Development and validation of a medication adherence tool for people with bipolar disorder to identify non-adherent behaviour and diagnose an individual's determinants of adherence

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Abstract

Background

Around 40% of patients with bipolar disorder are non-adherent due to a wide range of determinants. Adherence support strategies are not tailored to individual's determinants. This thesis aimed to develop and evaluate a medication adherence tool ('C-MABQ') to guide identifying adherence determinants.

Methods

Theoretical Domains Framework (TDF) underpinned the research programme comprising five empirical studies: 1) a systematic review of modifiable adherence determinants, 2) focus groups and interviews with patients and their families and friends to explore these determinants, 3) development of C-MABQ in collaboration with experts in the area, 4) consultation with healthcare professionals and patients to check face and content validity, and 5) psychometric evaluation of C-MABQ with patients.

Results

Literature identified determinants were mapped to 11 TDF domains; patients and their families and friends prioritised nine domains. A 50-item C-MABQ, developed from the prioritised determinants, had good face and content validity. The C-MABQ was completed by 325 patients for psychometric evaluation. Fifteen items representing six TDF domains, 'Emotion', 'Social Influence', 'Memory, attention and decision processes', 'Intention', 'Goal', 'Social/professional role and identity', fulfilled the Mokken Scale double monotonicity model criteria and demonstrated construct validity. The 15-item C-MABQ showed criterion validity with medication adherence report scale (ρ=0.32, P <0.001) but not with blood Lithium level. It showed good model fit (CFI=0.997, TLI=0.996, RMSEA=0.059), good internal consistency (α =0.91, 95% CI=0.89 to 0.93) and good test-retest reliability (ICC=0.74, 95% CI=0.61 to 0.82, P<0.001).

Conclusion

The 15-item C-MABQ identifies individual's prominent adherence determinants. Their mapping to the TDF enables C-MABQ items to be linked to behaviour change techniques, thus guiding patients and healthcare professionals to select adherence support strategies tailored to the prioritised adherence determinant. Blood Lithium levels may not present accurate and reliable measure of adherence. Thus, a feasibility study to establish an appropriate adherence measure for a definitive trial is required.

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Abbreviation	Explanation
AISP	Automated Item Selection Procedure
BCTs	Behaviour Change Techniques
BIPQ	Brief Illness Perception Questionnaire
CFI	Comparative Fit Index
C-MAB	Collaborative Medication Adherence in Bipolar disorder
C-MABQ	Collaborative Medication Adherence in Bipolar disorder Questionnaire
C-MABQdmm	C-MABQ double monotonicity model, 15-item C-MABQ
CTT	Classical Test Theory
DMM	Double Monotonicity Model
ICC	Intra-class Correlation Coefficient
IIO	Invariant Item Ordering
IMAB-Q	The Identification of Medication Adherence Barriers Questionnaire
IRT	Item Response Theory
MARS-5	Medication Adherence Report Scale - 5
MSA	Mokken Scale Analysis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSFT	Norfolk and Suffolk NHS Foundation Trust
PPI	Patient and Public Involvement
RMSEA	Root Mean Square Error of Approximation
TDF	Theoretical Domains Framework
TLI	Tucker-Lewis Index
UEA	University of East Anglia

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Publications and presentations

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- Prajapati AR, Dima A, Mosa G, Scott S, Song F, Wilson J, et al. Mapping modifiable determinants of medication adherence in bipolar disorder (BD) to the theoretical domains framework (TDF): a systematic review. Psychol Med 2021 May;51(7):1082-1098.

Thesis related conference presentations

- European Health Psychology Society 2019Conference: Mapping of determinants of medication adherence to the Theoretical Domains Framework - a systematic review (Poster)
- ESPACOMP, the International Society for Medication Adherence, 2019 Conference: Modifiable determinants of medication adherence in bipolar disorder - A systematic review (Poster)
- Norfolk and Suffolk NHS Foundation Trust Research Day (Oral)

Non-thesis related publications (During PhD)

- Prajapati AR, Wilson J, Song F, Maidment I. Second-generation antipsychotic long-acting injections in bipolar disorder: Systematic review and meta-analysis. Bipolar Disord. 2018 Dec;20(8):687-696. doi: 10.1111/bdi.12707. Epub 2018 Nov 11.

Non-thesis related presentation

- 10th Annual International Psychiatric Pharmacy 2019Conference of the College of Mental Health Pharmacy, Research Lecture: Feasibility of Introducing Medication Adherence Rating Scale in Clozapine Clinic (Oral)
- World Pharmacists Day 2020, Kathmandu University: Evolving role of Pharmacists (Oral)

Formal training and professional development

University of East Anglia

- Introduction to Research Method
- Introduction to Ethics in Health Research
- Survey design
- An Introduction to NVivo
- Basic Statistics
- Training in Qualitative Methods: Qualitative Interviewing
- Training in Qualitative Methods: Qualitative Analysis and Interpretation
- Introduction to Ethics in Health Research
- HOW TO make the most of UEA Library Resources
- Preparing for the Probationary Review Meeting
- An Introduction to Scale Development
- An Introduction to Structural Equation Modelling
- Critical Thinking
- Making the most of your slides for effective presentations
- Writing the Thesis
- Where to start with the thesis?
- Strategies for Success in Scientific Publishing and Conferences

National Institute for Health Research

- Good Clinical Practice
- NIHR Academy Members Conference
- NIHR Digital Leadership Training

Centre for Behaviour Change Summer School, University College London

- Key concepts in behaviour change
- How to do a behavioural diagnosis
- How to develop an intervention strategy from a behavioural diagnosis
- Going beyond the BCW
- Implementing behaviour change in practice

Cambridge Summer School, Cambridge University

- Introduction to R and Concerto
- Item response theory using R

Others

- Interview techniques by Social Research Association, UK
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THANK YOU (धन्यबाद 🙏)!

Asta

CHAPTER ONE

BACKGROUND

1.1 Bipolar disorder

Bipolar disorder affects around 45 million people worldwide (1). Bipolar disorder is a recurrent mental health condition associated with a significant socioeconomic burden, high risks of disability and excess mortality (2,3). As a long-term mental health condition, bipolar disorder can make it difficult for patients to hold on to a job or relationship, reduces their quality of life, and increases suicide risk. For example, around half of the patients with bipolar disorder experience at least one suicide attempt and 11 to 19% of patients commit suicide (4). Bipolar disorder, previously also known as manic depression, can cause mood to swing from an extreme high to an extreme low and can change the energy level and ability to function (5). International Classification of Diseases 11th Revision (6) describes bipolar disorder as "an episodic mood disorder defined by the occurrence of manic, mixed or hypomanic episodes or symptoms. These episodes typically alternate over the course of these disorders with depressive episodes or periods of depressive symptoms."

A manic episode is a distinct period of an extreme mood state characterised by abnormal and persistent euphoria, irritability, or expansiveness, and by increased activity or a subjective experience of increased energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalisation is necessary) (5,6). Such manic episode is accompanied by other characteristic symptoms such as rapid or pressured speech, flight of ideas, increased self-esteem or grandiosity, decreased need for sleep, distractibility, impulsive or reckless behaviour, rapid changes among different moods, and increase in sexual drive, sociability, or goal-directed activity (5,6). Hypomania can be seen as a milder form of mania with symptoms similar to mania but not severe enough to cause marked impairment in functioning (6). A depressive episode is a period of low mood or loss of interest or pleasure in all or almost all activities occurring most of the day, nearly every day during a period lasting at least two weeks. Such episode is accompanied by other symptoms such as changes in appetite or sleep, unintentional significant weight change, psychomotor agitation or retardation, fatigue, feelings of worthless or excessive or inappropriate guilt, feelings of hopelessness, difficulty concentrating, recurrent thoughts of death and suicidality (5,6). In a mixed episode, several prominent manic and depressive symptoms occur simultaneously or alternate very rapidly (from day to day or within the same day) (6). Bipolar disorder is classed as bipolar I if the

patient has experienced one or more manic or mixed episodes and bipolar II if a patient has experienced one or more hypomanic episodes and at least one depressive episode but no manic or mixed episodes (6). Term ‘bipolar disorder’ will be used in this thesis to cover both types of bipolar disorder.

The peak age of onset of bipolar disorder is 15 to 19 years but there is often a substantial delay in diagnosis (7). The lifetime prevalence of bipolar I disorder (mania and depression) is estimated at 1% of the adult population, and bipolar II disorder affects approximately 0.4% of adults (7,8). No clear gender difference is seen in the prevalence of bipolar disorder (9). Comorbidity in bipolar disorder is very common, particularly anxiety disorders, substance misuse, personality disorders and attention deficit hyperactivity disorders (7). The aetiology of bipolar disorder is not well understood and is a relatively under-researched area (8). Many risk factors for bipolar disorder have been suggested, such as genetic, perinatal infection, obstetric complications, childhood trauma, life events (e.g., death of loved ones, divorce), substance abuse, clinical risk factors (e.g., anxiety, irritable bowel syndrome, asthma, obesity etc.), ethnicity, lower age, family history (8). Someone with a first-degree relative with bipolar disorder can have a 13-fold increased risk of developing bipolar disorder (8).

1.2 Common long-term treatment for bipolar disorder

Medications remain the mainstay of the treatment of bipolar disorder. Psychotherapy, such as cognitive behavioural therapy is also recommended as an add on to medications for the management of bipolar disorder (7,10,11) but often not readily available (12).

This thesis, however, is only concerned with medications. Medications for bipolar disorder can be used to manage acute symptoms, e.g., antipsychotic injections to control agitation during manic episodes. These acute treatments are excluded in this thesis as they tend to be short term (single dose to a few days) and generally administered in hospital settings. This thesis focuses on long-term medications for bipolar disorder which are prescribed prophylactically to maintain a stable mood and to prevent a further relapse as it is an episodic condition.

Medications for long-term maintenance treatment of bipolar disorder can broadly be divided into two groups:

- Antipsychotics such as olanzapine, quetiapine, risperidone, aripiprazole
- Mood stabilisers such as Lithium, valproate, lamotrigine, carbamazepine

Patients can be prescribed just one medication for their bipolar disorder, known as monotherapy or they can be prescribed two or more medications known as combination therapy. Monotherapy is the preferred option and for approximately 50% of patients, monotherapy will significantly improve their symptoms (11). If monotherapy becomes ineffective, then combination therapy is recommended. However, combination therapy is more likely to have an increased side effect burden. Lithium is the gold-standard first-line long-term treatment for bipolar disorder and current evidence suggests that efficacy for Lithium > valproate > olanzapine > lamotrigine > quetiapine > carbamazepine (7,10) although this has been challenged (13). Newer medications such as asenapine, cariprazine and ziprasidone can also be used to manage bipolar disorder.

Choice of medication often depends on multiple factors such as comorbidities, predominant symptoms (depression or hypomania/mania), presence or absence of psychotic symptoms and previous history but will primarily depend on the effectiveness and tolerability of medication.

1.3 Medication non-adherence in bipolar disorder

“All the medicines in the world are for naught if we cannot get people to take them.” C Everett Koop, former US Surgeon General

Medication non-adherence is a common human experience in both physical and mental health (14). In bipolar disorder, an estimated 40% of patients do not adhere to their prescribed directions of medications (15-18). Figure 1.1 shows a comparison of non-adherence in bipolar disorder with other common physical health conditions such as hypertension, hypothyroidism and diabetes (16,19).

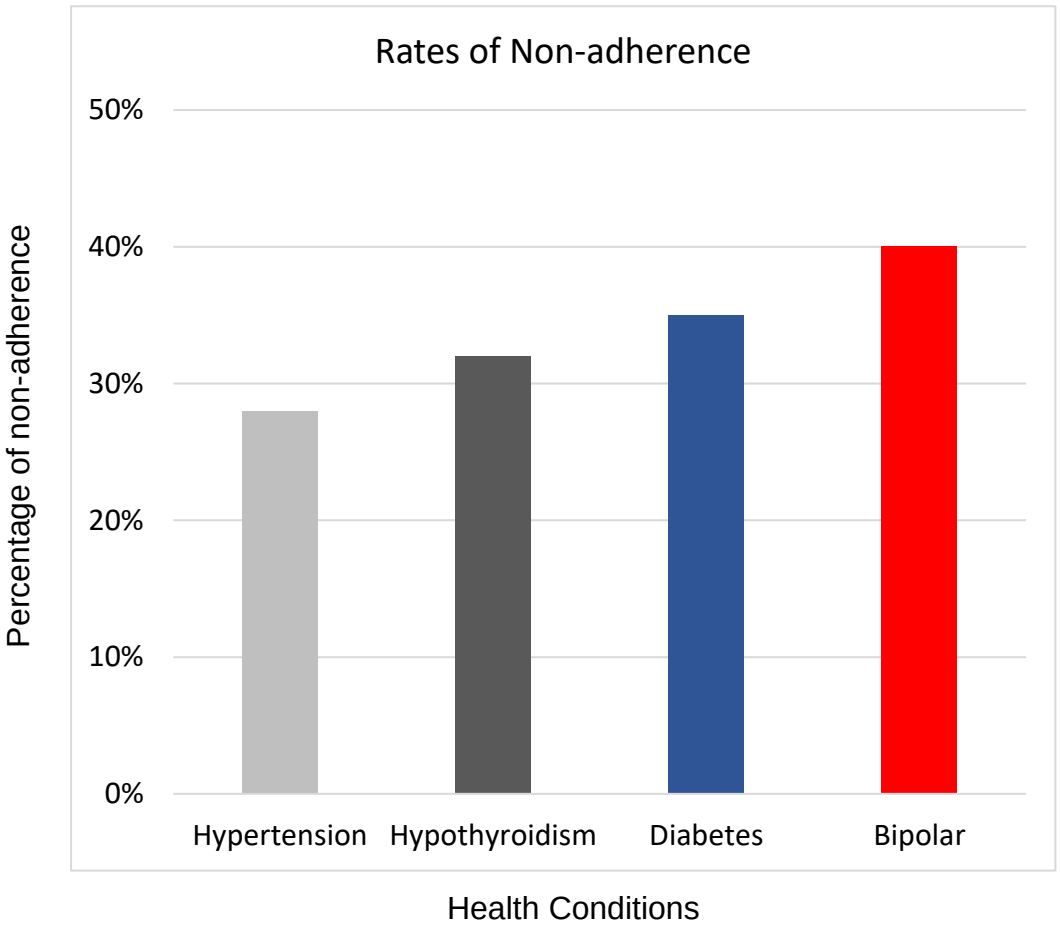


Figure 1.1: Rates of medication non-adherence in bipolar disorder and other common physical health conditions

The World Health Organization defines adherence as *"the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* (20). In the context of medication, adherence is described in terms of the proportion of medication taken against the prescribed amount. The National Institute for Health and Care Excellence (NICE) UK defined medication adherence as the extent to which the patient's action matches the agreed recommendations (21).

Medication adherence described in the literature is, however, wide and varied. In general, medication adherence is defined as administering ≥ 80% of the prescribed doses of antihypertensive medication (21). However, for some disease conditions such as HIV, medication adherence of ≥ 95% of prescribed doses is required for optimum benefit from the anti-retroviral treatment (22). Furthermore, in patients with schizophrenia, missing even one to ten days of medication over a year had twice the

risk of relapse compared to patients who did not miss a dose and patients missing >30 days have a nearly four-fold increased risk of relapse (23).

Even within bipolar disorder studies, medication adherence is defined inconsistently and varies widely. For example, some studies described medication adherence as taking ≥ 75% of the recommended dose (24) while others as taking ≥ 90% of the recommended dose (25). Some studies used broad questions such as *"In the past did you ever stop medicines without doctor's agreement?"* (26). In contrast, others used more specific questions if they missed one or more doses within the last ten days (27). Some authors divided adherence into partial adherence (e.g., ≥30% to <90% recommended dose) and non-adherence (<30% recommended treatment dose) (25). Others used terms such as 'always adherent' (never miss their medication), 'usually adherent' (rarely miss), 'occasionally adherent' (occasionally miss), 'rarely adherent' (frequently miss) (28). Others define medication adherence in gradient terms such as non-adherence (taking less than 20% of the time), low adherence (20% to 59% of the time), moderate adherence (60% to 79% of the time), and high adherence (≥ 80% of the time) (29). This shows the complexity and difficulties in measuring adherence and the wide variation in adherence rate reported in the literature.

Instead of taking less than the prescribed dose of medications, some patients take more than the prescribed dose which is also a form of non-adherence. However, this thesis is focused on nonadherence relating to taking less than the prescribed doses, as this is a more widespread problem (30).

1.3.1 Measuring medication non-adherence

There are two broad ways to measure medication adherence: objective and subjective. Objective measures include blood plasma level of medication, medication possession ratio (number of days a patient has obtained the medication divided by the number of days the patient is prescribed to have medication during a specific period of time, e.g., six months), a physical count of medication (known as pill count), Medication Event Monitoring System (with a special cap on the bottle of medication capable of recording each time the bottle is opened) and other use of technology (an ingestible sensor embedded in the medication that records administration of the

medication) (31,32). Subjective measures include reporting by patients or their families and friends, healthcare professionals, or measures using medication adherence tools or rating scales or questionnaires. In the literature, the terms medication adherence tools or medication adherence rating scales or medication adherence questionnaires have been used to mean the same. Thus, I will be choosing the term that best fits the context and creates a smooth flow in reading. Rating scales or questionnaires can be very short, containing four questions, or quite long with 30 or more questions.

Both objective and subjective measures have their own merits and disadvantages. For example, objective measures such as blood level of medication are considered more accurate and unbiased but quite intrusive, expensive, affected by patient variables (such as age, race, weight, comorbidities), may not be widely available and only measure adherence in recent time (14,33). Owing to these difficulties, subjective measures may be preferred and suitable in routine clinical practice (33). Subjective measures are generally non-invasive, cheap, simple, and easy to use but they can be prone to reporting and recall bias, pressure to conformity, and can significantly overestimate adherence (14,33).

Our systematic review described in Chapter 2, involving 57 studies evaluating modifiable determinants of medication adherence in bipolar disorder, found that less than half of the studies (n=23) used validated questionnaires and only five studies used other objective measures such as blood plasma level of the drug or medication possession ratio to define adherence and about half used self-reporting by patient or others (18). Objective and subjective measures can give a completely different picture in terms of the proportion of adherence even in the same patients. A prospective observational study of 1,848 outpatients with schizophrenia or schizoaffective disorders found a non-adherence rate of 49.5% (based on patients' self-reports), 65.0% (based on carers' reports), 68.5% (based on medication adherence rating scale), 71.2% (based on Medication Events Monitoring System) and 84.7% (based on pill count) (34). Therefore, in order to get a more accurate and reliable picture of non-adherence, it is necessary to combine both objective and subjective measures and corroborate this with clinical symptoms.

Notwithstanding the complexity and variation, it is generally regarded that around half of patients with chronic illness do not take their medication as prescribed (14,20,21).

