the whole spectrum of medication-taking behaviour.

5.3 Research Question 2: *What psychosocial factors are modifiable and need to be changed in order to optimize the medication-taking behaviour?*

Key findings

Anchoring the result of TDF, COM-B model refines behaviour change needs assessment to source the modifiability of key psychosocial factors. The results showed an interplay of psychological variables (i.e. knowledge, belief, expectation and emotion) and sociological variables (social and clinical support) were highlighted as the most salient and modifiable barriers across the whole spectrum of medication-taking behaviour. In the term of COM-B model, patients would be motivated to initiate and adhere medication if given the opportunity to have quality interaction with patients and possess the capabilities to manage treatment expectation, beliefs and emotion.

5.4 Comparison of Findings

Most of the review on medication adherence have highlighted the presence of medication side effects as the main hurdle to medication management (22,149,150). Interestingly, 6 studies included in this review reported that side effects have no impact on the adherence and discontinuation of treatment [6,16,21,29,34,40]. This review is in line with the findings of the previous reviews that psychological variables and social variables are the more salient and modifiable determinants of behaviour (46,151).

The included qualitative and quantitative research in this review have consistently acknowledged that psychological barriers such as negative beliefs, expectation and negative judgment affect patient's medication-taking behaviour [4,16,20,29,33,3452]. This is especially relatable to long-term medication regimen where the benefit of the treatment is not immediately apparent (152). As reported in the previous literature, patients who held negative beliefs were more likely to display intentional nonadherence behaviour (152,153). Our review consolidated current evidence and report that patients' free will to initiate and sustain medication adherence is dependent on the interplay between three type of beliefs, namely (a) belief in their capabilities (confidence in their ability to implement medication regimen), (b) beliefs in the consequences (beliefs on the necessity of and efficacy of the treatment) and (c) beliefs in treatment efficacy (beliefs on the protective effect and taking pills as prescribed is beneficial for their full recovery) (Table 4.6). Having these negative predisposing factors influence the way patient interpretation of information along the treatment process, which is the turning point of behaviour change from adherence to nonadherence behaviours. The role of necessity beliefs on patients' motivation to begin and adhere to treatment echoes the hypothesis of Necessity-Concerns Framework (NCF) (154,155).

As experimented in the study of other types of chronic illness, unrealistic beliefs and unmet expectations of care are determinantal to patient motivation on long-term medication regimen adherence (156–158). Patients commonly expect that they would have the ability to live a normal life after their primary treatment, have quality discussions with their

healthcare provider, and expect that AHT treatment is as easy as taking contraceptive pills (159). In reality, the changing role from being patients to survivors might render them to receive less clinical attention than they used to have. Depending on the individual clinical profiles, patients might experience side effect at different severity level and patients' quality of life might be affected. The discrepancy between the ideal expectation and reality causes patients to alter their necessity beliefs and thus compromises their needs by deciding to forgo therapy (157,160). Negative expectation effect was similarly reported in the past reviews, emphasizing the need for minimizing these responses to the extent possible (161,162).

The results have identified that psychological capability and social opportunity were modulated by the acquisition of knowledge and the presence of clinical support. The unmet needs of side effect information have downplayed the impact of side effects, causing patients to be unprepared to deal with symptoms or cause confusion of symptoms that would adversely influence their quality of life, therapy adherence and tolerability of side effect. In a review of medication adherence across 19 different diseases, some patients do not persist with treatment as they believe that the disappearance of symptoms is considered as being cured (163). This shows that if the patients did not expect or were not educated on the possibility of encountering side effects, the occurrence of side-effects may result in them confusing the side effects experienced with symptoms of menopause. Consequently, this may affect their trust in the treatment.

Similar to the reported findings from Van Liew and Lin C's reviews (Table 1.4.2), our review also noted patients who reported having poor interaction with healthcare providers are prone to displaying compromised adherence behaviour (46,47). Not only does the impact of social support on medication adherence extend across breast cancer population from a different background, but it also extends beyond breast cancer to other illness groups. The link between patient adherence and physician-patient communication has been observed sizably in other types of health behaviour such as cancer screening adherence (164), cancer prevention (165) and treatment adherence (166). A review of 14 articles on the racial and socioeconomic disparities in endocrine therapy adherence

concededly revealed that lack of provider recommendations and communication were the most commonly cited barrier across the racial group (167). Studies on factors that determine cancer treatment choice among minority group also reported that patient-provider communication and bias play a significant role (167,168).

These collective findings on how belief, knowledge, expectation and emotion affect medication-taking behaviour were not found exclusively on adjuvant hormonal therapy but also recognized in other clinical condition such as haemodialysis, bipolar disorder and antihypertensive (154,169,170). This review suggests that future intervention should priorities in developing ways to ameliorate psychological and social barrier of long-term of AHT medication adherence.

5.5. Research Question 3: *What are the intervention strategies that can be used to target the identified psychosocial barriers?*

Key findings

Resembling the concept of lock and key, the TDF and COM-B models enabled the results of the behavioural analysis to be displayed at the site and subsequently match it with relevant intervention functions. In order to optimize the effectiveness of the intervention, this review argues for prioritization of targeted education, persuasion and enablement as the potential solutions for the healthcare provider to advance AHT treatment management.

5.5.1 Currently tested interventions

The knowledge has shown to be a modulator of adherence behaviour but none of the current education intervention is effective at bringing optimal change. Our review identified five intervention strategies that provide written educational materials and follow up reminder service, all of which have reported no effect on 1-year compliance and persistence rates (171,172). The same conclusion was reported in two recent systematic reviews that evaluated the effectiveness of the educational intervention (173,174). Both reviews concluded that none of the educational intervention strategies (educational

materials, monthly reminders, follow up services and written information) yielded significant improvements in enhancing adherence in this population (173). Health behavioural research and randomized controlled trials have also demonstrated confirmatory evidence that just by simply informed patients about the treatment rationale is ineffective to change adherence behaviour (87,175).