1.3.2 Consequences of non-adherence

Medication non-adherence leads to relapse, hospitalisation, functional impairment, and suicidality in patients with bipolar, and a decreased likelihood of achieving remission and recovery (17,30,35-40). For example, in a 21 month long prospective observational study of patients with bipolar disorder (n=1341), Hong et al. found a nearly 2.5-fold increase in relapse rate, around threefold increase in hospitalisation and suicide attempts, and around 170% increase in recurrence in non-adherent patients (40). In the same study, remission and recovery were 30% lower in non-adherent patients. However, in other studies, the consequences of medication non-adherence were more pronounced. For example, Scott et al. followed 98 patients over 18 months and found that medication non-adherence increased the probability of hospitalisation by at least five times (38). Similarly, in a prospective study following 72 patients with bipolar disorder for ten years, there was a 5-fold increase in the rate of suicide and suicide attempts among non-adherent patients (37).

In addition to clinical consequences, medication non-adherence also leads to increased social and health care costs and personal suffering whilst reducing the productivity of the individual and carers (30,40,41). A study from the USA estimated re-hospitalization costs due to antipsychotic nonadherence alone to be $1.47 billion (2007) (42). In the UK, the Department of Health in 2011 estimated that non-adherence to medication is costing the NHS £500 million per year. The annual cost of managing bipolar disorder in the UK was estimated to be £342 million at 2009/2010 prices (60% of this accounted for by inpatient admissions) (43). Over 21 months follow up of 1341 patients with bipolar disorder; Hong et al. found the total costs incurred by nonadherent patients were £2852 per patient per year higher (£10,231 per non-adherent patient over 21 months compared with £7379 in adherent patients, $p < 0.05$) (40). The difference was mainly due to the high inpatient care costs among the nonadherent group (£4796) compared to adherent patients (£2150) (40). Indirect cost due to workplace absenteeism, short-term disability and workers' compensation is also shown to be higher in non-adherent patients (41).

Thus, improving medication adherence is not just of significant clinical importance but it is also of huge economic benefits.

1.4 Medication taking is a health behaviour

Health behaviours have been defined as ". . . overt behavioural patterns, actions and habits that relate to health maintenance, to health restoration and to health improvement" (44). Health behaviours can promote or detract from health and wellbeing (45). Medication adherence is a health behaviour like healthy diet, physical activity, smoking, substance use (44,45). As with any health behaviour, medication taking is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and the cognitive ability (practical function) and motivation (perceptual function) to take the medication (46,47). However, compared to other widely studied health behaviours such as smoking, binge drinking, healthy diet, and physical activity (44), medication adherence has been under-researched as a health behaviour and a lack of comprehensive behaviour change theories underpinning such research is evident.

1.5 Theories of behaviour change

Theories are beliefs or assumptions underlying actions and explanations of the phenomena of interest (48). A distinction can be drawn between grand (high-level generalisations that can be applied across domains), mid-range (limited to a specific area) and programme theory (specific to an individual intervention) (48). Behaviour change theories seek to explain why, when, and how behaviour does or does not occur and the important sources of influence to be targeted in order to alter the behaviour (49). In a review aimed to identify theories of behaviour and behaviour change of potential relevance to public health interventions across the field of psychology, sociology, anthropology and economics, Davis et al. identified 83 theories (50).

Some of the most widely cited and used theories of behaviour change are listed below (20,49,51-53):

- Social Cognitive Theory
- The Health Belief Model
- Transtheoretical Model/Stages of Change
- Protection Motivation Theory

- Theory of Reasoned Action and Theory of Planned Behaviour
- Health Action Process Approach
- The Information-Motivation-Behavioural-Skills Model

1.5.1 Social Cognitive Theory

The social cognitive theory was developed in 1986 from the Social Learning Theory of the 1960s by Albert Bandura (54). This theory posits that human behaviour is explained by a triadic reciprocal interaction of behaviour, personal and environmental factors, as shown in figure 1.2 (49,51).

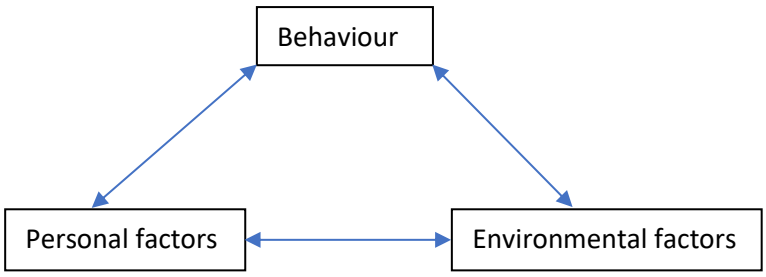


Figure 1.2: Social Cognitive Theory model (Sourced from World Bank (51))

There are six constructs in social cognitive theory, the first five were part of the social learning theory, and the sixth was added when the theory evolved into social cognitive theory (55):

I. Reciprocal Determinism - This central concept of the social cognitive theory refers to the dynamic and reciprocal interaction of individuals (with a set of learned experiences), environment (external social context), and behaviour (responses to stimuli to achieve goals) (55).
II. Behavioural Capability - People's ability to perform a behaviour through essential knowledge and skills. To successfully perform a behaviour, an individual must know what to do and how to do it. People learn from the consequences of their behaviour, which also affects the environment in which they live (55). Capability is further divided into the following five categories (ABC of behaviour change):

a) Symbolising Capability - Capacity to use symbols for transforming experiences into mental models that can be used to guide future behaviour and for ascribing meaning to these experiences.
b) Forethought Capability - Ability to regulate behaviour based on the future, e.g., through setting goals.
c) Vicarious Capability - Ability to learn through observation (i.e., by modelling others' behaviour, attitudes, etc.).
d) Self-Regulatory Capability - Ability to motivate or regulate own behaviour based on their personal standards and evaluations of their behaviour.
e) Self-Reflective Capability - Capacity to self-reflect through analysis of own experiences, thoughts, and knowledge.

III. Observational Learning - People can learn and reproduce behaviours through witnessing and observing others' behaviours, often described as "modelling" of behaviours (55).

IV. Reinforcements – This refers to the responses (both internal or external) to a person's behaviour that influence the likelihood of maintaining or stopping the behaviour. Reinforcements can be positive or negative and can be self-initiated or environment-induced (55). This construct of social cognitive theory most closely ties to the reciprocal relationship between behaviour and environment (55).

V. Expectations - The anticipated consequences of a person's behaviour which can be health-related or not. People anticipate the consequences of their behaviour before performing the behaviour which can influence whether the behaviour will occur. Expectations derive largely from previous experience.

VI. Self-efficacy - The level of a person's confidence in their ability to successfully perform a behaviour. Self-efficacy is influenced by an individual's specific capabilities and other individual factors and environmental factors (barriers and facilitators) (55).

1.5.2 The Health Belief Model

The health belief model is a health specific social cognition model developed in the context of explaining preventative health behaviour to reduce the risk to health

(49,52,56). Central to the health belief model is the idea that the likelihood of preventive behaviour is primarily determined by individuals' beliefs about their perceived susceptibility to the disease, perceived severity of the disease, perceived benefits of the behaviour and the perceived barriers to the behaviour (49). The health belief model has been further developed by adding different elements since its inception by Rosenstock in the 1960s (52). The updated health belief model with the core elements of the model is presented in figure 1.3 below (49,52):

- **Perceived susceptibility** - an individual's perception of the risk of contracting the relevant illness in question.
- **Perceived severity** - an individual's evaluation of the seriousness of the illness and its consequences.

Perceptions of susceptibility and severity are partially dependent upon knowledge about the illness and together reflect perceptions of the overall threat posed by the illness which may indicate the level of motivation an individual has to perform a particular behaviour.

- **Perceived benefits –** an individual's assessment of the positive benefits by adopting a behaviour to offset a perceived threat consequence. Behaviour is more likely if perceived benefits lead to a reduction in perceived threat.
- **Perceived barriers/costs** - an individual's perception of the barriers that hinder performing the behaviour or associated negative aspects of performing that behaviour (e.g., social isolation, financial costs).
- **Self-efficacy** – Following the introduction of the concept of the act or task specific self-confidence by Bandura in the late 1970s, self-efficacy has been added to the health belief model (52). Self-efficacy is defined as an individual's beliefs about whether they are capable of performing a behaviour in question (49).

Expectations, the product/sum of perceived benefits, barriers, and self-efficacy, may indicate the extent to which the individual will try to perform the behaviour (52).

- **Demographic and socio-economic variables** - The core components of health belief model, threat and expectations, are influenced by demographic variables (e.g., age, race, ethnicity), socio-economic variables (e.g., education

and income) and structural variables (e.g., knowledge about the relevant disease, prior experience of the disease) (49,52).

- **Cues to action** – Even when a perceived threat, perceived benefits and self-efficacy are high, and barriers are weak, individuals may still need a further force to trigger or prompt the behaviour, called cues to action (49,52). Cues to action can be internal such as bodily pain or depressed mood or external such as reminders to take medications.

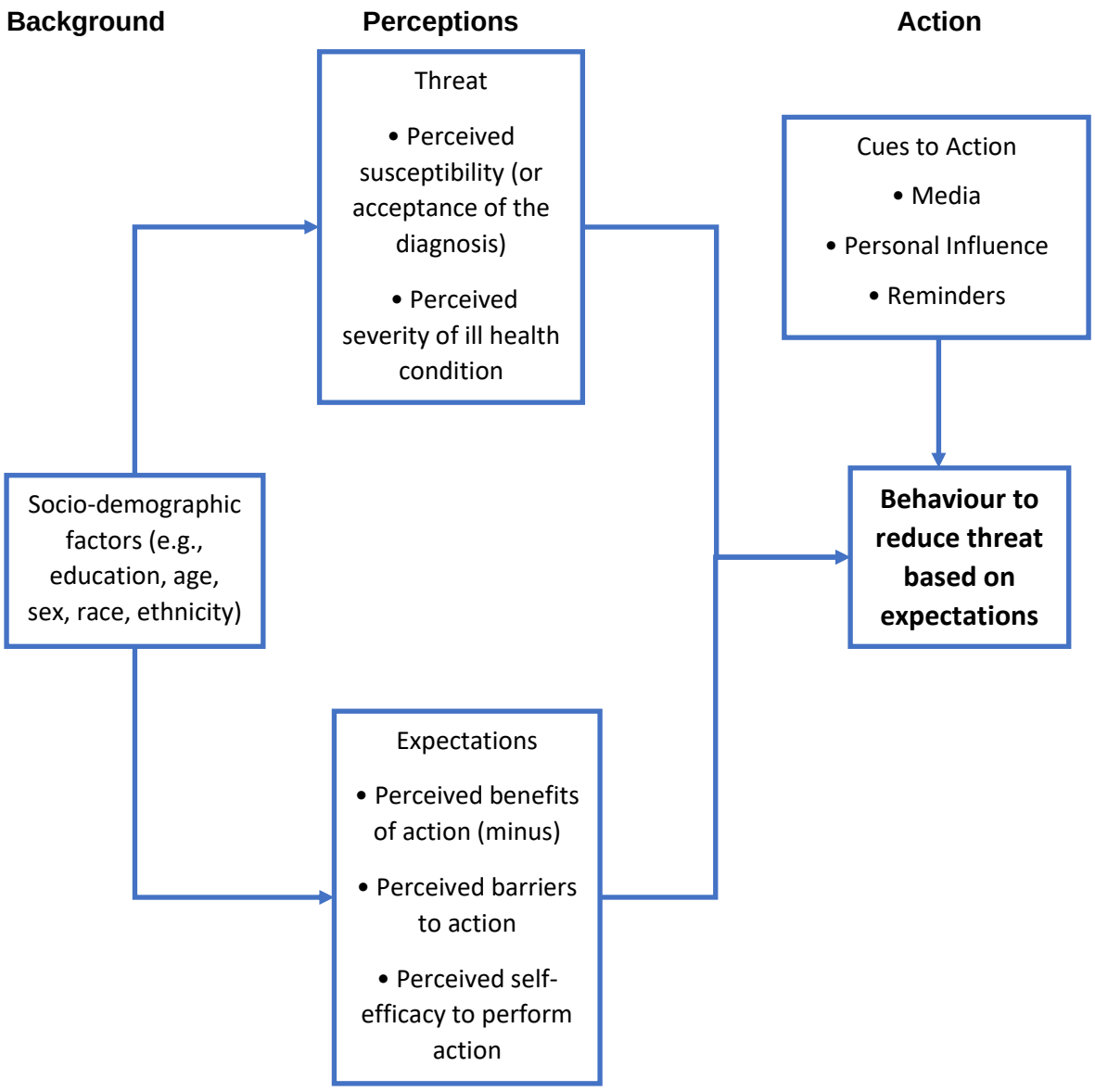


Figure 1.3 The extended Health Belief Model (Adapted from NICE PH6 (52)**)**

In essence, the health belief model explains that people make a risk/benefit analysis of the perceived threat of illness and balance this against their outcome expectations

(53). The health belief model depicts that the balance between these two principal components along with the cues to action will determine behaviour.

1.5.3 Theory of Reasoned Action and Theory of Planned Behaviour

The theory of reasoned action posits that an individual's intention to perform a particular behaviour is the most important determinant for that behaviour and the determinants of that intention are that individual's attitude toward that behaviour and subjective norms related to that behaviour (57). Attitude in turn, is influenced by the individual's behavioural beliefs (consequences of the behaviour, e.g., will I get better by taking medication as prescribed) and evaluation of the outcome from that behaviour (Have I got better after taking medication as prescribed for a week?). Similarly, the subjective norm is determined by the individual's normative beliefs, e.g., whether important people in their life approve or disapprove the behaviour and the degree to which the individual want to comply with those expectation (52,57). The theory of planned behaviour extends this theory by the inclusion of perceived control as an independent determinant of intention in addition to attitude and subjective norm (52,57). It was based on the idea that behaviour is determined jointly by intention and ability (behavioural control) (52,57). Perceived behavioural control is defined as the extent to which an individual feels able to perform the behaviour (49). It is a function of control beliefs, i.e., beliefs about the presence of barriers or facilitators to perform a particular behaviour and perceived power, i.e., the individual's self-efficacy, confidence in performing that behaviour (49,52). Other external factors such as demographics are assumed to operate through the construct of the model and do not directly and independently influence the behaviour (57). The integrative theory of reasoned action and theory of planned behaviour model is presented in Figure 1.4

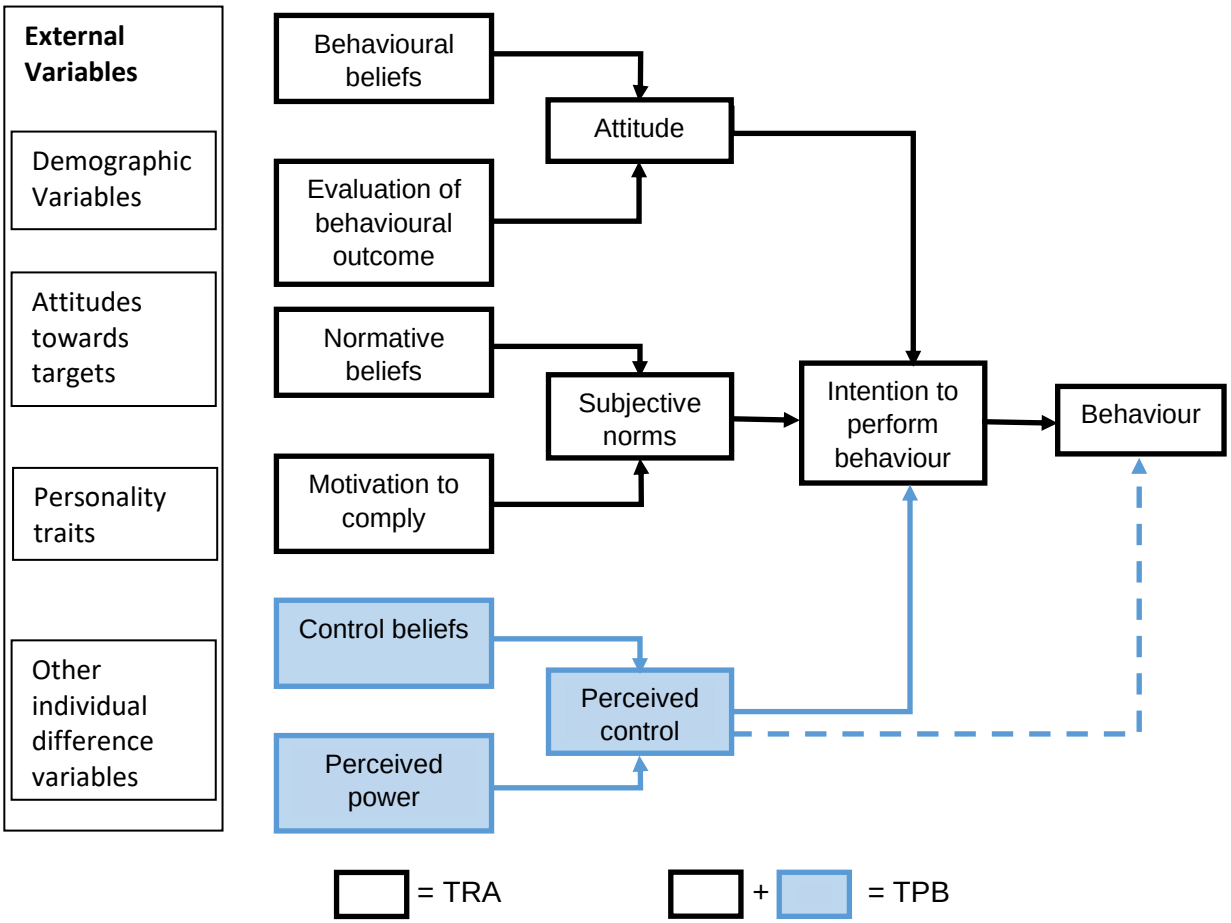


Figure 1.4 Theory of Reasoned Action (TRA) and Theory of Planned behaviour (TPB)

(Adapted from Montano and Kasprzyk (57) and NICE PH6 (52))

1.5.4 Protection Motivation Theory

Protection motivation theory seeks to explain the cognitive processes that occur in response to messages designed to instil fear ('fear appeals') or health threats (49). Figure 1.5 depicts the components of the protection motivation theory. This theory posits that individuals assess the severity of an illness, the probability of the illness without protective behaviour and the availability and effectiveness of coping or protective responses (49). These cognitive appraisals combine multiplicatively to determine 'protection motivation' which stimulates, sustains and motivates action (49). The amount of protection motivation determines the strength of intentions to perform the behaviour (49). Thus, protection motivation theory postulates that when individuals are confronted with a threat to health, two mediating cognitive processes are stimulated; threat appraisal and coping appraisal (53). Similar to the health belief

model, the threat is a function of perceived susceptibility to and the severity of the illness. Coping appraisal is influenced by individuals' perception of the effectiveness of behaviour in protecting them from the illness and whether they feel they are confident to perform such behaviour.