The ineffectiveness of education intervention may underlie the lack of incorporation of patients' need for side effect information and supportive care in cases of side effects (173). Instead of focusing predominantly on the general breast cancer knowledge acquisition, future educational efforts should assess, target and cater to fulfil the unmet needs of treatment information and knowledge translation (16). Future education intervention that focuses on ameliorating ambivalence about the value of treatment and symptoms confusion may be beneficial in balancing treatment expectation and increasing patients' reflective motivation to adhere.

5.5.2 Unexplored Potential Solutions

A. Communication and Intrapersonal Skills Training (Persuasion and Training)

Patient-provider relationships and patient-centred communication remain an unexplored intervention target in the area of AHT medication management despite being highly correlated with patient adherence (173). Many patients who do not adhere encounter isolation and feel themselves slipping through the healthcare gap as they are no longer considered as active patients. Consequently, little attention was assigned to their concern and limited opportunities were given to ask questions at the time of diagnosis.

Integral to improving patient-provider relationships is the training of the communication and intrapersonal skills of healthcare providers. Several studies have suggested that effective communication between patients and provider generate a therapeutic effect on treatment satisfaction, elicit medication knowledge and beliefs that would motivate patients to comply with prescribed medication regimen (176–178) . A meta-analysis study reported that patients of physician who have good communication skills are 2.16 times

more likely to stay adherent, and training physicians in communication skills improve patient adherence by 12% (176). Communication programs that embed skills or technique like open-ended questions, expressions of empathy, provision of comprehensible information, responding appropriately to patient cues were demonstrably effective on optimizing general drugs medication adherence (179–181). For patients with a language barrier, it is necessary for the physician to involve a third party such as a trained translator or family member in the consultation session to ensure adequate information comprehension.

B. Motivational Interviewing (Persuasion and Training)

Motivational interviewing applies four guiding principles (RULE) to assist an unmotivated patient to establish commitment and overcome the psychological resistance that impedes behaviour change (182,183). The acronym RULE stands for Resist the righting reflex; Understand the patient's own motivations; Listen with empathy; and Empower the patient (182,183). Recent studies have shown that motivational interviewing is effective in evoking patients' intrinsic motivation by identifying the discrepancy between their behaviour and goal, building confidences in their ability to change and honouring patients' beliefs and concerns (182). To resolve a patient's psychological ambivalence and resistance, this technique encourages healthcare provider to embody as a facilitator role rather than an expert role. Applying the combination of RULE, this technique adopts the nonintimidating approach to enhancing patients attitude and beliefs toward long-standing behaviour such as adherence to asthma medication(184), diabetes management (185), hypertensive medication (186) and antiretroviral therapy (187). Other alternative persuasion techniques such as cognitive behavioural therapy (188), health coaching (189) lies on the same ground as motivational interviewing, which stresses that patient-centred communication approach is the key to alter patients' motivation, expectations, thoughts, and emotion toward adherence (190,191). Taking a lesson from the successful adoption of these persuasive techniques on medication management, intervention on AHT medication adherence ought to improve open discussion of patient-reported barriers to adherence, patient engagement in decision making, building a collaborative therapeutic

relationship in order to improve treatment adherence (192,193).

C. Digital Adherence Technologies (Environment and Enablement)

As noted in this review, the event of missing a pill due to cognitive deficiencies such as forgetfulness have proportional effects on treatment adherence and premature discontinuation. This type of unintentional nonadherence is preventable if intervention devotes a way to prompt medication intake in a consistent context so that the behaviour can slowly adapt into a habit. As the saying “out of sight, out of mind” goes, we surmise that in order to reduce chances of a patient forgetting their medication, intervention in the form of a web-based or phone-based application that provides notifications or reminders or facilitates communication might be the potential solution.

Few ongoing clinical trials of AHT have ventured into implementing digital adherence technologies (DAT) intervention, mainly in USA (registration number: NCT01515800, NCT02400060, NCT02256670, NCT02707471, NCT02850939, NCT02957526), Singapore (registration number: NCT02524548) and Canada (registration number: NCT02876848) (174). Intervention media among these 8 ongoing web-app intervention trials encompass text reminder and patient navigation to record medication adherence and gather related medical data. The rationale of integrating DAT into the patient care pathways is to facilitate the provision of tailored care and allows behavioural management or self-control in the home environment. Although DAT interventions are still in the testing phase in AHT medication management, implementation of this technique has reported successful cases on managing adherence to antiretroviral treatment (194), adherence to antihypertensive drugs (195) and improve self-efficacy and intensifying insulin therapy (IIT) adherence among Type 1 diabetes patients (196). Echoing environmental enablement as the identified behaviour change techniques, the implementation of phone-based or web-based DAT intervention may reduce the event of missing a pill due to forgetfulness and compile dosing histories and record the presence of side effects to intervene non-adherence on AHT. Nevertheless, due to the limited shreds of evidence, the acceptability, accuracy, clinical effectiveness and cost-effectiveness of DAT on AHT adherence has not yet been validated (197). Alternatively, a stepped care approach might

be warranted to promote the set-up of environmental prompts such as setting calendar reminders and putting medication in the obvious places to promote routine medication use (198). Other types intervention that imparts and prompt repetition and routine process in the consistent context is warrant.

5.6 Study Strengths

This integrative systematic review is a novel attempt at undertaking triad level theoretical analysis and problem-solving approaches with the view to optimize future intervention design and implementation. No systematic review on the proposed topic was found when searching Cochrane Database of Systematic Reviews or PROSPERO in February 2018.

This study addresses shortcomings in past reviews and researches gaps in the lack of evidence-based and theoretical understanding of psychosocial factors associated with AHT adherence. The approaches used in this review is congruence with the United Kingdom's Medical Research Council guidance, which mandates the integration of theory in intervention development (49). To maximize the knowledge transfer, this review presents the overall impact of psychosocial factors on treatment initiation, implementation and discontinuation. Reiteratively, TDF-informed behavioural assessment has canvassed the full picture of the psychosocial influences on treatment management. Categorization of these factors into COM-B model has successfully clarified the problematic areas and highlighted what needs to change in favour of altering the nonadherence behaviour.

Interventions that are currently available or potentially responsive intervention were evaluated to indicate the future direction of the studies. Through the mapping of the behaviour change technique, we have identified research gaps and have postulated behaviour change strategies to direct research priorities in the intervention design. Application of these triad level theoretical framework presents a transparent evaluation process to generate much-needed linkage between the key problems and available interventions with the support of empirical evidence (199). This systematic, transparent and repeatable analytical process improve the efficiency of research efforts and generates results that can be tested or validated in empirical research.

In addition, the integrative design of this review consolidated qualitative, quantitive and mixed method evidence published from its inception to 2018 in 7 databases. By including evidence from multiple sources and diverse methodologies, this review ensures all the necessary elements were in place to maximise the values and benefits of the findings. To avoid fragmentation of the results, this review also evaluates a broad spectrum of medication-taking behaviour ranging from initiation to premature discontinuation. Compared to the past 4 reviews, this review includes the largest pool of research evidence (N=58), which enlighten a more in-depth understanding on the association between the psychological variables and medication adherence.

Additionally, this review followed a systematic, transparent process to generate three types of research questions. These three outcomes allow the researcher to interpret separately or collectively as each of them was mapped to a different yet compatible set of frameworks. In summary, the outcomes of this review lay the groundwork of identifying key adherence barriers and evaluated solutions that are currently being tested and listed the options of other potential unexplored potential solution to direct future intervention.

5.7 Study Limitations

The integrative approach used in this review may have raised question for the ambiguity of its analytical process (111). We address this limitation by adopting contingent methodologies that detail every step of how we generate the outcome to ensure rigour and transparency in the analysis. Two reviewers were involved in making analytic choices and evaluating interpretive strategies to present visible and auditable results. Although efforts have been made to maximize the retrieval of research evidence, there might still be a chance of missing some of the published studies.

This review focuses on the modifiable aspect of psychological, behaviour and social aspect of nonadherence behaviour. Hence, we did not evaluate non-modifiable factors such as age, race, ethnicity, education, side effects profiles, which has found to be

influencing factors on treatment management in other reviews (22,200,201). Noteworthily, the proposed intervention strategies are merely aiming to facilitate the process of intervention development, not to guarantee the effectiveness of the intervention design. This review did not assess the policy categories that is inclusive in the Behaviour Change Wheel due to limited data on the intervention studies. On top of the intervention content, external context such as policy categories and environmental resources are needed to be considered to scale up implementation of the intervention. In doing so, APEASE criteria, which evaluates Acceptability, Practicability, Effectiveness, Affordability, Safety, Equity should be applied in a structured way to increase the likelihood of success of intervention (86).

The prevalent rate of suboptimal medication intake was not calculated due to high heterogeneity of the included data. However, this review highlights the shortcomings of the current methodologies in term of the lack of standardization of the medication intake measures and behaviour definition. Currently, there is no gold standard measure and guidance for healthcare professionals and researchers in choosing the most suitable measures of MTB (202). Hence, this has led to the proliferation of inconsistent reports of MTB. Our review has identified various measurement methods employed to measure adherence, such as MMAT, MARS-5, MARS-8, MEMS, medical record, self-reports, patient interview and prescription refill record (section 4.3). Patient self-reports, patient interviews and medication refill record are the subjective measures that may not necessarily reflect or equate to the real medication intake, and in fact, might overestimate adherence (174,203). These types of subjective measures are prone to recall bias, where the patients might forget the dose taken as well as response bias, where respondent provide socially desired response that conforms to their perceived expectations of their interviewer (204,205) The objective measure, such as MMAT, MARS-5, MARS-8, MEMS warrant validation and the cost-effectiveness evaluation for the specific purpose of study (206). Future research should leverage on the method used in Oberguggenberger et al and Clarke et al studies, as they advocated the use of plasma concentrations and urine tests to check the level of the drug as the feasible and accurate reflection of adherence (207,208).

5.8 Study Implications

5.8.1 Implication for Researchers

To continue effectual research in medication non-adherence, future empirical research should address the challenge of methodological inconsistency by formulating a gold standard definition, terminology and measure of MTB. Having a gold standard guideline on the MTB measurement would enlighten a more accurate comparison of the findings and ensure the reliability of the report. For intervention trials, the researcher should account the effect of psychosocial factors at inclusion to identify the patients most in need of an adherence intervention. This review adds weights to the criticism of using one-size fits all approach to tackle the issue of nonadherence (209). Our review implicates researcher to finetune the education intervention content and venture into testing the unexplored behaviour change techniques to alter psychological variables. Nevertheless, nuanced research on the effectiveness of the adherence intervention is warranted.