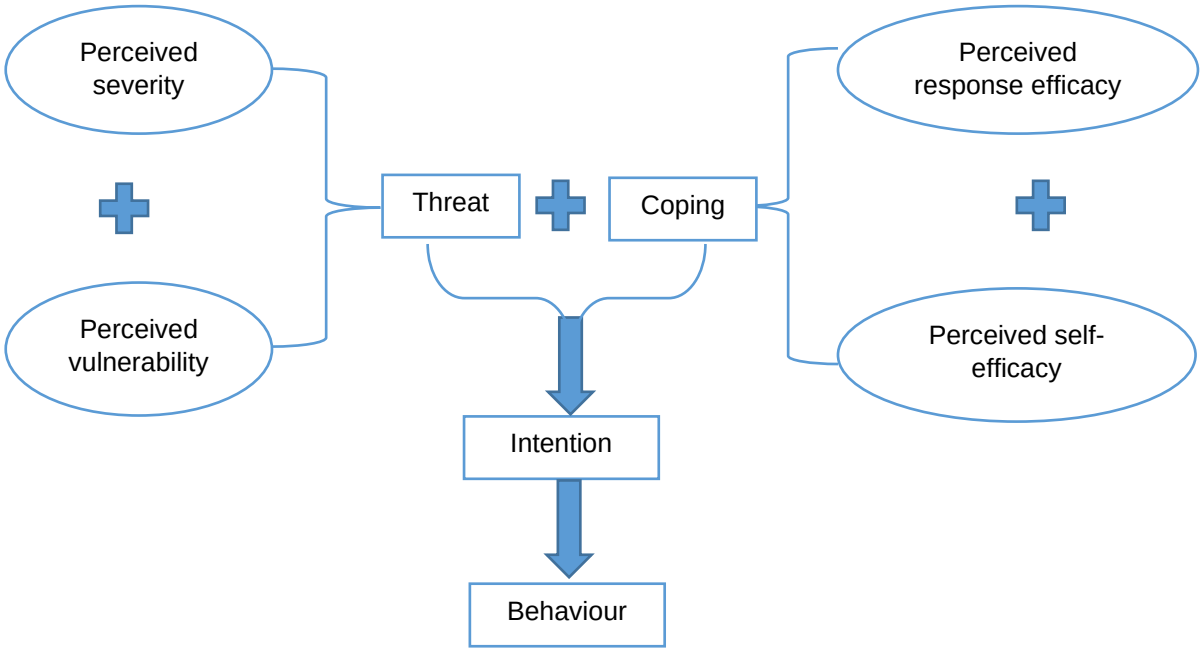


Figure 1.5 Protection Motivation Theory

(Adapted from Easthall 2014, Lee 2007 (53,58))

1.5.5 Transtheoretical Model of behaviour change / Stages of Change

The transtheoretical Model of behaviour change also known as the Stages of Change Model was one of the most frequently used theories accounting for one-third of the studies included in the review of behaviour change theories by Davis et al. (50). A meta-analysis also found that the transtheoretical model was one of the most widely used theories (59). The transtheoretical model was developed in 1983 by Prochaska and DiClemente and was originally related to smoking behaviour (60). The transtheoretical model proposes five sequential stages of behaviour change as shown in figure 1.6 (49,51,60).

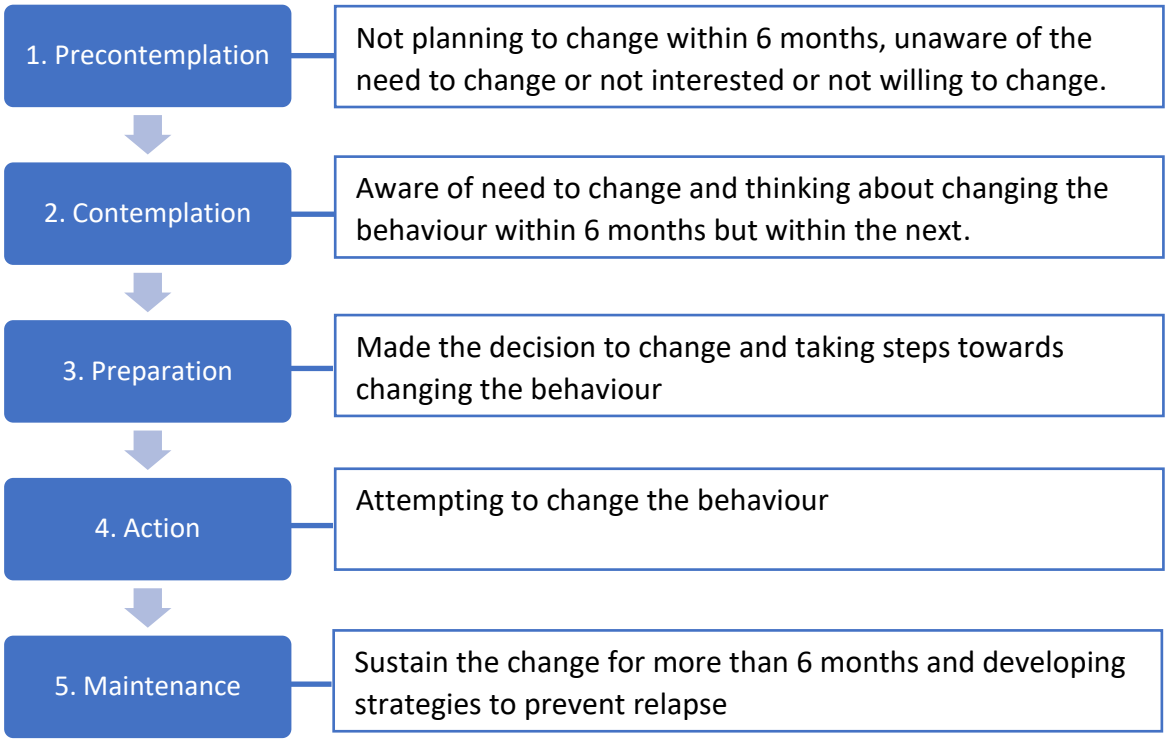


Figure 1.6: Transtheoretical Model of behaviour change

(Adapted from ABC of behaviour change, The World Bank, NICE PH6) (49,51,52)

It is noteworthy that the stages are often not linear, i.e., an individual may move from making a change to the behaviour (e.g., stop smoking for a few days) but may relapse to previous behaviour of smoking and can even move to contemplation or even precontemplation stage.

It often takes many attempts and people move from one stage to another forward or backward stage before successfully changing the behaviour. For example, after missing or skipping medication, a patient can go back to taking them exactly as prescribed but then start missing or skipping or stopping the medication again. This is frequently seen in clinical practice. Thus, some add a 6th stage termed 'Termination' where individuals have 100 percent efficacy and will not relapse, which is the most difficult stage. In reality, most people stay in the maintenance stage (51).

Decisional balance and self-efficacy are two determinants that influence movement between different stages in the transtheoretical model (49). Decisional balance is defined as an evaluation of the pros and cons of behaviour change (49). For an individual, if pros outweigh cons, then change is more likely and vice versa. Self-efficacy is defined as an individual's beliefs about their ability (or confidence) to change

the problem behaviour and the ability to resist the temptation to continue the problem behaviour (49,52).

Ten processes of change have been described which help individual progress through different stages of change in the transtheoretical model. Different processes play an important role in facilitating movement between different stages; for example, experiential processes are used more in the contemplation and preparation stages and behavioural processes are more important in the action and maintenance stages (49). The ten processes are as follows (49,51,52):

I. Consciousness raising - Increasing awareness about the problem or creating new awareness of the problem behaviour.
II. Dramatic relief – Emotional experience about the problem behaviour and the potential change.
III. Environmental re-evaluation – Consideration and assessments of the impact of the behaviour change on the social environment.

The above three processes are mediators between the precontemplation and the contemplation stage.

IV. Self-re-evaluation - Cognitive and emotional assessments of self-image. This process facilitates the progress from the contemplation stage to the preparation stage.
V. Self-liberation - Heightening awareness of alternative behaviour and the individual's belief in their ability to make the change and their personal sense of commitment to act on that belief. This process mediates between the preparation stage and the action stage.
VI. Helping relationships – Open, trusted, and empathic relationships supportive of the behaviour change.
VII. Counter conditioning - Adapting healthier behaviours as substitutes for problem behaviours.
VIII. Stimulus control – Controlling the stimuli or cues in order to make it easier to maintain the desired behaviour and make it difficult to revert to problem behaviour.
IX. Reinforcement management – Rewarding healthy behaviour and punishing unhealthy behaviour or not keeping healthy behaviour.

Processes VI to IX mediates individual move through the action stage to the maintenance stage.

X. Social liberation – Realising the social, policy or environmental changes that support behaviour change. This process can help across all the stages.

1.5.6 Health Action Process Approach

The health action process approach is influenced by other theories such as the health belief model, protection motivation theory, theory of planned behaviour and was developed by Schwazer in 1992 (49). Schwazer states that the "health action process approach is a health behaviour change framework with an open architecture for inclusion of new constructs and relationships" (61). One of the key distinctions between the health action process approach and other models is the idea that the intention to perform the behaviour does not guarantee that the behaviour will occur (61). Figure 1.7 summarises the health action process approach model.

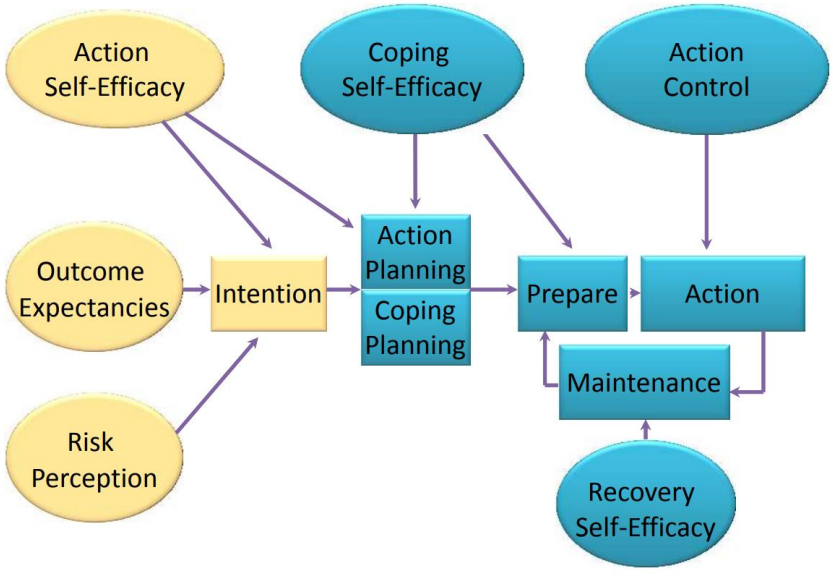


Figure 1.7 The Health Action Process Approach

(Sourced from Ralf Schwarzer (62))

The health action process approach can be divided into following five basic principles (61):

I. Behaviour change can be divided into two phases: motivation and volition. As in other previous models, the motivational phase is influenced by self-efficacy, outcome expectancies and risk appraisal. The motivation phase is characterised by what individuals choose to do while the volition phase describes how hard they try and how long they persist (62).

II. Volition can be subdivided into two groups: inactive (yet to perform the behaviour despite intention) and active (actively performing the behaviour). Thus, three groups of individuals are described in the health action process approach, namely, non-intenders (intention to perform a behaviour is not developed), intenders (inactive) and actors (active).

III. Planning is the key strategy for an individual to turn their intention into behaviour.

IV. Two types of planning are described: action planning (when, where and how to act) and coping planning (how to cope with barriers).

V. Self-efficacy plays an important role in developing intention, planning, and performing the behaviour. However, as shown in figure 1.7, the self-efficacy in each phase differs as the challenges individuals face in each phase differ.

1.5.7 The Information-Motivation-Behavioural-Skills Model

Developed from the field of AIDS prevention, the information-motivation-behavioural-skills model suggests that three independent determinants influence behaviour: information, motivation, and behavioural skills (20,49). Information and motivation mainly moderate behavioural skills to change behaviour but if the behavioural skills are familiar or simple and easy then information and motivation can have a direct influence on behaviour as shown in figure 1.8 (20).

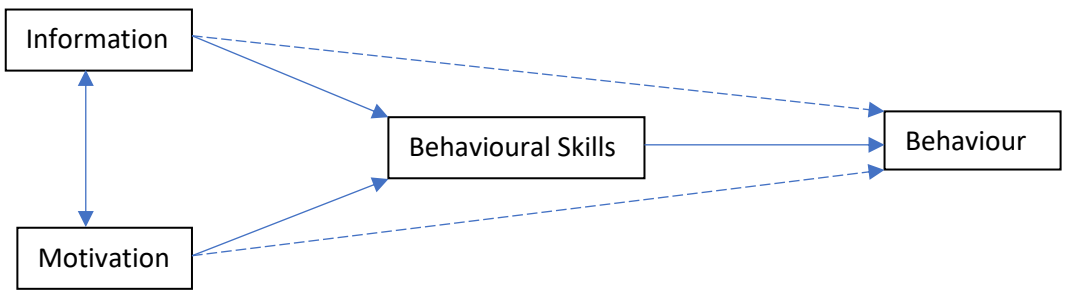


Figure 1.8: The Information-Motivation-Behavioural-Skills Model
(Adapted from WHO 2003 (20))

1.6 Relevance of behaviour change theories to medication adherence

As discussed in section 1.4, medication taking is a health behaviour and thus behaviour change theory can equip us with a better understanding of what may lead to medication non-adherence and what can be done to change non-adherent behaviour. For example, based on the health belief model, we can hypothesise that if patients see their symptoms as not severe or bipolar disorder is not a serious illness, then they may not take their medication. Similarly, if patients do not believe that medication will make them better, this can also lead to medication non-adherence. Such evidence of medication non-adherence in bipolar disorder due to denial of the severity of the illness or effectiveness of treatment is readily available in the literature. Furthermore, understanding the transtheoretical model / stages of change and the processes that facilitates the progress of an individual through different stages can help us target adherence support based on which stage the patient is at. For example, patients not yet willing to take medication for bipolar disorder may benefit from 'consciousness raising' through evidence-based information and 'helpful relationships' will likely support continued medication adherence. According to the health action process approach model, intentions to take medication do not necessarily guarantee that patients take them (61) and barriers such as forgetfulness are regularly quoted as a reason for medication non-adherence despite intentions (18,63).

Many theories of behaviour change have been applied in medication adherence behaviour (20,49-53) although they are relatively small in number in comparison to other fields such as physical activity and tobacco smoking. The health belief model is the most commonly used behavioural theory in the field of medication adherence despite its inconsistent use, limited predictive capacity and lack of 'intentions' construct (52,53,64). Application of theories in the medication adherence field is mainly found in the development of adherence intervention studies. Application of these theories in the development of adherence scales or questionnaires development is scarce. In a systematic review of theory-based interventions to improve medication adherence, Patton et al. found that many studies used a single theory and among them were the social cognitive theory, health belief model and transtheoretical model (65). Similar use of the theory of reasoned action/theory of planned behaviour, protection motivation theory, health action process approach and IMB can be seen in the field of medication adherence (20,49,50,52,66).

For example, Asgari et al. conducted a randomised controlled trial (n = 200) using the health action process approach model to promote medication adherence in rheumatoid arthritis patients (67). In the study, the intervention group received a health action process approach based intervention such as action planning (making detailed plans to follow medication regimen), coping planning (constructing plans to overcome potential obstacles that may arise in medication adherence), and self-monitoring (using a calendar to record medication adherence) with improved medication adherence in the intervention group (67). Another study used the theory of planned behaviour to understand mental health medication adherence and reported that adherence over a nine-week period was explained by intentions and perceived behavioural control (38.1% variance explained) (44). In the study, intentions to take medication were explained by attitudes, subjective norms, and perceived behavioural control (65.0% variance explained) (44). Beliefs about outcomes, normative pressure and control factors reliably distinguished high and low intenders and the authors argue that the theory of planned behaviour may form a useful basis for interventions to increase adherence (44). However, the application of behaviour change theories in mental health medication adherence is extremely low compared to physical health medication.

Owing to the importance of behaviour change theories, there is a broad consensus that behaviour change theories should be used to better understand health behaviour and to develop interventions to change health behaviour (49). NICE recommends that adherence interventions should be developed using an appropriate theoretical framework (21). Similarly, UK Medical Research Council's guidance for developing and evaluating complex interventions also emphasises the importance of using appropriate theory in developing interventions (48).

1.7 Commonalities and differences between different theories and limitations of behaviour change theories

Many behaviour change theories have overlapping elements, but each has its unique constructs too. Thus, the use of one theory to understand or change behaviour may leave some important determinants not covered by that theory.

For example, self-efficacy is unique to social cognitive theory although other theories have added this construct at later dates (55). The triadic reciprocal determinism, another unique feature of social cognitive theory, is described as the person, the environment and the behaviour interacting to influence each other. However, there are several limitations to the social cognitive theory (55): the assumption that changes in the environment will lead to changes in individual may not always be borne out, lack of important constructs such as emotion and motivation (except through past experiences), broad reaching so difficult to operationalise. The health belief model's 'perceived threat' construct differs from all others contained in the theory of reasoned action/theory of planned behaviour and the transtheoretical model (52). The updated health belief model also includes socio-demographic and other variables such as cues to action not included in most other models' specifications (52). However, the main components of the health belief model are found to have weak effect sizes, and its predictive capacity is limited compared to that of other social cognition models (52). The health belief model is also criticised for its emphasis on the individual rather than social and environmental factors and lack of other constructs such as emotion (53) and intentions.

Similarly, the health action process approach is unique in bridging the gap between intentions and behaviour which is not captured in most others. But the health action process approach failed to stipulate the role of social and environmental factors (53) although the later updated model includes barriers and resources including social support (62). States of change and processes of change components in the transtheoretical model distinguish it from others (52). The health belief model, protection motivation theory, health action process approach and the information-motivation-behavioural-skills model are health behaviour focused whereas the theory of reasoned action/theory of planned behaviour is framed at higher levels of generalisation and thus can be applied outside the health sphere (52). Some argue that the theory of reasoned action/theory of planned behaviour is better specified and more parsimonious in design which may enhance the efficiency and consistency of their use (52). Most theories focus on initiating the healthy behaviour but the social cognitive theory, the transtheoretical model and the health action process approach also consider the maintenance of the behaviour (52,55,61). For example, the social cognitive theory explains how people regulate their behaviour through control and reinforcement to achieve goal-directed behaviour that can be maintained over time

(55) whereas maintenance is explicitly included in the transtheoretical model and the health action process approach model. Despite the initiation of the behaviour, better health outcome is unlikely or negligible if the behaviour is not maintained; thus this aspect is important.