5.8.2 Implication for Healthcare Practice

Evident findings of this review advocate the crucial role of the healthcare provider in eliminating the wasted health care resources and cancer recurrent rate that result from medication nonadherence. Clinician and other healthcare providers need to be mindful that the provision of educational materials is insufficient on its own to enhance adherence. Rather than reiterating the biomedical view on issues of nonadherence, the healthcare provider should understand the complex nature of the psychosocial factors that may affect the patients' behaviour. Active engagement of healthcare providers in the patient recovery pathway is the potential strategic solution to improving the coordination of medical care and treatment management. Residency training for physicians should incorporate training in intrapersonal and communication skills in order to build the collaborative patient-provider relationship, facilitate discussions of patient-reported barriers and the creation of opportunities for active patient involvement (210). Other than intrapersonal skills training, this review encourages healthcare provider to explore potential useful behaviour change technique such as embedding digital adherence technology into the existing healthcare system to streamline the patient-care pathway.

5.8.2 Implication for Policymakers

Taking into account that intermittent use of therapy was accompanied with intrusive impact on the pharmaceutical industry and healthcare resources, ministries of health and development agencies play a major role in promoting and coordinating research efforts (32). This review lay the foundation of the decision making of policymakers in terms of research prioritization, evidence-based intervention options and fund distribution. Policymakers should extend support by funding fundamental and applied research that aims to modify psychosocial factors associated with medication adherence behaviour.

5.9 Study Declaration

This thesis was not supported by any external funding and all the reviewers involved declare no conflict of interest. Level 1 ethnic form was submitted to The University of Edinburgh and there are no ethical concerns regarding this review.

CHAPTER 6: CONCLUSION

Intervening psychosocial factors affecting medication adherence during life-threatening diagnosis like breast cancer are an important lever in reducing cancer recurrence rate. Underpinned by TDF, COM-B model and BCW, this study asserts a theoretical understanding of psychological factors across a full spectrum of treatment management behaviour and derive matching interventions strategies at changing identified mediators of behaviour. This integrative systematic review has narrowed the empirical evidence of 58 primary studies to conclude psychological and social variables as key barriers. Psychologically, patients' negative beliefs, unmatched expectation and negative emotion affect optimal medication-taking behaviour. Socially, the lack of social support and clinical support increase chance of nonadherence behaviour.

The current education intervention used to improve AHT medication adherence does not produce ideal results and many of the intervention employed in other types of chronic medication management remains elusive in AHT. Findings from the BCW suggested a multifaceted intervention that is designed to educate patients specifically on potential side effect while also conducting communication skills training are the cornerstone of improving adherence. The findings of this thesis lay the foundation for evidence-based intervention design and urge the formation of concerted intervention to manage nonadherence in the ever-growing breast cancer population. The results are pertinent to the healthcare provider, researcher and policymakers who are likely to initiate interventions.

Appendix A: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	6-7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	15-18
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	19,32
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	35
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	36-38
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	38-39
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	38-39
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	42-26
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	42-26
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	41
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	39-40
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	39-40
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	42-46

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	39-40
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	39-40
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	48-49
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	50-61
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	61-66
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	67-81
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	67-81
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	61-66
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	83-90
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	91-92
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	95
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	94

Appendix B

Search syntax

List 1: Search strategy developed for MEDLINE trial

Group 1: Adjuvant hormone therapy

1. (selective estrogen receptor modulator or tamoxifen or tomerifin or toremifene or fareston).mp
2. (aromatase inhibitors or anastrozole or letrozole or exemestane).mp
3. (luteinizing hormone-releasing hormone analogs or goserelin or zoladex or leuprolide or lupron)
4. (estrogen-receptor downregulators or fulvestrant or faslodex or megestrol acetate or megace)
5. (adjuvant hormon* or adjuvant endocrine).mp
6. Or/1-5

Group 2: medication taking behaviour

7. exp patient compliance/
8. exp medication adherence/
9. exp medication persistence/
10. (initiat* or accept* or nonadheren* or adher* or non-adherence or complian* or persist* or discontinu* or continuance or dropout* or drop-out or concordance or complet*).mp.
11. (patient* adj3 [attitude* or acceptance*]).mp
12. (treatment* adj3 [stop* or abandon*]).mp
13. Or/7-12

Group 3: psychosocial factors

14. health knowledge, attitudes, practice/ or health behaviour /
15. (cognitive or emotion or mood or distress or medication belief or concerns or stigma or psychology or perceived benefits or perceived barrier or perceived susceptibility).mp.
16. (interpersonal or patient* relationship or family support or social network or social support or social relations).mp.
17. (behavio?r or avoidance or denial or self-efficacy or self-control or self-management or communication).mp
18. Psychosocial factors.mp. or psychology/
19. Or/14-18

Group 4: breast cancer patients

20. (breast cancer or breast carcinoma).mp

21. breast neoplasm.mp. or exp beast neoplasms/
22. male breast cancer.mp
23. female breast cancer.mp.