Most theories cover a limited number of constructs or elements of behaviour change (49). Those most widely used theories used to predict or explain health behaviours tend to focus on beliefs rather than emotion or habits (49). So, if a behaviour under investigation is fundamentally under the influence of habitual or emotional factors then a theory that focuses exclusively on beliefs and reflective thought processes may not be appropriate (49). They also tend to focus on intra-individual and sometimes interpersonal and pay less or no attention to broader social and environmental factors (49) which may be more or equally important, particularly in the context of medication adherence (18,63).

Despite the significant importance of theory in understanding and changing behaviour (21,48), there is little guidance on how to choose an appropriate theory for a particular purpose (49). The result is often a selection of theory based on personal preference or fashion (49). The application of theory is further complicated by considerable differences in how a construct is conceptualised. For example, a narrative review of the construct of ‘control’ identified more than 100 conceptualisations (49,68).

The complexity of different theories, their overlapping concepts or exclusion of concepts, different conceptualisations of the same construct, and difficulty in choosing appropriate theory limits their use in the wider field beyond theoretical psychology (49,53). Furthermore, many theories and models explain and predict behaviour but pay very little focus on techniques to modify it, making it poor usability (49,53). For behaviour change interventions to be widely theoretically based and therefore better designed behaviour change theories need to become more accessible to researchers in the wider field who are not necessarily adept at psychology (69). It is also clear that each theory has its unique value but on its own is not enough to explain the behaviour comprehensively. Moreover, theories may contain similar or identical constructs but may use different terminology due to the lack of consensus on what to call certain constructs leading to fragmented literature (70). Theoretical integration has been proposed to address these challenges (70).

In the last two decades, novel work has emerged which aims to address these deficits and provide a theoretical framework for the models of behaviour and integrate the models to form a singular, definitive model comprised of the core constructs of behaviour (53).

1.8 Theoretical frameworks of individual behaviour change

Integrative Models of Behavioural Prediction, also known as the Fishbein Framework (71), and the Theoretical Domains Framework (TDF) (69,72) are two theoretical frameworks that have emerged over the last two decades or so. These theoretical frameworks pool the different models of behaviour and identify common domains to form a scaffold for identifying individual patient barriers to behaviour change (53). Therefore, these frameworks are the logical mediators in understanding theories of behaviour and developing a theory-based medication adherence intervention (53).

1.8.1 Integrative Models of Behavioural Prediction

Fishbein's Integrative Model of Behavioural Prediction is an integration of theories of behaviour change that aims to provide a theoretical basis for the design of behaviour change interventions (49). Developed in the context of HIV prevention, the model is presented in figure 1.9 below.

According to the model, intentions to perform a behaviour (e.g., to take medication as prescribed), environmental constraints preventing that behaviour (e.g., medication not being available at the time of the dose) and skills facilitating the performance of the behaviour (e.g., being competent to open the pill box and take them as directed) are the primary determinants of that behaviour (49,71). So, if intentions are strong, environmental constraints are minimal and skills are present, the probability of the behaviour occurring is high (49,71). However, despite strong intentions, behaviour may not occur due to a lack of skills and/or the presence of environmental constraints (49).

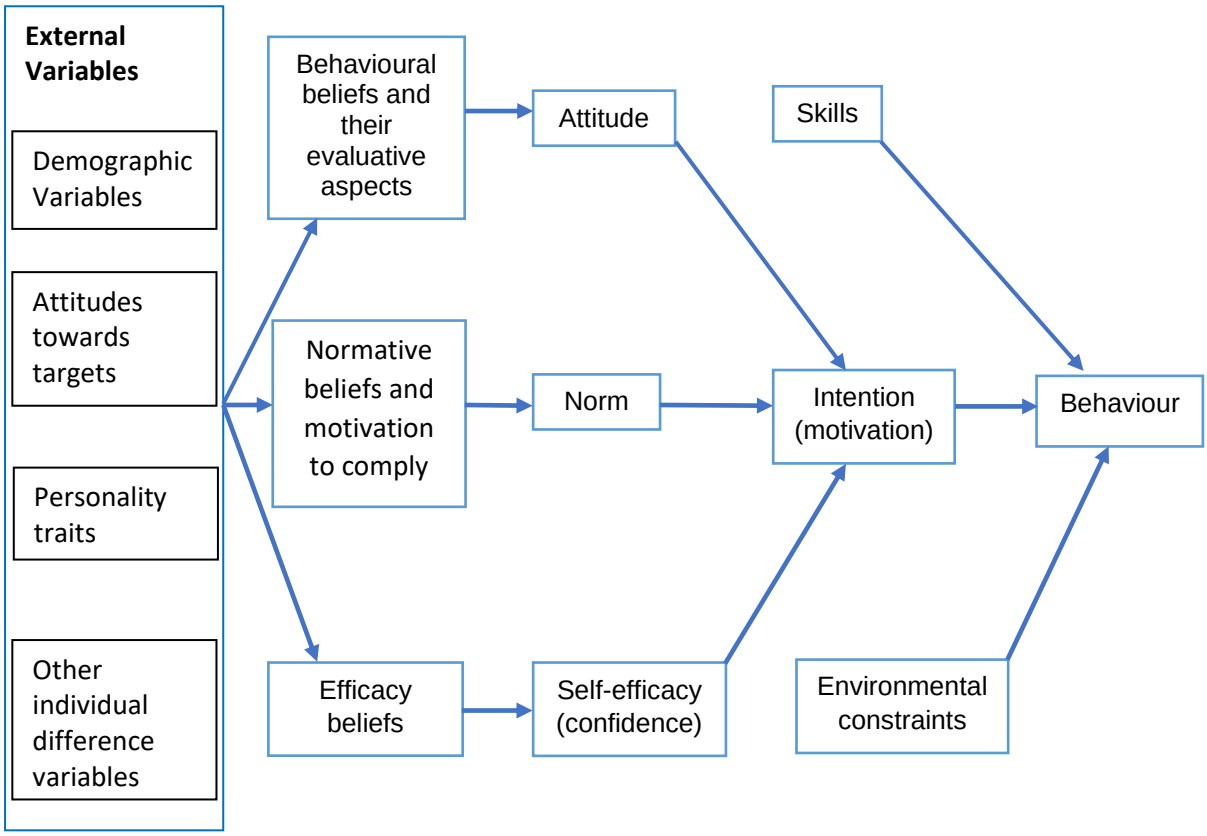


Figure 1.9 The Integrative model (Sourced from Fishbein (71))

As shown in figure 1.9, intentions are influenced by attitudes, perceived norms, and self-efficacy (confidence). Attitude in turn, is based on an individual's beliefs on whether the behaviour's advantages will outweigh its costs (52). The perceived norm is influenced by normative beliefs and their motivation to comply with them. Normative belief has two aspects; individuals' perceptions of what others think they should do and their perception of what others are doing about the behaviour (49). Self-efficacy refers to a person's beliefs/confidence about whether they can perform the behaviour, even under difficult circumstances (49). Positive attitudes, alignment of perceived norms to carry out the behaviour and greater self-efficacy will result in stronger intentions or commitment to perform the behaviour (49). The model also includes several external variables (see figure 1.9) that indirectly influence behaviour, which is proposed to play a role in shaping beliefs about specific behaviours (49). Fishbein and colleagues used a consensus approach to arrive at these domains, but precise methodological details could not be found (53). The lack of important determinants of medication adherence, such as emotion, is also apparent. The Integrative Model

represents a useful foundation for collating health behaviour models, but not comprehensive enough, may not be sufficient to provide a fully accessible and widely used tool (53).

1.8.2 The Theoretical Domains Framework (TDF)

The TDF was developed in 2005 in response to the limitations of individual theories, difficulty in selecting an appropriate theory among many overlapping theories and inaccessibility of behaviour change theories outside of psychology (49,69,72). The original TDF (69) was developed by an international panel of 32 behaviour change experts who assimilated 128 explanatory constructs from 33 behaviour change theories and simplified them into 12 behavioural domains (49). The TDF was originally developed in the context of professional behaviour change but has later been adopted for patient health behaviours (49). The TDF was later refined and validated in 2012 by an international panel of 36 experts in behaviour change (72). The detailed methods of the development of the original TDF and refinement are provided by Michie et al. (69) and Cane et al. (72), respectively. The refined TDF contained 84 constructs (complex ideas or concepts formed from a synthesis of simpler ideas) across 14 domains (49,72). The TDF domains, their definitions and constructs within the domains are detailed in table 1.1 below:

Table 1.1: TDF Domains, Definitions and Constructs

(Sourced from Atkins et al. (73)**)**

Behavioural domain of the TDF	**Definition of the domain**	**Constructs within the domain**
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	Outcome expectancies Chars. of outcome expectancies Beliefs 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
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 Trans. model/stages of change [b] (pre-contemplation, contemplation, preparation, action, maintenance, relapse)
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 Barriers and facilitators Organisational culture /climate Person x environment interaction Salient events/critical incidents
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 Intergroup conflict Power Group identity Alienation 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	Anxiety Fear 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

*New domains from TDF 2012

The TDF was refined in 2012 following a comprehensive three-step validation process: identification of the domains, the establishment of the domain content, and finalising the domain labels (72). Key changes in the refined version Further refinements to the TDF are summarised in table 1.2.

Table 1.2 Summary of key changes to updated TDF (72)

Nature of change	Rationale
'Motivation and goals' domain separated into 'intentions' and 'goals'	Domain split to differentiate between 'goals' which focus on a preferred outcome or end state and 'intentions' which concern the resolve to initiate or terminate a behaviour.
'Beliefs about consequences' domain split into two domains, one retaining the original name and one termed 'reinforcement'	Domain split to differentiate between 'reinforcement' which focuses on the constructs of associative learning and 'beliefs about consequences' which focuses purely on beliefs.
'Beliefs about capabilities' domain split into two domains, one retaining the original name and one termed 'optimism'	Domain split to differentiate between 'optimism' which concerns a general disposition and 'beliefs about capabilities' which focuses on specific capabilities
'Behavioural regulation' domain clarified	Clarification enables focus on self-regulatory processes
'Nature of the behaviours' domain removed	Analysing the nature and influences of behaviour are two distinct processes

The integrative model by Fishbein and the TDF are relatively similar, but the TDF includes additional domains: 'Knowledge', 'Memory, attention and decision processes', 'Optimism', 'Goals', 'Emotion' and 'Behavioural regulation'. The additional domains may be reflective of the wider group of expertise employed in the development of the TDF but could also be due to the advancement in the research since Fishbein's work (53,69).

Use of TDF in medication adherence

Both versions of the TDF have been cited over 1500 times and have been widely used to understand a range of different health behaviours such as fruit and vegetable intake, smoking cessation, hand hygiene among healthcare professionals, management of lower back pain by physiotherapists, prevention of childhood obesity etc (49). Another new but growing area of research using the TDF is medication adherence albeit mostly in physical health medication. For example, a systematic review of medication adherence in hypertension mapped the determinants of adherence to the TDF and suggested that the TDF domains 'beliefs about capabilities', 'beliefs about consequences', 'environmental context and resources', and 'social influences' were important in antihypertensive adherence (74). Another study of medication adherence in chronic kidney disease mapped the determinants of non-adherence to the TDF (75).

The TDF has also been used to match adherence interventions to the patient's determinants of adherence (76).

Strengths and limitations of the TDF

Cane et al. list three key advantages of the TDF (72): comprehensive coverage of possible influences of behaviour; clarity about each kind of influence due to each domain being specified by component constructs; and the links between the TDF domains and behaviour change techniques (BCTs) to address implementation problems. The TDF has assimilated common and overlapping constructs from 33 behaviour change theories assuring its comprehensiveness. Each TDF domain is clearly defined, and constructs are clear and consensually agreed upon by international experts in behaviour change thus increasing its accessibility to researchers outside of the behaviour science field. Each TDF domain is coupled with BCTs (77) which significantly increases its utility.

A BCT is defined as an observable, replicable and irreducible component or an active ingredient of an intervention designed to change behaviour and can be used on its own or in combination with other BCTs (78,79). The BCT taxonomy v1 (80) is a consensus-based taxonomy of BCTs for reporting intervention content (81). Ninety-three BCTs, grouped into 16 categories, from the BCT taxonomy v1 were examined for their mapping to the TDF domains by 18 behaviour change experts who took part in (78,79,82) developing BCT taxonomy v1 (81). Fifty-nine BCTs were successfully linked to the TDF domains (81). For example, the BCT group 'Goals and planning', which includes BCTs such as 'Action planning', 'Behavioural contract', 'Commitment' etc., are mapped to the TDF domain 'Intentions' (80,81). Similarly, the BCT group 'Regulation' which includes BCTs such as 'Pharmacological support', 'Reduce negative emotions', 'Conserving mental resources', is linked with the TDF domain 'Emotion' (80,81).

Effective BCTs have been identified in many areas of health behaviour such as physical activity and healthy eating, smoking cessation, changing professional behaviour and medication adherence (78,79,82). For example, BCTs such as 'Motivational interviewing', 'Restructuring the physical environment' (by

simplifying/individualising medication regimen etc.) and 'Prompts/cues' have been shown to improve medication adherence (82).

1.9 Using the TDF to develop a questionnaire to identify medication adherence determinants in bipolar disorder

"Poor adherence to treatment of chronic diseases is a worldwide problem of striking magnitude. Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments." World Health Organization, 2003 (20)

And yet, progress with medication adherence to date has been modest (83,84). The challenges to successfully addressing non-adherence are three-fold (47):

I. Accurately identify medication non-adherence
II. Determine an individual's determinants of medication adherence
III. Select the most appropriate individualised adherence intervention(s) underpinned by health psychology theory and empirical evidence

First, healthcare professionals need to be able to identify medication non-adherence accurately and easily in regular clinical practice. Different measures to identify medication non-adherence have been discussed in section 1.3 above. Historically, medication non-adherence tends to be addressed using the 'One-size-fits-all' approach by focussing on patient education, medication side effects, treatment choice etc (14,21,85). Some recommend using 'SIMPLE' strategy to improve adherence: **S**implify regimen, **I**mparting knowledge, **M**odifying health beliefs, **P**atient communication, **L**eaving bias and **E**valuation (86). However, decades of research inform us that most adherence efforts so far had little success (21,39,83).

So, the second challenge is to establish the reasons for medication non-adherence. Thus, a systematic way underpinned by health behaviour theory to identify determinants of adherence pertinent to individual patients is essential. Only then we would have a better chance of addressing the 3rd challenge by designing and developing patient-tailored adherence support based on the individual's determinant of medication adherence. NICE highlights the need to understand the reasons for medication non-adherence (21).

No gold standard exists for identifying and addressing determinants of medication non-adherence in the mental health population, including bipolar disorder. A systematic review of self-report medication adherence scales identified 43 adherence scales (87). The systematic review excluded five adherence scales due to lack of development or validation studies or lack of full text or lack of comparison measures (87). Table 1.3 provides a list of the nine adherence scales that have been validated in populations with mental health problems.

Table 1.3: Medication Adherence Scales in Mental Health (87)

Adherence Scales	**Validated in**	**Based on**	**No. of Questions**
Adherence Starts with Knowledge - 20 (ASK-20)	Depression	Literature review, patient focus groups and expert input	20
Beliefs about Medicines Questionnaire (BMQ)	**Bipolar disorder, Depression and Schizophrenia or related disorder**	**Health Belief Model and Patient Beliefs**	**18**
Brief Adherence Rating Scale (BARS)	**Bipolar disorder and Schizophrenia or related disorder**	**Drug trial**	**4**
Brief Evaluation of Medication Influences and Beliefs (BEMIB)	**Bipolar disorder, Depression and Schizophrenia or related disorder**	**Health Belief Model and Patient / Investigator feedback**	**8**
Drug Attitude Inventory (DAI)	Schizophrenia or related disorder	Literature review and patient report	30
Medication Adherence Assessment Tool (MAAT)	Schizophrenia or related disorder	Literature review and Expert healthcare professionals	12
Medication Adherence Rating Scale (MARS)	**Bipolar disorder, Depression and Schizophrenia or related disorder**	**Medication Adherence Questionnaire, and Drug Attitude Inventory**	**10**
Medication Adherence Report Scale - 5 (MARS - 5)	**Bipolar disorder and Schizophrenia or related disorder**	**Medication Adherence Report Scale - 10 (MARS - 10) (different from MARS and mainly used in Asthma)**	**5**
Reported adherence to medication scale (RAM)	**Bipolar disorder, Depression and Schizophrenia or related disorder**	**Literature review**	**4**

Note: Bold are validated in bipolar disorder

Six of these are validated in bipolar disorder as shown above in table 1.3 (87)**.** However, there were some consistent limitations of these scales (87):

- Most scales focus on measuring the behaviour, i.e., the extent of stopping or missing doses and very little on determinants of adherence.
- Most scales ask patients to report whether they have been taking their medication or how often they miss or skip. This can lead to self-reporting and recall bias as well as white coat adherence and therefore over-estimation of adherence (88-95).
- Limited feasibility and acceptability work with end users, i.e., patients and healthcare professionals during the development of these scales are reported.
- Lack of focus on deriving the content of the scale based on extensive work with patients limits the face and content validity.
- Lack of patients' families and friends' involvement in the scale development is evident and thus their perspective on the determinants of medication adherence has not been captured. Patient's families and friends are often pivotal in managing medicines for patients with mental health problems. Adequate social support, including patients' families and friends' support, is a key factor influencing medication adherence in physical health problems (96). The role of the patients' families and friends is likely to be even more important in bipolar disorder.
- Most scales are decades-old; therefore, uses literature review instead of a more robust systematic review and thus may have missed important studies and determinants of adherence, raising a question about content validity.
- Most scales development is not underpinned by behaviour change theories and none reflect the significant advances made in behavioural science such as the Theoretical Domains Framework (TDF).
- Use of scales is limited to research and rarely used in clinical practice.

The systematic review highlighted the need for a scale or questionnaire that is feasible to administer, acceptable to patients, identifies non-adherence and practical and perceptual factors negatively influencing medication adherence (87). In addition, the need for *"primary research involving theory as a central component of intervention development"* has been highlighted by a recent systematic review of theory-based interventions to improve medication adherence (65). TDF is a very useful approach

to assessing implementation and other behaviour problems and laying the foundation for theoretically informed interventions (72).

The TDF has been used to develop a questionnaire to identify barriers to medication adherence (46). In a study, Easthall et al. pooled literature reported modifiable determinants of medication adherence and mapped them to the TDF domains (46). The domains and determinants were then discussed in patient focus groups to better understand their interpretation of the determinants, to ensure TDF mapping is correct and to identify any barriers not reported in the literature (46). The authors then developed a questionnaire called 'The Identification of Medication Adherence Barriers Questionnaire (IMAB-Q)' to identify non-adherence to cardiovascular medication and their barriers (53). Each IMAB-Q question is linked to the TDF domains. Unlike other scales mentioned above, the IMAB-Q does not ask patients whether or not they are taking their medicines. Instead, it gives them a short list of things that might stop them from taking their medicine and asks them if they have any of these problems. The IMAB-Q has been tested and validated in 608 patients taking cardiovascular medications (47).