24. Or/ 20-23

Search hits

25. 6 AND 13 AND 19 AND 24

Limit

26. Limit 25 to yr="1998-2018"

Appendix C: MMAT

Part I: Mixed Methods Appraisal Tool (MMAT), version 2018

Category of study designs	Methodological quality criteria	Responses			
		Yes	No	Can't tell	Comments
Screening questions (for all types)	S1. Are there clear research questions?				
	S2. Do the collected data allow to address the research questions?				
	Further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.				
1. Qualitative	1.1. Is the qualitative approach appropriate to answer the research question?				
	1.2. Are the qualitative data collection methods adequate to address the research question?				
	1.3. Are the findings adequately derived from the data?				
	1.4. Is the interpretation of results sufficiently substantiated by data?				
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?				
2. Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?				
	2.2. Are the groups comparable at baseline?				
	2.3. Are there complete outcome data?				
	2.4. Are outcome assessors blinded to the intervention provided?				
	2.5 Did the participants adhere to the assigned intervention?				
3. Quantitative non-randomized	3.1. Are the participants representative of the target population?				
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?				
	3.3. Are there complete outcome data?				
	3.4. Are the confounders accounted for in the design and analysis?				
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?				
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research question?				
	4.2. Is the sample representative of the target population?				
	4.3. Are the measurements appropriate?				
	4.4. Is the risk of nonresponse bias low?				
	4.5. Is the statistical analysis appropriate to answer the research question?				
5. Mixed methods	5.1. Is there an adequate rationale for using a mixed methods design to address the research question?				
	5.2. Are the different components of the study effectively integrated to answer the research question?				
	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?				
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?				
	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?				

Part II: Explanations

1. Qualitative studies	Methodological quality criteria
"Qualitative research is an approach for exploring and understanding the meaning individuals or groups ascribe to a social or human problem" (Creswell, 2013b, p. 3). Common qualitative research approaches include (this list if not exhaustive): **Ethnography** The aim of the study is to describe and interpret the shared cultural behaviour of a group of individuals. **Phenomenology** The study focuses on the subjective experiences and interpretations of a phenomenon encountered by individuals. **Narrative research** The study analyzes life experiences of an individual or a group. **Grounded theory** Generation of theory from data in the process of conducting research (data collection occurs first). **Case study** In-depth exploration and/or explanation of issues intrinsic to a particular case. A case can be anything from a decision-making process, to a person, an organization, or a country. **Qualitative description** There is no specific methodology, but a qualitative data collection and analysis, e.g., in-depth interviews or focus groups, and hybrid thematic analysis (inductive and deductive). Key references: Creswell (2013a); Sandelowski (2010); Schwandt (2015)	1.1. Is the qualitative approach appropriate to answer the research question? Explanations The qualitative approach used in a study (see non-exhaustive list on the left side of this table) should be appropriate for the research question and problem. For example, the use of a grounded theory approach should address the development of a theory and ethnography should study human cultures and societies. This criterion was considered important to add in the MMAT since there is only one category of criteria for qualitative studies (compared to three for quantitative studies). 1.2. Are the qualitative data collection methods adequate to address the research question? Explanations This criterion is related to data collection method, including data sources (e.g., archives, documents), used to address the research question. To judge this criterion, consider whether the method of data collection (e.g., in depth interviews and/or group interviews, and/or observations) and the form of the data (e.g., tape recording, video material, diary, photo, and/or field notes) are adequate. Also, clear justifications are needed when data collection methods are modified during the study. 1.3. Are the findings adequately derived from the data? Explanations This criterion is related to the data analysis used. Several data analysis methods have been developed and their use depends on the research question and qualitative approach. For example, open, axial and selective coding is often associated with grounded theory, and within- and cross-case analysis is often seen in case study. 1.4. Is the interpretation of results sufficiently substantiated by data? Explanations The interpretation of results should be supported by the data collected. For example, the quotes provided to justify the themes should be adequate. 1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation? Explanations There should be clear links between data sources, collection, analysis and interpretation.

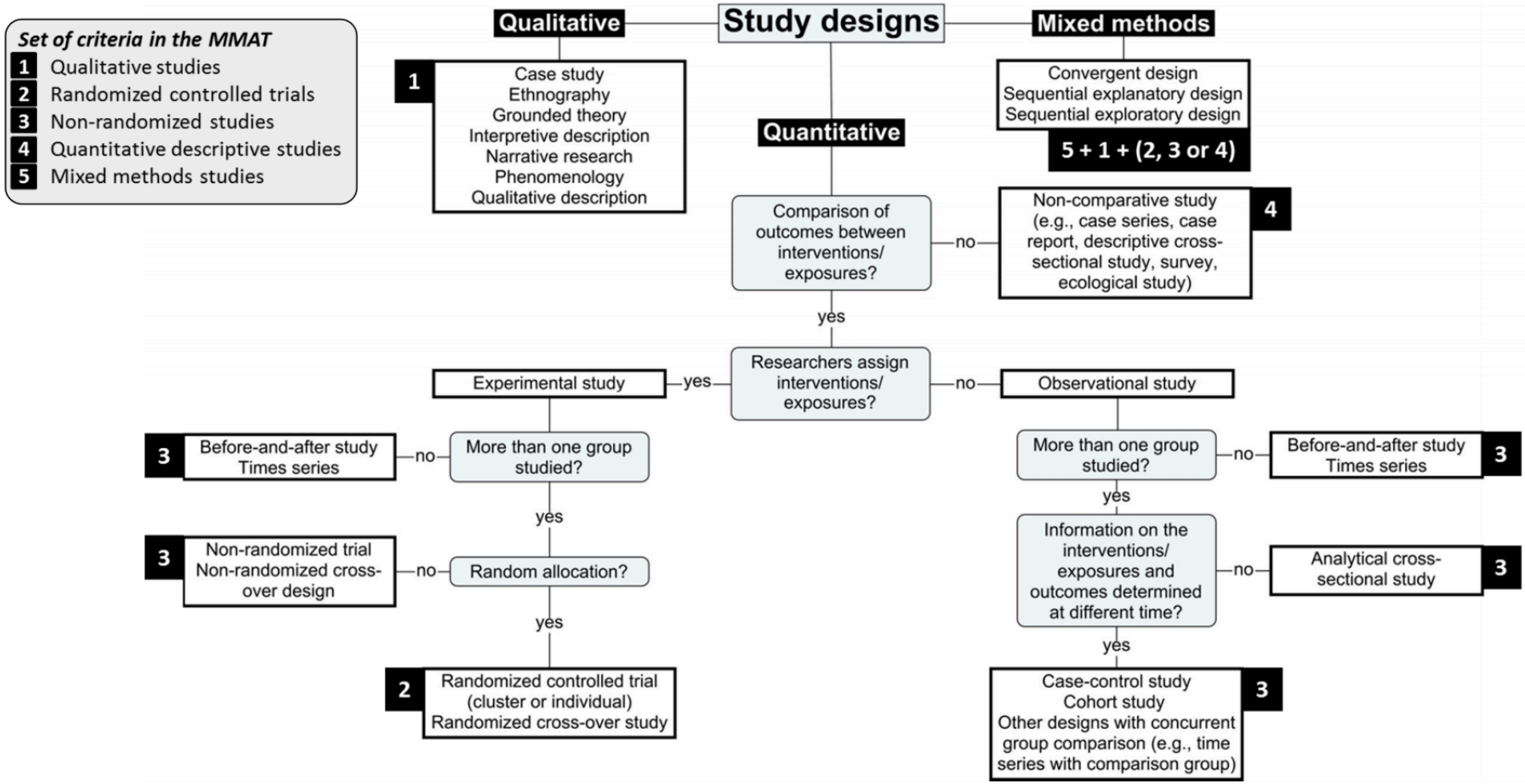
2. Quantitative randomized controlled trials	Methodological quality criteria
Randomized controlled clinical trial: A clinical study in which individual participants are allocated to intervention or control groups by randomization (intervention assigned by researchers). Key references: Higgins and Green (2008); Higgins et al. (2016); Oxford Centre for Evidence-based Medicine (2016); Porta et al. (2014)	2.1. Is randomization appropriately performed? Explanations In a randomized controlled trial, the allocation of a participant (or a data collection unit, e.g., a school) into the intervention or control group is based solely on chance. Researchers should describe how the randomization schedule was generated. A simple statement such as 'we randomly allocated' or 'using a randomized design' is insufficient to judge if randomization was appropriately performed. Also, assignment that is predictable such as using odd and even record numbers or dates is not appropriate. At minimum, a simple allocation (or unrestricted allocation) should be performed by following a predetermined plan/sequence. It is usually achieved by referring to a published list of random numbers, or to a list of random assignments generated by a computer. Also, restricted allocation can be performed such as blocked randomization (to ensure particular allocation ratios to the intervention groups), stratified randomization (randomization performed separately within strata), or minimization (to make small groups closely similar with respect to several characteristics). Another important characteristic to judge if randomization was appropriately performed is allocation concealment that protects assignment sequence until allocation. Researchers and participants should be unaware of the assignment sequence up to the point of allocation. Several strategies can be used to ensure allocation concealment such relying on a central randomization by a third party, or the use of sequentially numbered, opaque, sealed envelopes (Higgins et al., 2016).
	2.2. Are the groups comparable at baseline? Explanations Baseline imbalance between groups suggests that there are problems with the randomization. Indicators from baseline imbalance include: "(1) unusually large differences between intervention group sizes; (2) a substantial excess in statistically significant differences in baseline characteristics than would be expected by chance alone; (3) imbalance in key prognostic factors (or baseline measures of outcome variables) that are unlikely to be due to chance; (4) excessive similarity in baseline characteristics that is not compatible with chance; (5) surprising absence of one or more key characteristics that would be expected to be reported" (Higgins et al., 2016, p. 10).
	2.3. Are there complete outcome data? Explanations Almost all the participants contributed to almost all measures. There is no absolute and standard cut-off value for acceptable complete outcome data. Agree among your team what is considered complete outcome data in your field and apply this uniformly across all the included studies. For instance, in the literature, acceptable complete data value ranged from 80% (Thomas et al., 2004; Zaza et al., 2000) to 95% (Higgins et al., 2016). Similarly, different acceptable withdrawal/dropouts rates have been suggested: 5% (de Vet et al., 1997; MacLehose et al., 2000), 20% (Sindhu et al., 1997; Van Tulder et al., 2003) and 30% for a follow-up of more than one year (Viswanathan and Berkman, 2012).
	2.4. Are outcome assessors blinded to the intervention provided? Explanations Outcome assessors should be unaware of who is receiving which interventions. The assessors can be the participants if using participant reported outcome (e.g., pain), the intervention provider (e.g., clinical exam), or other persons not involved in the intervention (Higgins et al., 2016).
	2.5 Did the participants adhere to the assigned intervention? Explanations To judge this criterion, consider the proportion of participants who continued with their assigned intervention throughout follow-up. "Lack of adherence includes imperfect compliance, cessation of intervention, crossovers to the comparator intervention and switches to another active intervention." (Higgins et al., 2016, p. 25).