However, its development and validation did not include the mental health population and their families and friends. So, it may or may not be right for patients with bipolar disorder. Determinants of medication adherence in the mental health population particularly, in bipolar disorder, may be different. For example, stigma, denial of illness, social support may be more pronounced. Patients with mental health illness should be provided with the same opportunities as people with physical health problems. Hence, this thesis is primarily focused on developing a questionnaire to investigate individuals' determinants of medication adherence in bipolar disorder. Since the development of IMAB-Q, which used the original TDF with 12 domains, the TDF has been refined and updated with 14 domains. This thesis will take this into account and will use updated TDF with refined constructs and extended behavioural domains.

Modifiable determinants and corresponding statements for the questionnaire will be mapped to the 14 TDF domains. Mapping modifiable determinants to their relevant TDF domains enables the determinant also to be linked to evidence-based behaviour change techniques. The modest improvements in adherence achieved from many adherence interventions are due to the lack of systematic theory underpinning intervention planning and modelling (21). NICE recommends that health behaviour

change interventions should incorporate accurate identification of barriers to change and that medication adherence interventions should be grounded in empirical evidence and theory (52). Furthermore, the Medical Research Council Guidelines on intervention development strongly recommend the incorporation of theory into interventions (48). The use of the TDF to underpin the development of an adherence questionnaire fulfils these recommendations from NICE and Medical Research Council.

1.10 Plan of research

The research project is named 'Collaborative Medication Adherence in Bipolar disorder (C-MAB)'. This research aimed to develop and test a questionnaire for patients with bipolar disorder which will identify non-adherence and, more importantly, establish their individual determinants of non-adherence. The questionnaire is called 'Collaborative Medication Adherence in Bipolar disorder Questionnaire (C-MABQ)'.

This thesis uses the terms 'questionnaires' instead of 'scales' or 'tools' for easy understanding by patients and their families and friends, as recommended by patients and their families and friends' representatives on the Research Advisory Board.

1.10.1 Objectives

The objectives of this research, with respect to patients with bipolar disorder, are:

I. Describe the determinants of medication adherence reported in the literature and map these determinants to TDF domains (Chapter 2)
II. Refine and prioritise the determinants from the patient and their families' and friends' perspectives and explore any new determinants not reported in the literature (Chapter 3)
III. Develop a questionnaire to identify non-adherence and individuals' determinants of non-adherence (Chapter 4)
IV. Evaluate the questionnaire in patients with bipolar disorder and report psychometric properties (Chapter 5)

While the questionnaire developed may be appropriate for use in a wide variety of mental health illness, the rationale for focusing on bipolar disorder for the development

and validation of the questionnaire is to: reduce heterogeneity at the validation stage; target a therapeutic area associated with significant disability, functional impairment and NHS resource use; and make use of a nationally recognised patient database held by NSFT.

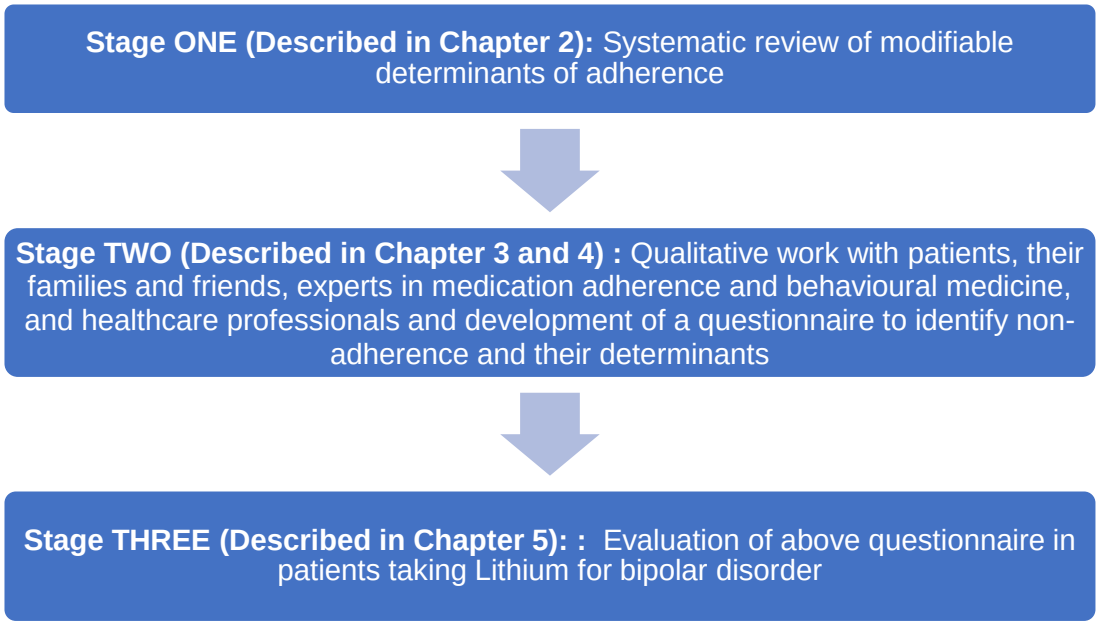
1.10.2 Three stages of the research

The best practice guidelines for developing and validating questionnaires for health and behavioural research outline three phases: the development of items for the questionnaire, the development of the questionnaire and the evaluation of the questionnaire (97). These three phases are further divided into nine steps as listed below (97):

I. Identification of Domain and Item Generation: Selecting which items to ask
II. Content Validity: Assessing if the items adequately measure the domain of interest
III. Pre-testing Questions: Ensuring the questions and answers are meaningful
IV. Survey Administration and Sample Size: Gathering enough data from the right people
V. Item Reduction: Ensuring the questionnaire is parsimonious
VI. Extraction of Factors: Exploring the number of latent constructs that fit observed data
VII. Tests of Dimensionality: Testing if latent constructs are as hypothesised
VIII. Tests of Reliability: Establishing if responses are consistent when repeated
IX. Tests of Validity: Ensuring the questionnaire measures the latent dimension as intended

The thesis broadly followed the best practice guideline in developing and evaluating C-MABQ. There are three stages to this research as shown in figure 1.10 below:

Figure 1.10: Three stages of this research project



The research explicitly focussed on modifiable determinants of medication adherence in bipolar disorder as they can be modified by the patient or their families and friends or healthcare professionals to improve adherence. Definitions and examples of modifiable determinants are provided in Chapter TWO. Details of the method for each stage and study are described in respective Chapters.

Stage ONE is detailed in Chapter TWO and covers the first objective of this research. During this stage, a systematic review was undertaken to identify modifiable determinants of medication adherence in bipolar disorder. These determinants were then mapped to the TDF domains.

Stage TWO covers the 2nd and 3rd objectives of the research. It includes four studies and is detailed in Chapters 3 and 4 as below:

I. Focus group discussion and individual interviews with patients and their families and friends - As per 2nd objective of the research, the modifiable determinants from stage ONE are explored further with patients and their families and friends in focus group discussions and individual interviews. This qualitative work was carried out to refine and prioritise the literature reported modifiable determinants and to identify any other determinants not reported in the literature.

II. Development of a questionnaire - For the 3rd objective, a questionnaire to identify non-adherence and their determinants was developed in collaboration with experts in medication adherence and behavioural medicine.
III. Consultation of the questionnaire with healthcare professionals - The questionnaire was then consulted with healthcare professionals for face and content validity to fulfil 3rd objective of the research.
IV. Cognitive interviews with patients - After incorporating feedback from the consultation, the refined questionnaire was tested for its face validity with patients using cognitive interviews.

Stage THREE is described in Chapter 5 and covers the 4th objective. The questionnaire was evaluated using paper and electronic survey methods with 325 patients taking Lithium for bipolar disorder and re-tested with 100 patients. Mokken Scale Analysis (MSA), a non-parametric item response theory, was carried out. Descriptive statistics, construct and criterion validity, internal consistency reliability and test-retest reliability are presented.

1.11 Patient and Public Involvement in this research

This research project stems directly from discussions with mental health patients and their families and friends. Mental health patients and their families and friends at various meetings (including in my clinical practice and at various patients and representatives' forums) indicated to me that they did not recall any specific discussions with their healthcare professionals regarding whether they had been taking their medication as prescribed. Consequently, some formed the opinion that medication adherence was not essential and unimportant to healthcare professionals. This and my own experience of seeing the revolving door patients (patients who keep coming back to the hospital with relapse) frequently led me to think about the extent to which non-adherence may be contributing to readmissions.

The PPI has therefore identified that overt assessment of medication adherence is lacking and patients feel that they are not currently receiving individualised support for adhering to their medications. When asked about barriers to medication adherence and how best to overcome these, one patient said, “Some days I’m just not motivated to take my pills, but a reminder (e.g., a text) would have made the difference.” This suggested a personalised approach was needed.

Having identified the research goals, I worked with patients and their families and friends, in addition to psychiatrists and academics, to design the research. Patients and their families and friends were members of the Research Advisory Board and had been attending regular team meetings. They have played a significant role in designing this research. They suggested key changes to the planned research; for example, initially, I intended to involve only patients in the focus groups to explore determinants of adherence. However, a family member recommended that families and friends' views should also be considered since they are often heavily involved in the management of medications for mental health patients. Additionally, patients suggested that in addition to focus groups, individuals should also be offered an individual interview as some patients may not feel comfortable discussing it in a group. They have also helped me by reviewing communication materials for patients and their families and friends such as participant information leaflets and consent forms, to ensure the appropriateness of terminology, clarity and user-friendliness.

1.12 Research Advisory Board

From the outset of the research project, a Research Advisory Board was established with the following members:

- Asta R Prajapati (AP), Consultant Pharmacist at Norfolk and Suffolk NHS Foundation Trust and PhD Student at University of East Anglia, UK.
- Prof. Debi Bhattacharya (Primary Academic Supervisor), Professor of Behavioural Medicine, University of East Anglia (now at University of Leicester), UK.
- Dr Allan Clark (Secondary Academic Supervisor), Associate Professor of Statistics, University of East Anglia, UK.
- Dr Alexandra Dima (Secondary Academic Supervisor), Miguel Servet Senior Researcher, Barcelona, Spain.
- Dr Jo Taylor (Secondary Academic Supervisor), Lecturer in Applied Health Research, University of York, UK.
- Dr Jon Wilson (Clinical Supervisor), Research Director and Consultant Psychiatrist, Norfolk and Suffolk NHS Foundation Trust / University of East Anglia, UK.

- Dr George Mosa (Clinical Supervisor), Consultant Psychiatrist, Clinical Supervisor, Devon Partnership NHS Trust, UK.
- Dr Chris Sidney-Gibbons, Associate Professor and Deputy Chair, Director, MD Anderson Center for INSPiRED Cancer Care, USA.
- Prof Fujian Song, Professor in Research Synthesis, University of East Anglia, UK.
- Claire, PPI Representative
- James, PPI Representative
- Sherise, PPI Representative
- Mandi, PPI Representative
- Mary, PPI Representative
- John, PPI Representative

The roles and responsibilities of the Research Advisory Board are to:

- Provide advice and recommendation to me and my supervisors on the conduct of the research
- Provide academic, clinical and logistical support to conduct the research project
- Encourage patients and their families and friends' involvement in the research
- Attend a bi-annual meeting to keep updated on the research

1.13 Funding

I was funded by the National Institute of Health Research (NIHR) as a part of the Clinical Doctoral Research Fellowship program. Full funding details are available at https://fundingawards.nihr.ac.uk/award/ICA-CDRF-2017-03-054. The letter of intent to fund the research and the letter of support from NSFT are provided in Appendices 1.1 and 1.2.

CHAPTER TWO

Identification of modifiable determinants of adherence in bipolar disorder and mapping these determinants to the Theoretical Domains Framework (TDF)

This chapter is derived from the study registration and the following publications:

- Asta Prajapati, A., Scott, S., Song, F., Wilson, J., Mosa, G., Dima, A., Bhattacharya, D. (2018). A systematic review of the modifiable barriers and facilitators of medication adherence in bipolar disorders. PROSPERO 2018 CRD42018096306. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018096306
- Prajapati, A. R., Dima, A., Clark, A. B., Gant, C., Gibbons, C., Gorrod, R., . . . Bhattacharya, D. (2019). Mapping of modifiable barriers and facilitators of medication adherence in bipolar disorder to the theoretical domains framework: A systematic review protocol. *BMJ Open,* 9(2). doi:10.1136/bmjopen-2018-026980
- Prajapati, A., Dima, A., Mosa, G., Scott, S., Song, F., Wilson, J., & Bhattacharya, D. (2021). Mapping modifiable determinants of medication adherence in bipolar disorder (BD) to the theoretical domains framework (TDF): A systematic review. *Psychological Medicine, 51*(7), 1082-1098. doi:10.1017/S0033291721001446

2.1 Introduction

Chapter ONE described behaviour change theories and their relevance to health behaviour. This chapter will focus on the modifiable determinants of medication adherence and their mapping to the Theoretical Domains Framework (TDF). For the purpose of this study, modifiable determinants are defined as “any determinants (barriers or facilitators) of medication adherence that can be modified by the patient, their families and friends, or the prescriber within a short timeframe (days or weeks) to improve adherence.” A barrier is “a circumstance that prevents the patient from taking their medication as prescribed”, whereas a facilitator is “a circumstance that makes the process easy or easier” (98).

The problem of non-adherence and its clinical and economic consequences have already been discussed in Chapter ONE. Efforts to date to improve medication adherence have had marginal effects (46,83). As described in Chapter 1, one of the key challenges to support adherence is to establish individuals’ determinants of adherence. However, there are no validated tools for comprehensively eliciting from patients their individual determinants of adherence to their prescribed medication for bipolar disorder. There is also an absence of theory and evidence-informed guidance for practitioners to work with patients in selecting the most effective interventions for identified determinants. In order to generate such a tool, there is, therefore, a need to synthesise the available evidence regarding determinants of medication adherence in patients with bipolar disorder.

Some evidence syntheses report determinants of adherence to mental health treatment, but they do not clearly distinguish between those that are modifiable, such as difficulty in remembering to take medication and non-modifiable, such as age and gender that have no related specific evidence-based behaviour change techniques (76). Such distinction is vital to allow adherence interventions to target modifiable determinants.

Furthermore, any differences between the perspective of healthcare professionals and patients on the determinants of medication adherence require exploration. Healthcare professionals are the treatment experts, but patients are the experts of their lived experiences. Their goals, priorities and knowledge of the situation may differ. Thus, healthcare professionals and patients may see the determinants of medication

adherence differently (39,99). Exploring such differences will help design adherence support based on the patient's needs.

A recent systematic review (literature search restricted to 1990 - 2015) of adherence to antipsychotic medication in bipolar disorder and schizophrenia has provided a good overview of the likely barriers experienced by people with bipolar disorder (63). However, it failed to explore factors that might facilitate adherence and excluded studies involving medication other than antipsychotics. It, therefore, did not identify determinants of adherence to Lithium and other mood stabilisers. This is a significant omission as Lithium is considered the gold-standard first-line treatment for bipolar disorder (7,10,11). The determinants of adherence may differ among patients taking Lithium relative to other antipsychotics due to various factors, including regular blood test requirements of Lithium, dietary restrictions and significant interactions with other medications. Furthermore, the review does not delineate modifiable from non-modifiable determinants, which lack specific behaviour change techniques (BCTs) (77).

Additionally, the lack of behavioural theory underpinning the evidence synthesis in medication adherence in bipolar disorder (39,63,100) is of concern given its importance for informing intervention design and implementation (48,52). A literature review matching adherence intervention to determinants of adherence concluded that adherence interventions are often incongruent with the modifiable determinants of adherence (76). The TDF detailed in Chapter 1, therefore, offers an appropriate theory for underpinning an evidence synthesis of modifiable determinants of adherence as it will enable determinants to be linked to evidence-based BCTs. This, in turn, will inform the development of an adherence intervention to support practitioners and patients to work together in identifying an individual's key determinants of adherence and select the most appropriate evidence-based interventions.

Thus, a systematic review of modifiable determinants of all treatment options in bipolar disorder underpinned by a theoretical framework and without the date restrictions and limits of the previous systematic review is needed. This systematic review aimed to identify literature reported modifiable determinants of medication adherence in bipolar disorder from the perspectives of the patient and their families and friends and health care professionals and map those determinants to the TDF domains.

2.2 Method

The study was registered with PROSPERO, www.crd.york.ac.uk/PROSPERO/ - international prospective register of systematic reviews, registration number: CRD42018096306.

2.2.1 Approach to searching, search strategy and data sources

A pre-planned search strategy (See Appendix 2.1) was used to seek all relevant studies. The search strategy consisted of three parameters: disease (bipolar disorder), treatment (medication) and outcome (adherence). Following a scoping exercise of search terms (on Pubmed, Medline and Embase) to define the search strategy, the Medical Subject Heading terms "Treatment Adherence and Compliance", “Bipolar Disorder” AND "Psychotropic Drugs" were used for the searching literature. These search terms were adapted for the databases that did not permit Medical Subject Heading terms or use different terms.

The following seven databases were searched from the database inception to Oct 2018 (updated search in Feb 2020): CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Library (CENTRAL), Embase, LiLACS (Latin American and Caribbean Health Sciences Literature), Medline, PsychINFO and Pubmed.

2.2.2 Study Inclusion criteria

Both qualitative and quantitative primary studies published in the English language and studies explicitly reporting modifiable determinants of medication adherence in bipolar disorder in adults were included. Reviews, intervention studies to improve adherence, case reports, letters, editorials, commentaries, opinion pieces, clinical guidelines or general disease management articles, studies involving short-term treatment of acute agitation, or treatment other than medication such as psychotherapy were excluded. Studies where the effect of individual barriers/facilitators to adherence could not be isolated/extracted from composite measures (such as adherence rating scale) were excluded.

2.2.3 Study screening methods

A computer software Covidence (101), an online systematic review program, was used for screening retrieved studies. Screening of studies for inclusion in this review involved three distinct stages:

I. Title Screening: After removing duplicates, the remaining studies were screened for their relevance to the review. Definite non-relevant studies were excluded, while relevant or unclear studies were retained for abstract screening.
II. Abstract Screening: Abstracts of the remaining studies were screened by the primary reviewer (AP) and second reviewers (CG, DB, FS, GM, JW and SS) independently to identify studies that potentially met the inclusion criteria outlined above. Any disagreement between the two reviewers was resolved through further discussion and referral to a third reviewer (DB) if there is a failure to achieve agreement.
III. Full Article Screening: Full articles were reviewed independently by two reviewers (AP, CG, DB, FS, GM, JW and SS) using pre-defined inclusion/exclusion criteria. Any disagreement between the two reviewers was resolved through discussion or the involvement of the third reviewer.

Within published syntheses of qualitative research, there is often a lack of transparency about the search processes employed, with neither the search strategy nor databases detailed (102). For a comprehensive approach, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used for reporting the different phases of searching, screening and identifying studies for inclusion in the qualitative synthesis as recommended by Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) (102) .