3. Quantitative non-randomized studies	Methodological quality criteria
Non-randomized studies are defined as any quantitative studies estimating the effectiveness of an intervention or studying other exposures that do not use randomization to allocate units to comparison groups (Higgins and Green, 2008). Common designs include (this list if not exhaustive): **Non-randomized controlled trials** The intervention is assigned by researchers, but there is no randomization, e.g., a pseudo-randomization. A non-random method of allocation is not reliable in producing alone similar groups. **Cohort study** Subsets of a defined population are assessed as exposed, not exposed, or exposed at different degrees to factors of interest. Participants are followed over time to determine if an outcome occurs (prospective longitudinal). **Case-control study** Cases, e.g., patients, associated with a certain outcome are selected, alongside a corresponding group of controls. Data is collected on whether cases and controls were exposed to the factor under study (retrospective). **Cross-sectional analytic study** At one particular time, the relationship between health-related characteristics (outcome) and other factors (intervention/exposure) is examined. E.g., the frequency of outcomes is compared in different population subgroups according to the presence/absence (or level) of the intervention/exposure. Key references for non-randomized studies: Higgins and Green (2008); Porta et al. (2014); Sterne et al. (2016); Wells et al. (2000)	3.1. Are the participants representative of the target population? Explanations Indicators of representativeness include: clear description of the target population and of the sample (inclusion and exclusion criteria), reasons why certain eligible individuals chose not to participate, and any attempts to achieve a sample of participants that represents the target population.
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? Explanations Indicators of appropriate measurements include: the variables are clearly defined and accurately measured; the measurements are justified and appropriate for answering the research question; the measurements reflect what they are supposed to measure; validated and reliability tested measures of the intervention/exposure and outcome of interest are used, or variables are measured using 'gold standard'.
	3.3. Are there complete outcome data? Explanations Almost all the participants contributed to almost all measures. There is no absolute and standard cut-off value for acceptable complete outcome data. Agree among your team what is considered complete outcome data in your field (and based on the targeted journal) and apply this uniformly across all the included studies. For example, in the literature, acceptable complete data value ranged from 80% (Thomas et al., 2004; Zaza et al., 2000) to 95% (Higgins et al., 2016). Similarly, different acceptable withdrawal/dropouts rates have been suggested: 5% (de Vet et al., 1997; MacLehose et al., 2000), 20% (Sindhu et al., 1997; Van Tulder et al., 2003) and 30% for follow-up of more than one year (Viswanathan and Berkman, 2012).
	3.4. Are the confounders accounted for in the design and analysis? Explanations Confounders are factors that predict both the outcome of interest and the intervention received/exposure at baseline. They can distort the interpretation of findings and need to be considered in the design and analysis of a non-randomized study. Confounding bias is low if there is no confounding expected, or appropriate methods to control for confounders are used (such as stratification, regression, matching, standardization, and inverse probability weighting).
	3.5 During the study period, is the intervention administered (or exposure occurred) as intended? Explanations For intervention studies, consider whether the participants were treated in a way that is consistent with the planned intervention. Since the intervention is assigned by researchers, consider whether there was a presence of contamination (e.g., the control group may be indirectly exposed to the intervention) or whether unplanned co-interventions were present in one group (Sterne et al., 2016). For observational studies, consider whether changes occurred in the exposure status among the participants. If yes, check if these changes are likely to influence the outcome of interest, were adjusted for, or whether unplanned co-exposures were present in one group (Morgan et al., 2017).

4. Quantitative descriptive studies	Methodological quality criteria
Quantitative descriptive studies are "concerned with and designed only to describe the existing distribution of variables without much regard to causal relationships or other hypotheses" (Porta et al., 2014, p. 72). They are used to monitoring the population, planning, and generating hypothesis (Grimes and Schulz, 2002). Common designs include the following single-group studies (this list if not exhaustive): **Incidence or prevalence study without comparison group** In a defined population at one particular time, what is happening in a population, e.g., frequencies of factors (importance of problems), is described (portrayed). **Survey** "Research method by which information is gathered by asking people questions on a specific topic and the data collection procedure is standardized and well defined." (Bennett et al., 2011, p. 3). **Case series** A collection of individuals with similar characteristics are used to describe an outcome. **Case report** An individual or a group with a unique/unusual outcome is described in detail. Key references: Critical Appraisal Skills Programme (2017); Draugalis et al. (2008)	4.1. Is the sampling strategy relevant to address the research question? Explanations Sampling strategy refers to the way the sample was selected. There are two main categories of sampling strategies: probability sampling (involve random selection) and non-probability sampling. Depending on the research question, probability sampling might be preferable. Non-probability sampling does not provide equal chance of being selected. To judge this criterion, consider whether the source of sample is relevant to the target population; a clear justification of the sample frame used is provided; or the sampling procedure is adequate. 4.2. Is the sample representative of the target population? Explanations There should be a match between respondents and the target population. Indicators of representativeness include: clear description of the target population and of the sample (such as respective sizes and inclusion and exclusion criteria), reasons why certain eligible individuals chose not to participate, and any attempts to achieve a sample of participants that represents the target population. 4.3. Are the measurements appropriate? Explanations Indicators of appropriate measurements include: the variables are clearly defined and accurately measured, the measurements are justified and appropriate for answering the research question; the measurements reflect what they are supposed to measure; validated and reliability tested measures of the outcome of interest are used, variables are measured using 'gold standard', or questionnaires are pre-tested prior to data collection. 4.4. Is the risk of nonresponse bias low? Explanations Nonresponse bias consists of "an error of nonobservation reflecting an unsuccessful attempt to obtain the desired information from an eligible unit." (Federal Committee on Statistical Methodology, 2001, p. 6). To judge this criterion, consider whether the respondents and non-respondents are different on the variable of interest. This information might not always be reported in a paper. Some indicators of low nonresponse bias can be considered such as a low nonresponse rate, reasons for nonresponse (e.g., noncontacts vs. refusals), and statistical compensation for nonresponse (e.g., imputation). The nonresponse bias is might not be pertinent for case series and case report. This criterion could be adapted. For instance, complete data on the cases might be important to consider in these designs. 4.5. Is the statistical analysis appropriate to answer the research question? Explanations The statistical analyses used should be clearly stated and justified in order to judge if they are appropriate for the design and research question, and if any problems with data analysis limited the interpretation of the results.