2.2.4 Data extraction

A computer software program, Nvivo 12 (103), was used to extract the determinant and map the modifiable determinants of medication adherence to the domains of the TDF. Acknowledging this wide variation of description and measure of medication adherence as described in Chapter 1, the definition used for adherence in included studies was reported for transparency and comparison among studies. The extracted information included study characteristics (e.g., title, year of publication, country, study

design, population, number of participants, definition and rate of adherence) and modifiable determinants of medication adherence in patients with bipolar disorder.

The PRISMA checklist (104) was used for data extraction and reporting.

2.2.5 Underpinning theoretical framework and mapping of modifiable determinants to this theoretical framework

TDF, described in Chapter 1, was used as an *a priori* framework for the review. The extracted determinants were mapped to one of the following 14 domains of the TDF. The constructs within the domains and definitions of the TDF domains (72) were used to inform mapping decisions. Two independent reviewers (AP, AD, DB and SS), experienced in using the TDF, extracted modifiable determinants and coded them to the TDF domains using Nvivo 12 (103). For example, the extracted text “lack of awareness that medication needed to be taken regularly led to non-adherence” in the study was coded to the TDF domain ‘Knowledge’. Agreement between two reviewers in mapping modifiable determinants to the same TDF domain was calculated in SPSS version 25 (105) using Cohen’s kappa.

Four categories were created in Nvivo12 (103) in line with the aim of the study:

I. Patient Perspective
II. Patient’s Families and Friends’ Perspective
III. HealthCare Professional Perspective
IV. Any other

Within each category, two themes, ‘Barriers’ and ‘Facilitators’, were created, and within each of these themes, 15 domains (14 TDF domains plus ‘Others’) were created. The extracted modifiable determinants were grouped into overarching themes (106).

Two reviewers piloted the data extraction and coding of determinants of adherence to the TDF domains from four studies. For example, the following text, “Forgetting to take medication or being careless at times about taking medication was reported to be experienced by x participants”, was extracted from a study. This would be coded to the TDF domain ‘Memory, attention and decision processes’. The reviewers then compared and discussed their coding to generate consensus in interpreting literature-

identified determinants. After piloting, all data were extracted by one reviewer and independently checked by a second reviewer for completeness. Two reviewers independently mapped all extracted determinants onto the TDF domains or 'Others' category. The two reviewers met and discussed their mapping regularly. Any disagreement in mapping was resolved through discussion between the two reviewers and referral to a third reviewer as adjudicator if the two reviewers failed to agree. Cohen's kappa was used to report agreement between the 1st and 2nd reviewers as we are dealing with nominal data, i.e., agreement or not with the domain to which a determinant is mapped onto the TDF.

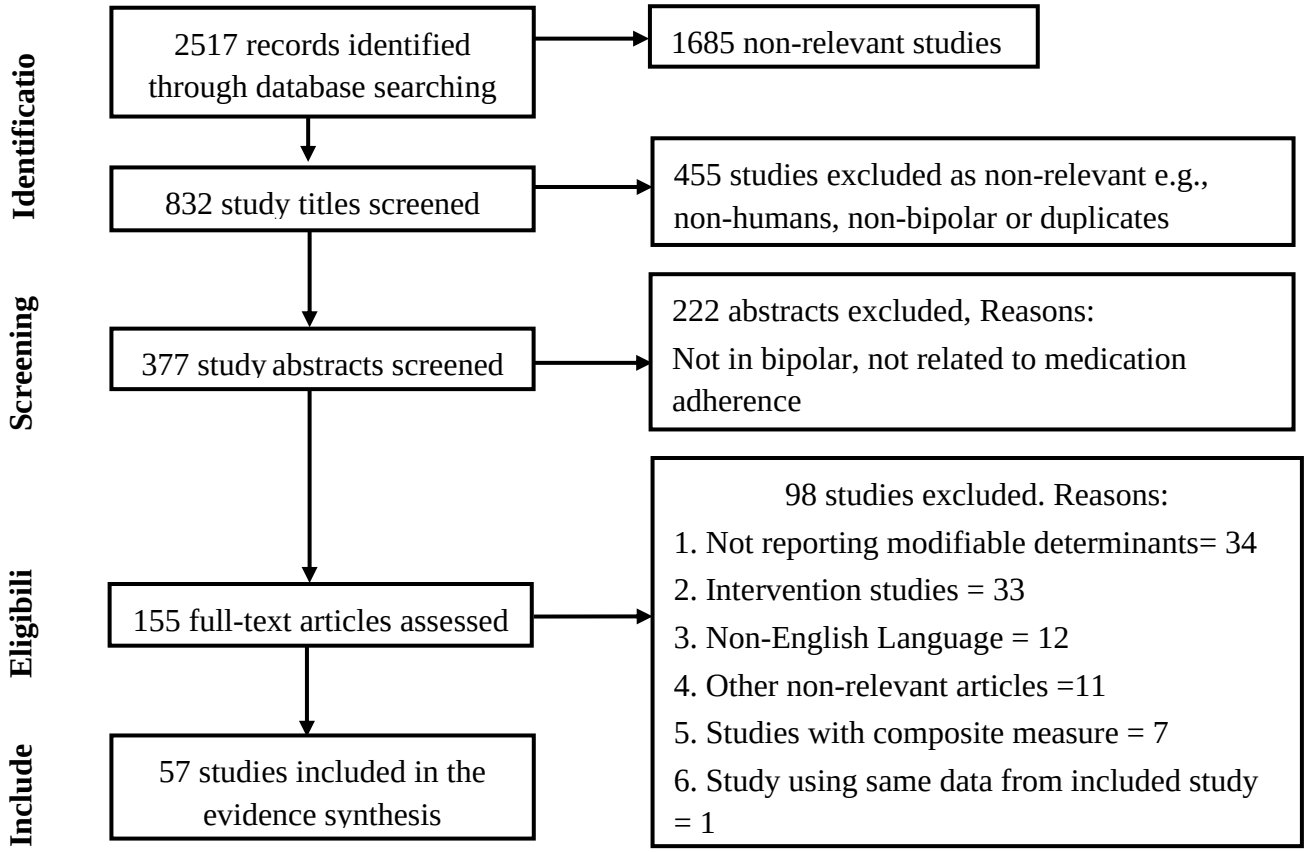
2.2.5 Quality assessment

No studies were excluded based on quality as this study aimed to identify determinants of medication adherence as comprehensively as possible. However, a quality assessment was undertaken to characterise included studies. There is no gold standard tool for any study design, nor is there any widely accepted generic quality assessment tool that functions across multiple study types (107). Bespoke Critical Appraisal Skills Programme qualitative (108), Critical appraisal of survey (109) and Cochrane risk of bias tool (110) were used to critically appraise qualitative studies, surveys and trials, respectively. These tools meet the requirements of the study and provide key quality criteria such as validity, reliability and objectivity (111). Quality assessment was carried out by two reviewers independently. Any disagreement between the reviewers was resolved through discussion and, if necessary, referral to a third reviewer for arbitration.

2.3 Results

Of the 2517 studies retrieved, 57 were included comprising 32894 patients and healthcare professionals. The PRISMA flow diagram in Figure 2.1 below provides the screening process, number of retrieved studies, number of studies included and excluded during title screening, abstract screening and full-text screening, and the reasons for exclusion. The primary reasons for exclusion at full-text screening were failure to report modifiable determinants or reporting an intervention to address adherence.

Figure 2.1: PRISMA Flow Diagram



Study Characteristics

Summary characteristics such as study design, participant details and, the country in which the study was conducted are presented in table 2.1. Fifty studies explored determinants from the perspective of patients and two (112,113) from healthcare professionals' perspectives. Three studies included both patient and healthcare professionals' perspectives (27,114,115). Further two studies were based on database (116,117). However, none of the studies included patient's families and friends. Most of the included studies collected data via surveys or interviews. The majority (79%) of the studies were conducted in the US and Europe. A majority of the studies (64%) were focused purely on BD. Of the 57 included studies, 33% (24,27,112,114,118-129) explicitly focused on exploring barriers to adherence.

Table 2.1: Summary of included studies

Study Reference	Study Design	Study included	Study Aims	No. of participants	Country	Non-adherence rate
(130)	Cross-sectional survey	Bipolar disorder, Schizophrenia, depression	Assessment of associated factors that might influence compliance	409	Ireland	Not reported
(128)	Structured Clinical Interviews	Bipolar disorder only	Explored barriers of adherence: to investigate reasons were for treatment discontinuation	168	Finland	Not reported
(131)	Face to face Interview	Bipolar disorder only	To explore associations between illness perceptions and adherence	38	France	Not reported
(27)	Survey	Bipolar disorder only	Explored barriers of adherence: risk factors to guide clinical prediction of nonadherence	429 patients + 131 psychiatrists	US	33.8%
(132)	Web-based cross-sectional survey	Bipolar disorder only	To identify and describe correlates of medication adherence	1052	US	49.5%
(122)	Naturalistic study where patient recorded their medication taking in self-reporting software	Bipolar disorder only	Explored barriers of adherence: to investigate regularity in the daily mood stabilizer dosage taken by patient and factors associated with irregularity	206	Germany	Not reported

(133)	Cross-sectional survey and interviews	Bipolar disorder only	To explore adherence behaviour and characterize the sociodemographic and clinical factors associated with adherence	382	France	25% of patients exhibited clear poor adherence
(134)	Survey	Bipolar disorder, schizophrenia, depression, anxiety and others	To examine the extent of compliance and non-compliance and examine the factors that affect compliance.	564	Qatar	41.8%
(135)	Semi-structured interviews	Bipolar disorder only	To explore in-depth beliefs about BD and its treatment that are associated with adherence to medication prescribed for BD	16	UK	8 reported non-adherence in the past and 5 reported current non-adherence.
(136)	Questionnaire Survey	Bipolar disorder only	The utility of the necessity concerns framework for understanding patient attitudes towards and levels of adherence	223	UK	30%
(137)	Semi-structured interviews	Bipolar disorder only	To determine the factors affecting treatment compliance	78	Turkey	42.3%
(138)	Cross-sectional survey	Bipolar disorder only	To determine the association of insight and adherence	435	US	27% had poor adherence based on missed dose and 46% had poor adherence based on Morisky

(139)	Cross-sectional observational	Bipolar disorder only	To investigate influence of age and neuropsychological functioning on adherence	353	France	47.3%
(140)	Survey/interview	Bipolar disorder only	The influence of family and health stress, level of coping, and internal health locus of control upon the life contentment of adherent and non-adherent individuals	100	US	Not Applicable as purposive sampling to include 50 adherent and 50 non-adherent patients
(141)	Survey	Bipolar, depression and dysthymia	To identify potential modelling factors influencing adherence	145	Spain	46.2%
(142)	Survey	Bipolar disorder, schizophrenia, depression and others	To examine the role of perceived health control variables in psychiatric patients' adherence to prescribed treatment.	966	Spain	A quarter of patients self-reported a high level of adherence; 46.8% medium adherence and 28.2% a low adherence
(143)	Interviews	Bipolar disorder, Schizophrenia, major depression, and others	To understand how people with psychiatric disorders demonstrate the capacity for resilience in the ways they use or do not use psychiatric medications	29	US	Not Reported
(24)	Interviews	Bipolar disorder only	Explored barriers of adherence: to examine rates, self-perceived reasons and attitudes associated with non-adherence	50	US	45% African American and 50% whites totally non-adherent

(117)	Retrospective analysis of database	Bipolar disorder only	The study investigated monotherapy versus polypharmacy	3626	US	Variable (depending on the medication and combination of medication)
(116)	Retrospective analyses from database	Bipolar and Schizophrenia (here we included only Bipolar)	To compare differences in medication adherence and discontinuation between those who initiated a long-acting injection and those who changed from one oral antipsychotic monotherapy to another.	11344	US	61.1% in LAIs group and 78.5% in oral group
(144)	Survey	Bipolar disorder only	This report hypothesised that acceptance coping would correlate positively, and denial coping would correlate inversely with adherence	32	US	75% of participants reported perfect adherence during the previous week
(129)	Survey and semi structured interview with the patient and spouse/partner	Bipolar disorder only	Explored barriers of adherence: to evaluate the prevalence of sexual dysfunction in patients with bipolar disorder receiving Lithium and to study the correlates of sexual dysfunction.	100	India	Varied (used BARS, MAQ) 84% took the prescribed doses of medications.
(127)	Survey	Bipolar disorder only	Explored barriers of adherence: to determine the relationship between current adherence, medication	33	Czech Republic	Nineteen (57.6%) patients discontinued medication

			discontinuing in the past and self-stigma			at least once in the past.
(145)	Survey	Bipolar disorder only	Explored barriers of adherence: to assess the prevalence and factors associated with medication non-adherence among patients with bipolar disorders	410	Ethiopia	51.2%
(146)	Survey	Bipolar disorder only	To investigate the impact of treatment and illness beliefs on medication adherence	35	UK	54.3% (probably non-adherent)
(147)	Interviews	Bipolar disorder only	Analysis of medication adherence	36	New Zealand	NA
(28)	Survey	Bipolar disorder only	Explored barriers of adherence: to investigate factors associated with nonadherence and to assess the effect of patient preference on hypothetical medications	469	US	23% always adherent, 37% usually adherent, 23% occasionally adherent, 17% rarely adherent
(119)	Interviews	Bipolar and Schizophrenia	Explored barriers of adherence: to investigate potential risk factors for medication nonadherence	255	Norway	13% Nonadherent, 31% partial adherent

(126)	Survey	Bipolar disorder only	Explored barriers of adherence: to identify the reason for non-compliance	96	India	Not applicable (purposive sampling)
(148)	Survey	Bipolar, Schizophrenia, depression, anxiety disorder and others	Explored barriers of adherence: To examine associations between self-stigma and adherence to treatment and discontinuation of medication in patients from various diagnostic groups.	332	Czech Republic	124 patients (37.35%) admitted they had discontinued their medication previously.
(149)	Cohort study – patients evaluated at admission and followed up at 6 months	Bipolar disorder only	To identify clinical factors associated with maintenance antipsychotic treatment in patients with bipolar disorder	77	US	Varied, 41% to 68%
(150)	Interviews	Bipolar disorder only	To assess patients' compliance with pharmacotherapy	140	US	51%
(151)	Observational study	Bipolar disorder only	To assess the duration of time on different mood stabilizing medications and retention rates in standard clinical care	761	Germany	28.4%

(29)	Observational study	Bipolar disorder only	To determine factors associated with better compliance and to assess compliance between patients stabilized on olanzapine monotherapy and those stabilized on combination therapy	657	Austria, Romania, Hungary, Korea, Taiwan, and Mexico	High levels of compliance (≥80%) were observed in 67% of patients at baseline, increasing to 80% in study completers
(115)	Survey	Psychiatrists and patients with bipolar disorder	An analysis and comparison of patients' and psychiatrists' beliefs regarding the most important aspects of bipolar disorder treatment.	100 psychiatrists and 100 remitted patients	Poland	Not Applicable
(121)	Structured Interviews	Bipolar disorder only	Explored barriers of adherence: to examine patterns and reasons of non-adherence	115	US	17.5% in non-substance users, 34.5% in substance users
(26)	Survey	People with bipolar and non-bipolar (unipolar depression, or dysthymia or atypical depression)	To gain a better understanding of what it is like to live with bipolar disorder	1732	Austria, Finland, France, Hungary, Holland, Italy, Portugal, Russia, Spain, Sweden and UK	47%

(123)	An interviewer-assisted questionnaire-based study	Acute and transient psychotic disorder, Borderline personality disorder, Major depressive disorder, Bipolar disorder	Explored barriers of adherence: to assess the level of patients' adherence to psychotropic medications and to explore factors associated with non-adherence to medication	156	India	Adherence rate varied from low adherence (24.4%) through medium (34%) to high adherence (41.7%) among participants
(152)	Post hoc analysis of 1-year observational study	Bipolar and Schizophrenia	To explore non-adherence with Oro-dispersible versus standard normal tablet of olanzapine	903	France, Germany, Greece	Only reported average MARS scores
(153)	Survey	bipolar, cyclothymia, or schizoaffective disorder-bipolar subtype	To examine concurrent and predictive associations between provider support and adherence, access to care and health related quality of life	433	US	Not Reported
(114)	Survey	Patients with bipolar disorder and their treating healthcare professionals	Explored barriers of adherence: likely reasons for non-adherence identified by patients, the most common concerns of adherent and non- adherent subjects and the similarities and differences between healthcare professionals'	72 patients taking Lithium and 41 psychiatrists treating them	UK	46%

			perceptions and patient concerns.			
(120)	Focus group	Bipolar disorder only	Explored barriers of adherence: to identify patients' perspectives on the reasons for nonadherence to psychiatric medication	22	Puerto Rico	68% of participants reported nonadherence during the week of recruitment
(124)	Semi-structured interviews	Bipolar and Schizophrenia	Explored barriers of adherence: to explore why and how people with a serious mental illness choose to stop taking prescribed medication	7	Israel	Not Applicable
(154)	Survey	Bipolar disorder only	To determine plasma and red blood cell Lithium concentrations in bipolar patients at the same time as estimating attitudes and knowledge about Lithium treatment in adherence scales	106	Brazil	33.06% based on MARS>7 14.4% based on plasma Lithium
(155)	Survey	Bipolar depression and Major depressive disorder	Explore factors that impact treatment decisions	896	Canada	Bipolar depression and Major depressive disorder
(156)	Interview and self-report	Bipolar disorder only	Evaluated factors related to adherence	184	US	38.6%

(157)	Interviews	Bipolar disorder only	This cross-sectional analysis examined clinical and subjective variables in relation to adherence	140	US	19.3%
(158)	Interview plus Quantitative assessments, adherence behaviour and treatment attitudes	Bipolar disorder only	This mixed-method analysis evaluated factors related to adherence among 20 poorly adherent community mental health clinic patients with bipolar disorder	20	US	Not Applicable
(118)	Structured Clinical Interviews	Bipolar disorder (n=78) and major depressive disorder (n=20)	Explored barriers of adherence: to explore the prevalence and predictors of nonadherence with mood stabilizers	98	UK	Variable (47% had been non-adherent within last 2 years)
(159)	Survey	Bipolar disorder, Schizophrenia and depression	This study examined the rates of medication non-adherence, associated disease, illness, treatment and physician-related factors of compliance	400	India	40.2%
(125)	Interviews	Bipolar disorder, schizophrenia, schizotypal and delusional disorder, depression	Explored barriers of adherence: to examine potential determinants of non-adherence for patients with severe mental disorders.	127	Germany	54% of the participants reported some kind of non-adherence

(160)	Interviews	Bipolar disorder only	The study examined the impact of substance use disorder history with regards to medication-taking behaviours and attitudes.	54	US	Not Reported
(15)	Semi-structured interviews	Bipolar disorder only	To characterize the patients' perceptions and to give information that can help identify some of the factors involved in the treatment nonadherence	50	Mexico	Not Reported
(112)	Survey	Psychiatrist treating bipolar patients	Explored barriers of adherence: to canvas the opinions of psychiatrists treating patients with bipolar disorder and ascertain their perceptions of potential reasons for partial and non-adherence.	2448	Austria, France, Germany, Italy, Spain, Switzerland, Turkey, and UK	Psychiatrists estimated that 57% of their patients were partially or non-adherent
(161)	Structured Interviews	Coexisting bipolar disorder and substance use disorder	The study examined the pattern of medication compliance and reasons for non-compliance	44	US	Variable and dependent on individual medication
(113)	Interviews	Mental Health Pharmacists	To explore the views and experiences of UK mental health pharmacists regarding the use of Shared Decision Making in antipsychotic prescribing in people with serious mental illness.	13	UK	Not Applicable

(162)	Survey	Bipolar disorder, cyclothymia, or schizoaffective disorder-bipolar subtype	The study examined the association between adherence and therapeutic environment perceptions among veterans with bipolar disorder.	435	US	27%

Table 2.2 describes the quality of the included studies. The majority (65%) of the studies were moderate quality, 19% were high quality, and 16% were low quality.