5. Mixed methods studies	Methodological quality criteria
Mixed methods (MM) research involves combining qualitative (QUAL) and quantitative (QUAN) methods. In this tool, to be considered MM, studies have to meet the following criteria (Creswell and Plano Clark, 2017): (a) at least one QUAL method and one QUAN method are combined; (b) each method is used rigorously in accordance to the generally accepted criteria in the area (or tradition) of research invoked; and (c) the combination of the methods is carried out at the minimum through a MM design (defined *a priori*, or emerging) and the integration of the QUAL and QUAN phases, results, and data. Common designs include (this list if not exhaustive): **Convergent design** The QUAL and QUAN components are usually (but not necessarily) concomitant. The purpose is to examine the same phenomenon by interpreting QUAL and QUAN results (bringing data analysis together at the interpretation stage), or by integrating QUAL and QUAN datasets (e.g., data on same cases), or by transforming data (e.g., quantization of qualitative data). **Sequential explanatory design** Results of the phase 1 - QUAN component inform the phase 2 - QUAL component. The purpose is to explain QUAN results using QUAL findings. E.g., the QUAN results guide the selection of QUAL data sources and data collection, and the QUAL findings contribute to the interpretation of QUAN results. **Sequential exploratory design** Results of the phase 1 - QUAL component inform the phase 2 - QUAN component. The purpose is to explore, develop and test an instrument (or taxonomy), or a conceptual framework (or theoretical model). E.g., the QUAL findings inform the QUAN data collection, and the QUAN results allow a statistical generalization of the QUAL findings. Key references: Creswell et al. (2011); Creswell and Plano Clark, (2017); O'Cathain (2010)	5.1. Is there an adequate rationale for using a mixed methods design to address the research question? Explanations The reasons for conducting a mixed methods study should be clearly explained. Several reasons can be invoked such as to enhance or build upon qualitative findings with quantitative results and vice versa; to provide a comprehensive and complete understanding of a phenomenon or to develop and test instruments (Bryman, 2006).
	5.2. Are the different components of the study effectively integrated to answer the research question? Explanations Integration is a core component of mixed methods research and is defined as the "explicit interrelating of the quantitative and qualitative component in a mixed methods study" (Plano Clark and Ivankova, 2015, p. 40). Look for information on how qualitative and quantitative phases, results, and data were integrated (Pluye et al., 2018). For instance, how data gathered by both research methods was brought together to form a complete picture (e.g., joint displays) and when integration occurred (e.g., during the data collection-analysis or/and during the interpretation of qualitative and quantitative results).
	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? Explanations This criterion is related to meta-inference, which is defined as the overall interpretations derived from integrating qualitative and quantitative findings (Teddlie and Tashakkori, 2009). Meta-inference occurs during the interpretation of the findings from the integration of the qualitative and quantitative components, and shows the added value of conducting a mixed methods study rather than having two separate studies.
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? Explanations When integrating the findings from the qualitative and quantitative components, divergences and inconsistencies (also called conflicts, contradictions, discordances, discrepancies, and dissonances) can be found. It is not sufficient to only report the divergences; they need to be explained. Different strategies to address the divergences have been suggested such as reconciliation, initiation, bracketing and exclusion (Pluye et al., 2009b). Rate this criterion 'Yes' if there is no divergence.
	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved? Explanations The quality of the qualitative and quantitative components should be individually appraised to ensure that no important threats to trustworthiness are present. To appraise 5.5, use criteria for the qualitative component (1.1 to 1.5), and the appropriate criteria for the quantitative component (2.1 to 2.5, or 3.1 to 3.5, or 4.1 to 4.5). The quality of both components should be high for the mixed methods study to be considered of good quality. The premise is that the overall quality of a mixed methods study cannot exceed the quality of its weakest component. For example, if the quantitative component is rated high quality and the qualitative component is rated low quality, the overall rating for this criterion will be of low quality.

Algorithm for selecting the study categories to rate in the MMAT*



*Adapted from National Institute for Health Care Excellence. (2012). *Methods for the development of nice public health guidance*. London: National Institute for Health and Care Excellence; and Scottish Intercollegiate Guidelines Network. (2017). *Algorithm for classifying study design for questions of effectiveness*. Retrieved December 1, 2017, from http://www.sign.ac.uk/assets/study_design.pdf.

Appendix D: Data extraction elements

Pilot data extraction:

Sheet I

1. Author, publication year
2. Location
3. Data year
4. Data source
5. MMAT
    - Category
    - Score

Sheet II

6. Study details
    - Aim
    - Study type
    - Settings
7. Study population
    - Population criteria
    - Sample size
    - Mean age
    - Respond rate
    - Ethnicity
    - Inclusion criteria
    - Exclusion criteria
8. Settings
    - Baseline measure
    - Follow up duration
    - Follow up measure
    - Intervention measure
9. Statistical information
    - Continuous measure
    - Categorical measure
    - Significant level
    - Correlation analysis method
    - Analysis method (qualitative studies)
10. Medication taking behaviour measure
    - Outcome type (initiation/adherence / persistence/ discontinuation)
    - Definition
    - Measure
    - Scale

- Validity
- Reliability
- Rate
- Duration

11. Psychosocial measure
    - Domains
    - Measure
    - Scale
    - Validity
    - Reliability
    - Significant result
    - Non-significant result

Sheet III

12. Study limitation
13. Strategy to improve medication intake
14. Main conclusion

Revised data extraction:

1. Author, publication year
2. Study type (follow up, *If applicable*)
3. Study aim
4. Sample size
5. Medication taking behaviour type and measure
6. Psychosocial measure and finding

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