Table 2.2: Quality of included studies

High Quality (n=11)	Moderate Quality (n=37)		Low Quality (n=9)
(133)	(130)	(151)	(134)
(136)	(128)	(29)	(139)
(138)	(131)	(115)	(144)
(143)	(27)	(121)	(127)
(142)	(132)	(26)	(126)
(146)	(122)	(123)	(150)
(148)	(135)	(152)	(153)
(156)	(137)	(114)	(154)
(157)	(140)	(120)	(159)
(158)	(142)	(124)	
(15)	(24)	(155)	
	(117)	(118)	
	(116)	(125)	
	(129)	(160)	
	(145)	(112)	
	(147)	(161)	
	(28)	(113)	
	(119)	(162)	
	(149)		

Reported modifiable determinants of medication adherence

Two hundred ninety modifiable determinants were extracted, which were grouped into 33 themes and mapped to 11 TDF domains. Inter-rater reliability for mapping the modifiable determinants to the TDF domains was 76% (Cohen's kappa 0.71), indicating substantial agreement between reviewers (163). Examples of the modifiable determinants, themes of determinants and TDF domains to which they were mapped are reported in table 2.3.

Table 2.3: TDF domains, themes of determinants, and examples of determinants (barriers and facilitators)

TDF Domain (No. of studies reporting the domain)	Themes	Examples of determinants of medication adherence	
		Barriers	Facilitators
Environmental Context and Resources (n=36)	Side effects of medication*	• Experience of actual side effects such as sedation, weight gain, sexual dysfunction, fatigue, cognitive impairment, extra-pyramidal and hormonal side effects	
	Medication formulation and treatment regimen	• Number and frequency of prescribed medication regimens with more complex/demanding regimens being negatively associated with adherence	• Long-acting injections had higher adherence than oral medications
	Ineffective medications*	• Medication not working or worsening symptoms after taking medication	
	Cost of medication	• Too expensive or inability to pay	• Free medication
	Irregular routine*	• Irregular daily routine or work schedule	
	Access to health care providers	• Poor access to mental health services, including unavailability of doctors, difficulty getting transportation to appointments	
	Belief about the necessity of medication either during	• Belief they "did not need" medications for bipolar disorder	

Belief about Consequences (n=36)	treatment initiation or maintenance phase*	• "Felt well, saw no need to take medication." • "If there are no symptoms, why take medications."	
	Belief about the positive or negative effects of medications*	• Felt less creative, less productive, less of myself, 'missing highs' • Concern about side effects	• Not wanting to be sick, to keep mood stable and functioning • The high belief that treatment would be helpful
	Doubt about the effectiveness of medication	• Belief that medication does not work	
	Belief that it is unnatural to take psychotropic medications	• Belief that it is unhealthy and unnatural to take medication to keep mood stable	
	To avoid punishment/trouble		• Belief that they will be sectioned or hospitalised if they did not take their medication
Knowledge (n=23)	Knowledge about bipolar disorder and its treatment*	• A lack of knowledge and awareness about the course of illness and treatment • Majority of the non-compliant patients were not aware that the Lithium stabilises the mood • Not knowing the need to take medication regularly • Not knowing that medications should be continued even when free of symptoms	• Better insight into illness • A high coherent understanding of their disorder • Being sufficiently informed about the disorder and its treatment • "My mental health care provider team made me aware of what to expect from good bipolar disorder care."
	Understanding how and when to take medication	• Unclear about prescription directions • Misunderstanding prescription directions	
Social Influences	Personal support by the care provider		• "My mental health care provider team makes sure that we stay in regular contact."

(n=19)			• "I feel understood by my mental health care provider team."
	Feeling stigma	• The more self-stigmatized the patients were the lower their adherence. • Ironically, as though the mental illness was not associated with enough stigma, the decision to cease medication, even when experienced as an important part of one's personal recovery, was stigmatising in its own right, leading them to conceal their decision and thus feel alone.	
	Support or opposition from family, friends, relatives to diagnosis and treatment*	• Family and friends discouraging from taking medication • "My mother said I should think about it and try to use…reason and creativity instead of the medication."	• Having someone to support medication taking, monitoring symptoms etc. • "I used medication to please my parents, who strongly supported it."
Memory, Attention and Decision Processes (n=19)	Forgetfulness/carelessness	• Forgetting or not remembering to take the medication as prescribed • Laziness or careless at times about taking medications	• Individuals had a variety of methods to help them remember to take medications, including putting them in a consistent/specific place, labelling or writing reminders, taking medications at a consistent/specific time.
	Medication taking routine	• Difficulties in maintaining pill-taking routines	Attaching medication taking to other routine behaviours (e.g., taking medication after cleaning teeth)

Emotion (n=12)	Fear of addiction or side effects of medication	• Worried about being dependent on medications • Fear of side effects of medications	
	Feeling threatened		• The threat of hospitalisation if medication is not taken
	Feeling of not being able to fulfil a social role	• Could not take care of my kids while on medication because I did not have the drive, or I just slept and slept on that medication.	
	Negative feelings with medication prescribing and administration process	• Negative experience of how the medication was prescribed or administered • Taking medication every day is a frustration • Bothered that mood was controlled by medication	
Intentions (n=12)	Denial of illness or illness severity	• Among reasons for non-adherence, denial of illness was the most commonly specified. With higher denial, adherence decreased exponentially.	• Adherent patients tended to accept that they are ill
	Acceptance or denial of the need for treatment	• More than half of the non-compliant patients expressed that they do not accept Lithium treatment for a long time and as a normal routine.	• From the compliant patients, there was 100% of acceptance of Lithium treatment.
	Intentional non-adherence	• Not wanting to take medication • Wanting to take too much medication to get intoxicated	
Social, Professional Role & Identity (n=9)	Listening and shared decision making*	• Absence of shared decision making was believed to result in non-adherence and high rates of re-admission to hospitals.	• “I feel that my health care practitioner has provided me choices and options about my health.”
	Relationship with the prescriber		• Better patient-physician relationship

			• Satisfied with the competence of the doctor
	Being in control of the treatment regime	• Wanted to self-adjust the dose • Using regularly prescribed medication as 'standby drugs' to stop mania.	
Belief about capabilities (n=6)	Belief in self and control*		• I think it is like any other condition…the more autonomy you give the patient…the more likely they are to comply.
	Conflicting beliefs between clinician and patient	• Some research participants reported that healthcare professionals interpreted their valued personal strengths and self-assessed health resources as part of psychopathology. Unsurprisingly, this led to non-adherence.	
Goals (n=3)	Different priorities over medication taking	• Psychiatric medications interfered with the things that give life meaning and purpose • Relief from personal stress was more important than taking medications	
	Desire to experience manic symptoms.	• Stopping medication to experience mania	
Skills (n=2)	Provision of training to manage bipolar disorder		• "My mental health care provider team has provided training in what I need to do to carry out good bipolar disorder care."
Optimism (n=0)	No determinants mapped to this domain		
Reinforcement (n=0)	No determinants mapped to this domain		
Behavioural Regulation (n=0)	No determinants mapped to this domain		

*Note: * = Healthcare professionals only reported these themes of determinants.*

Some facilitators were reported as the opposite of barriers. For example, 'cost of medication' was identified as a barrier in the ‘Environmental context and resources’ domain, for which 'medication being free of charge' represented the corresponding facilitator. In other cases, facilitators were occasionally worded as BCTs. For example, forgetfulness represented a barrier in the ‘memory, attention, and decision processes’ domain, for which the corresponding facilitators were reminders and formulating routines; these were classified in the BCT category of ‘prompts and cues’ which may successfully modify behaviour by addressing determinants in this TDF domain (164).

The TDF domain represented in the greatest number of studies were ‘Environmental context and resources’ (63% of studies) and ‘Beliefs about consequences’ (63% of studies). Experience of side effects (49% of studies) and the nature of the medication, e.g. tablet, injection and dose frequency (22% of studies) were the main determinants mapped to the former, acting as barriers when unacceptable and facilitators when acceptable to patients. Whereas beliefs about the likely positive/negative outcomes arising from adhering (36% of studies) and a belief that the medication is not needed (25% of studies) were the main determinants mapped to the latter.

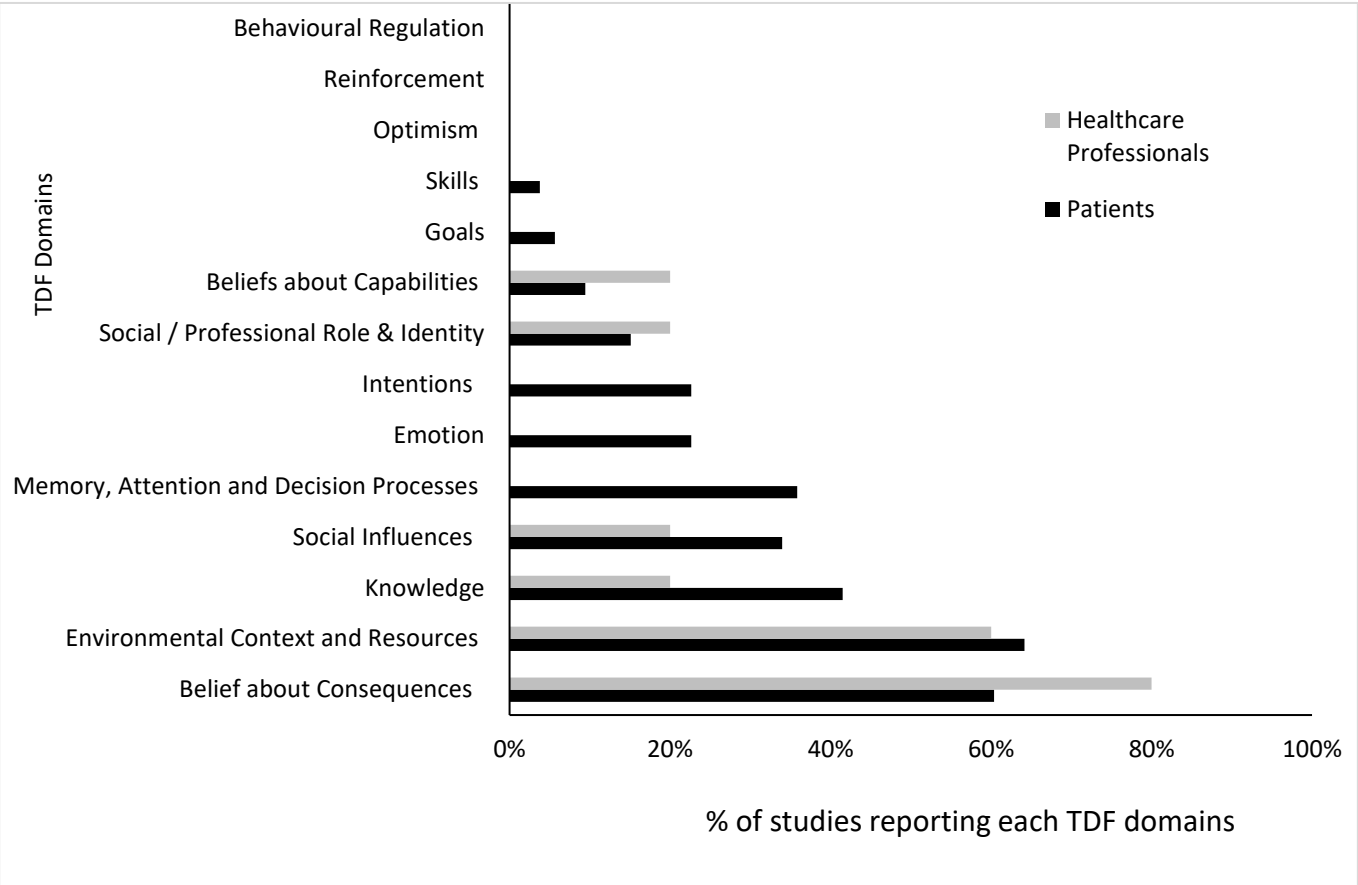
Other TDF domains (and corresponding themes of determinants) reported in 20% or more studies, among all studies, were ‘Knowledge’ (whether the patient had sufficient knowledge about BD or its treatment); ‘Social influences’ (support or opposition from family, friends, relatives, healthcare professionals regarding adherence); ‘Emotion’ (fear of addiction to or side effect from medication); ‘Memory, attention, and decision processes’ (forgetfulness/carelessness with medication taking) and ‘Intentions’ (denial of illness or need for treatment).

Modifiable determinants were most frequently reported in the context of barriers rather than facilitators. However, unlike most other TDF domains, for ‘social influences’, facilitators and barriers were reported with similar frequency. This trend was also observed for ‘Social/Professional Role and identity’. Modifiable determinants related to ‘Goals’ and ‘Skills’ were infrequently reported. No determinants were mapped to the TDF domains of ‘Optimism’, ‘Reinforcement’ and ‘Behavioural regulation’.

Determinants from the perspectives of patients and healthcare professionals

Figure 2.2 illustrates the TDF domains reported in patient studies compared to clinician studies. 'Beliefs about consequences' and 'Environmental context and resources' were the two most frequently reported TDF domains in both patient studies as well as healthcare professionals studies. There were, however, noticeable differences in the range and nature of determinants reported by patients relative to healthcare professionals.

Figure 2.2: Comparison of TDF domains reported by Patients and Healthcare professionals



Note: No. of patients only studies = 50; No. of Healthcare professionals only studies = 2; No. of studies including patients and healthcare professionals = 3. Two database-based studies were not included in this graph.

Determinants reported by healthcare professionals were mapped to only six TDF domains compared to 11 TDF domains covered by patient studies. Only patient

studies reported determinants which were mapped to the TDF domains ‘Intention’, ‘Memory, attention and decision processes’ and ‘Emotion’. These domains included determinants such as denial of the illness or need for treatment, forgetfulness/carelessness and fear of addiction to or side effects of medication, respectively (see Table 2.3 for more details).

Furthermore, ‘Goals’ and ‘Skills’ domains were reported in patient studies, albeit infrequently. An example of determinants in these two domains includes different priorities over medication taking and provision of training to manage bipolar disorder.

Healthcare professionals reported modifiable determinants of adherence themed around lack of knowledge about medication, shared decision making, belief in self and perceived control, belief that medication is not needed, belief about positive or negative effects of medication, side effects, ineffective medication and irregular routine.

Two database-based studies (116,117) reported medication formulations (such as tablets, injections) and the number of medications as determinants, both of which were mapped to ‘Environmental context and resources’ domain.

2.4 Discussion

Synthesis of the literature through the theoretical lens of the TDF has enabled us to identify those negative emotions evoked by medication taking and intentional non-adherence make a notable contribution to non-adherent behaviour. In contrast to the focus of existing interventions on practical barriers to adherence (165,166), healthcare professionals should additionally address negative emotions and lack of intentions.

In common with previous evidence syntheses, modifiable determinants were primarily barriers to adherence (39,63) with few reported facilitators. This may be an artefact of the included studies focussing on the challenges experienced by patients rather than seeking to explore potential solutions. This hypothesis is supported by a third of the included studies explicitly seeking only barriers to medication adherence. For the few studies exploring facilitators, determinants that are not the opposite of barriers, such

as wanting to keep the mood stable and not wanting to be hospitalised, have also been reported (135,140). A strength of the present review is that we did not restrict the search to only adherence barriers; thus, we have identified a gap in the literature.

Current adherence interventions in bipolar disorder focus mostly on education regarding medication and bipolar disorder, cognitive therapy to address negative attitudes and beliefs, family therapy to encourage social support, and technology such as text messaging to address forgetfulness (21,85,165,166). Furthermore, adherence support in the UK focusses on shared decision making regarding the choice of medication, side effects profile of medication, cost of medication, and exploring patients' beliefs (21,85). However, in this study, we found a broad range of other modifiable determinants that may be affecting medication adherence. This study provides healthcare professionals with a comprehensive list of modifiable determinants of medication adherence, some of which are underappreciated by healthcare professionals and unaddressed by existing adherence interventions.

Advantages of mapping modifiable determinants to the TDF

Mapping determinants to the TDF allows them to be linked to BCTs. Thus, this study provides a foundation for developing a complex adherence intervention tailored to patients' needs based on their predominant determinants of adherence. The most frequently reported TDF domains of 'Beliefs about consequences' and 'Environmental context and resources' indicate that working with the patient's belief system, medication acceptability and tolerability are vital to support medication adherence. However, other modifiable determinants, particularly in 'Intentions', 'Memory, attention and decision processes' and 'Emotion' domains, presented in this study may be equally or more relevant to individual patients. Thus, identifying the modifiable determinants most pertinent to an individual patient is critical to providing patient-centred adherence support.

The most frequently reported domain 'Environmental context and resources' was primarily related to medication characteristics such as side effects, treatment regime, medication effectiveness or cost etc. This finding accords with previous studies

(39,63,167,168). Side effects were represented in the domains of both ‘Environmental context and resources’ and ‘Beliefs about consequences’. This was because patients reported non-adherence arising from both experiencing side effects and being concerned that side effects may result from taking the medication. Each requires a different BCT; for example, the former may be better addressed by ‘restructuring the physical environment,’ e.g., by changing medication with a lower propensity of a particular side effect that the patient is experiencing. In contrast, the latter aligns with BCTs such as ‘pros and cons,’ e.g., discussing the risk and benefits of taking and not taking the medication (80).

The dominance of ‘Beliefs about consequences’ on medication adherence in this review is supported by other studies using the TDF (46,169). Belief about the necessity or concerns of medication were frequently reported determinants of adherence within this domain. As often noted in clinical practice, many people stop taking their medication once they feel better, believing they no longer need them. On the other hand, some people believe they do not need medication at the start of the treatment and thus do not initiate them. Therefore, BCTs such as ‘pros and cons’ may play a vital role in medication adherence (80).

The absence of determinants mapped to the TDF domains ‘Optimism’, ‘Reinforcement’, and ‘Behavioural regulation’ does not necessarily mean that these three domains are unimportant to medication adherence in bipolar disorder. Previous studies may not have explored these specific domains. Some adherence intervention studies suggest that ‘Reinforcement’ using financial incentives may improve adherence (170). Similarly, optimism, as measured by the revised Life Orientation Test (171), was reported to lead to improved adherence in acute coronary syndrome (172). Revised Life Orientation Test includes statements such as “Overall, I expect more good things happen to me than bad.”, “In uncertain times, I usually expect the best.”(171). However, these may not be modifiable. Future work should explicitly investigate the extent to which these unrepresented domains are relevant to non-adherence in this population and whether they are modifiable in the context of medication adherence.

While there was a significant overlap between determinants reported by healthcare professionals and patients, there were also notable distinctions. These distinctions

may explain the limited progress made by healthcare professionals in identifying and addressing non-adherence (83,84). However, these distinctions may also have arisen due to the small number of studies exploring the clinician's perspective.

Healthcare professionals reported determinants mapped to less than half of the TDF domains, suggesting that healthcare professionals may not be aware of the broad range of determinants affecting medication adherence or studies were not designed to elicit this information from healthcare professionals. The influence of negative emotion evoked by taking medication and intentional non-adherence was the most notable omission from healthcare professionals' perspectives. This incomplete picture may result in adherence support poorly reflecting patients' needs (47). This is evident from current adherence support being focused on a very limited number of determinants (21,165,166,173).

Strengths and Limitations

This systematic review offers three novel aspects in the field of medication adherence research in bipolar disorder. Firstly, the study focuses on potential adherence intervention targets by reporting only modifiable determinants. Secondly, as the application of theory is a core requirement for developing and implementing complex interventions, our use of a theoretical framework provides the foundations for developing future medication adherence interventions and their implementation. Finally, the comprehensive nature of a theoretical framework rather than an individual theory has enabled us to identify gaps in the literature.

The deductive nature of the framework synthesis method (30–33) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable the identification of all determinants relevant to the behaviour change (34). Moreover, any determinants which cannot be mapped to a TDF domain would have been mapped to the 'Other' domain if needed. A lack of detailed description of the determinants in some studies risked mapping them to incorrect TDF domains. For example, some studies described 'hassle to acquire medication' as a determinant of adherence. It could mean the patient has difficulty obtaining medication

due to not knowing how to order their prescription or difficulty remembering to order a prescription or lack of transport/money/time to order a prescription. Each interpretation would be mapped to a different TDF domain. Further qualitative work with patients will facilitate these further refinements in mapping.

The study presented the modifiable determinants of adherence identified from a wide range of study designs. We recognise that the medium via which data are collected can influence the range of determinants captured. For example, interviews may elicit a greater range of determinants that are personal to the individual versus a structured survey of potentially relevant determinants (174). This non-restrictive approach has contributed to identifying a list of modifiable determinants as comprehensively as possible which was one of the goals of this study.

Implications for research

The application of a theoretical framework to the systematic review has enabled us to identify gaps in the literature where researchers have not sought to investigate the relevance of facilitators of adherence. Further work to explicitly capture the facilitators of adherence may help design future adherence interventions. The existing literature mostly represents the patient voice; absence of the patient's families and friends' voice is a notable gap given their role in supporting medication adherence in people with mental health problems (175). Future research exploring patients' families and friends' views on modifiable determinants of medication adherence in bipolar disorder is therefore needed.

CHAPTER THREE

Interviews and Focus Group Discussions with Patients with bipolar disorder and their families and friends

3.1 Introduction

The magnitude of the problem of non-adherence, its clinical and financial implications have been previously discussed in Chapter 1. The systematic review, described in Chapter 2, identified extensive lists of modifiable determinants and also described studies exploring these determinants. However, there are clear gaps in the literature exploring such determinants of adherence. This chapter will explain the qualitative research with patients with bipolar disorder and their families and friends.

Medication taking is a health behaviour, but the rare use of behaviour change theory in investigating modifiable determinants of adherence is notable. Moreover, studies utilising behaviour change theory to explore adherence determinants typically focus on a single theory, e.g. necessity concern framework (176). Such an approach may identify only a limited number of determinants that come within the scope of that theory. A comprehensive framework, such as the Theoretical Domains Framework (73), which captures most theories and theoretical constructs related to behaviour change, is a valuable tool to explore an extensive list of adherence determinants.

The majority of studies investigating adherence determinants were surveys and interviews (18)**.** This is understandable as patients may feel more comfortable discussing in individual interviews than in group discussions like a focus group. However, focus groups have their own advantages such as the generation of new ideas from brainstorming and group dynamics absent in interviews (177). The focus groups are more natural environment than interviews due to group interaction where participants are influencers and are influenced by others at the same time (177). Focus groups thus benefit from spontaneity where respondents reveal more than their own frame of reference (177). Moreover, from a practical point of view, focus groups are cheaper, quicker and able to get opinions from many participants at once.

And finally, the lack of families and friends' perspectives on modifiable determinants of adherence is a significant gap because families and friends play an important role in supporting adherence in mental health. Involving families and friends in the focus group and interviews was also suggested by a patient and public representative in our Research Advisory Board before identifying this gap through our systematic review. The board acknowledged that families and friends play a significant role in medication

adherence, particularly among patients with a mental health disorder. Yet, our systematic review did not find any studies exploring determinants of medication adherence from families and friends' perspectives. Thus, including families and friends in our qualitative work will help bridge knowledge gaps in this area.

Therefore focus groups and interviews with patients with bipolar disorder and their family and friends were conducted with the following objectives:

- To establish patients and their families and friends' interpretations of literature reported modifiable determinants of adherence
- To identify any modifiable determinants of adherence not reported in the literature
- To establish the relevance and importance of literature identified modifiable determinants of adherence from the perspective of patients and their families and friends

Study Design and rationale

Focus groups are popular and widely used method in qualitative research across the social sciences (178), representing a cost-effective and flexible approach to elicit peoples' understanding, views or opinions about a particular topic (178,179). They are now a standard part of developing valid and reliable survey instruments, representing a cost effective and flexible approach to exploring participants' attitudes and responses (179). Interaction between research participants is a key feature of focus group research (174). It is, therefore, an excellent choice of methodology when the purpose of the research is to elicit peoples' understanding, views or opinions about a particular topic (178). Moreover, individual views can be collated to explore group perspectives and seek consensus. The focus group method will also be beneficial in eliciting the language that participants use with relation to adherence determinants, which will be utilised to further develop and refine the determinants to reflect patient terminology and expression (178). Focus groups can also help participants explore the prioritisation of the prominent issues (174) and will thus facilitate the prioritisation of determinants of adherence for each behavioural domain.

The decision to conduct interviews in addition to focus group discussions was led by a PPI representative in the Research Advisory Board because the topic of conversation can be highly sensitive for some patients who may not want to discuss it in group settings. Thus, offering an option of individual interviews will likely attract patients and their families and friends who otherwise might not have participated in this research. Individual interviews also allow the researcher to understand the issue in greater depth from the patients or their families and friends' perspectives and may also generate a broad range of determinants compared to focus groups (180). Using both interviews and focus groups will also provide a degree of triangulation.

The importance of using qualitative exploration to establish determinants to particular behaviour has been established by many researchers. For example, McEachan et al. used focus groups to establish determinants to worksite physical activity (181) and reported that the focus groups facilitated the identification of additional determinants and offered a greater depth of understanding to those already elicited in the literature. A similar finding was also reported by other focus groups and semi-structured interviews to identify obstacles to and motivations for adherence to glaucoma therapies (182).

Whilst I anticipate that our systematic review would have produced a robust list of determinants of medication adherence, the focus group and interviews with patients and their families and friends will explore any further determinants not already elicited in the literature; provide their own interpretation, refinement and prioritisation of the determinants. The findings from the focus group and interviews will help us develop questionnaire statements.

In addition, undertaking the focus groups and interviews will also facilitate the incorporation of clinical guidelines into the intervention design. Guidelines issued by NICE recommend that researchers should work in partnership with individuals when developing behaviour change interventions and involve the target population in the planning and design phases of the intervention development. Moreover, the guidelines also stipulate that collaborations with the target population should be used to take account of lay wisdom about determinants and change where possible (52).

3.2 Method

3.2.1 Patient & Public Involvement in preparation for the study

In preparation for this study, I organised an informal discussion with six patients and a family member for an hour in October 2018 in Norwich. The discussion was semi-structured to get the views of participants on recruitment strategies, logistics (choice of venue, location, time, duration etc.) to carry out focus groups and interviews, things that may support or hinder people attending focus groups and interviews, facilitators and barriers for open and honest discussion during the focus group and interviews, and any other issues we need to take into account. The outcome of this informal discussion guided our method. Our objectives for this informal discussion were to explore:

I. Recruitment strategies (best way to recruit patients and their families and friends for the study): While we had thought of the clinical team at NSFT and NSFT Recovery College as our main route of recruitment patients and their families and friends group suggested Norwich and Norfolk MIND might also attract participants.

II. Logistics (choice of venue, location, time etc., to carry out focus group and interviews): Most participants preferred venues outside NHS or University settings. Their preferred duration of the meeting is 1.5 to 2 hours with comfort breaks.

III. What would support and hinder people attending focus groups and interviews?
The group suggested that the good transport link to the venue, being clear about any benefits or incentives from the beginning, informing and ensuring the protection of privacy and confidentiality would support people joining the study.
Some people may be late or might not turn up for various reasons. AP will call all participants in the study the day before the meeting as a reminder to attend focus groups or interviews as appropriate.

IV. What would encourage or discourage open and honest discussion during focus group and interviews (including terminologies, language etc., to use)?
The group said that the people would likely to speak their mind if they knew for sure what was said at the meeting would be confidential and if they understood

that the research would have potential benefit to patients. The group also suggested that providing specific topic/questions about the research in advance would be helpful, so is a less hierarchal dress for the moderator/facilitator (not in a business suit but should be clear that who is leading the discussion). Some in the group felt strongly that many patients might speak their minds freely in online settings than in person.

V. Any other issues we need to consider

Online focus groups or interviews may be better for some patients as some may not want to talk in person or may not feel comfortable. As a direct result of this informal discussion, we are now offering participants a choice to attend face to face or online focus groups or telephone or online interviews.

The group also highlighted the importance of plain language in documents and during the focus group discussion or interviews. Patient and their families and friends in the Research Advisory Board helped me review the patient information sheet, screening survey and consent form. Patients felt this was an important topic of research and would really like to be part of the research.

3.2.1 Study settings, eligibility criteria and recruitment

Participants for the focus group and interviews were from Norfolk and Suffolk counties in England. Participants from both primary and secondary health care services took part. Eligibility criteria for participants are described below.

Patient inclusion criteria:

- Adult 18 years or older with a diagnosis of bipolar I or II AND
- Prescribed at least one medication for bipolar

Patient's families and friends inclusion criteria

- Caring for a person who meets the patient inclusion criteria above AND
- At least two hours per week contact time with the patient AND

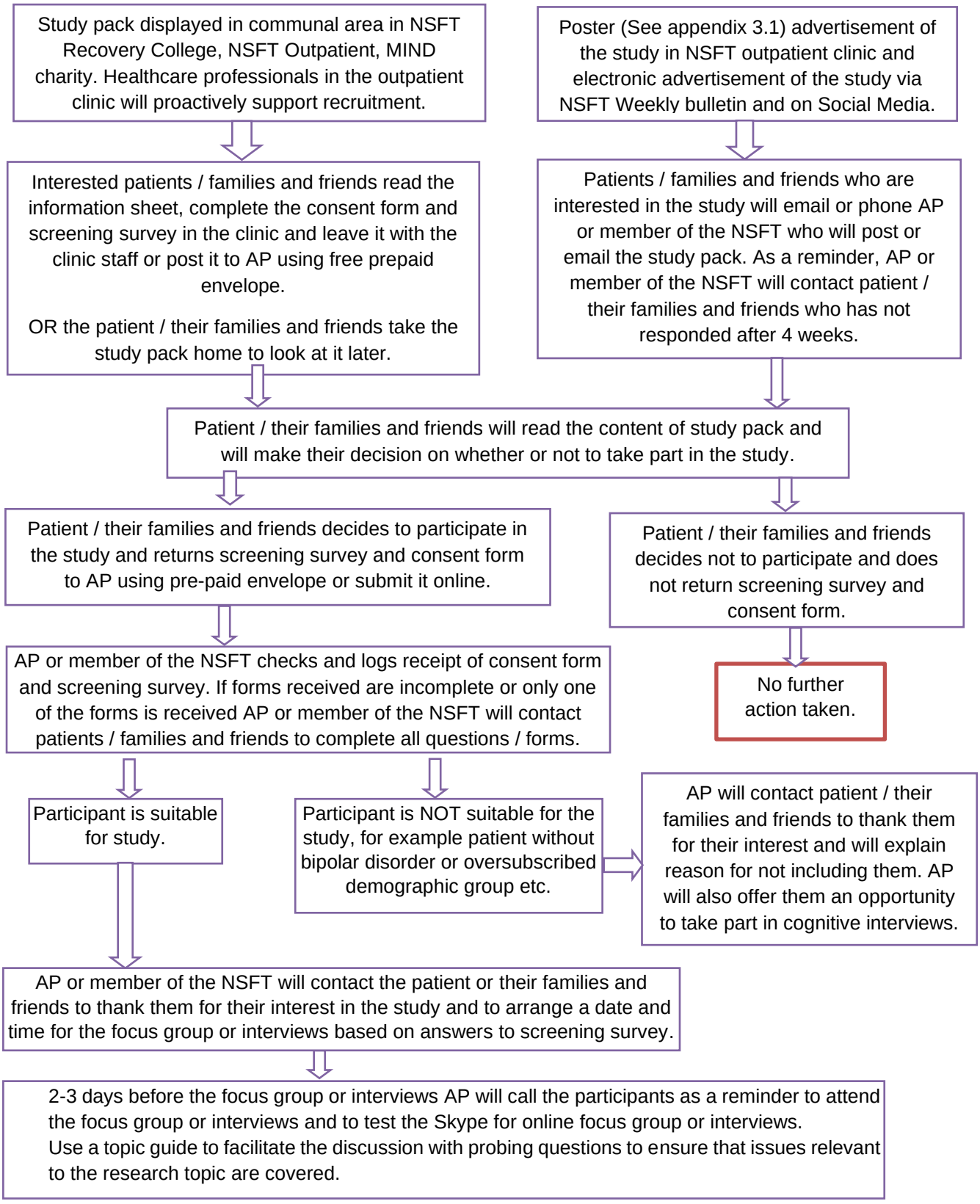
- 18 years or older

Exclusion criteria

- Unable to read and/or speak English OR
- In-patients in the hospital wards OR
- Patients who lack capacity OR
- Unable to provide informed consent OR
- Paid professional carer for the patient

Figure 3.1 below summarises the participant recruitment process for this study.

Figure 3.1: Recruitment process for focus group/interviews with patients and their families and friends



Participants were offered £10 for up to an hour-long interview and £20 for up to 2 hours focus group discussions.

We used a maximum variation purposive sampling technique (183) to ensure that a wide range of demographic characteristics and people in different spectrums of the disorder (e.g., managed with one medication or multiple medications) are included. We will achieve this by capturing non-modifiable factors known to influence medication adherence in a screening survey.

We recruited participants through NSFT Recovery College, NSFT outpatient clinics Norwich and Central Norfolk MIND and social media (e.g., Twitter).

Study packs

The study pack was available in both paper copy or online and contained:

I. Participant information sheet (See Appendix 3.2)
II. Screening survey (Appendix 3.3)
III. Consent form (Appendix 3.4)
IV. Pre-paid self-addressed envelope for returning screening survey and consent form (only for paper copy)

Potential participants could complete the screening survey and consent form on paper and return it using the pre-paid envelope provided or online by scanning the QR code found on the Patient Information Sheet, Consent form and Screening Survey.

The rationale behind including the screening survey in the study pack was to support our aim of having a good mix of people in the study. We will purposively sample according to the following known non-modifiable factors associated with non-adherence (184,185):

- Age
- Gender
- Length of bipolar diagnosis
- Number of regularly prescribed medicines
- Paying prescription fee
- Health literacy level

Health literacy level will be measured using a single validated item relating to how frequently the participant needs assistance with reading health related materials (186). Additionally, the screening survey will capture preference for attending a focus group or interview, whether face-to-face, online or by telephone. The inclusion of each section of the screening survey was explained to participants in the patient information sheet so that the rationale behind being asked the questions is understood. Informed consent was obtained from all participants.

3.2.2 Sample size

Focus group sample size recommendations vary widely and can range from two focus groups to 40 or more per study (180). A recent systematic review reported that more than 80% of all themes were discoverable within two to three focus groups, and 90% were between three to six focus groups (180).

We planned to conduct up to five focus groups in a convenient location, each with six to eight participants. Given that we already have an extensive list of modifiable determinants from our systematic review, five focus groups should suffice. We also offered an option for one-to-one interviews to provide an opportunity to collect views from patients, families, and friends who may find it difficult to discuss issues in open group discussion. We anticipate six to eight one to one interviews. Two to three focus groups will include patients with bipolar disorder, and two focus groups will consist of families and friends. Separating patients and families and friends in focus groups was recommended during our informal consultation with patients and their families and friends as detailed in section 3.2.1.

The focus group discussions and interviews were based on the TDF domains, and the modifiable determinants of adherence mapped to these domains as discussed in Chapter 2. Fourteen TDF domains were not possible to be covered during an hour-long interview or a 2-hour focus group. And interviews lasting over an hour or focus group for longer than two hours is neither reasonable nor desirable (177). Thus, we divided the TDF domains into: Group ONE and Group TWO. Each group's participants covered nine TDF domains as shown in table 3.1 below.

Table 3.1: TDF domains and number of determinants of adherences discussed by two groups of focus groups and interviews participants

Group One: TDF domains (number of determinants of adherences)	Group Two: TDF domains (number of determinants of adherences)
1. Environmental Context and Resources (8) 2. Emotion (8) 3. Social influences (5) 4. Intentions (5) 5. Social/professional role and Identity (3) 6. Skills (2) 7. Reinforcement (0) 8. Optimism (0) 9. Behavioural Regulation (0) (Total number of determinants in Group One = 31)	1. Belief about consequences (11) 2. Knowledge (7) 3. Memory, attention and decision processes (4) 4. Belief about capabilities (3) 5. Goals (3) 6. Skills (2) 7. Reinforcement (0) 8. Optimism (0) 9. Behavioural Regulation (0) (Total number of determinants in Group Two = 30)

Colour codes: The colour of text indicates how frequently these TDF domains were reported as adherence determinant in the systematic review described in Chapter 2.

Blue = Most frequently reported (>50% of studies reporting these TDF domains)

Green = Frequently reported (>20% <50% studies reporting these TDF domains)

Amber = Less frequently reported (>10% <20% studies reporting these TDF domains)

Yellow = Frequently reported (>20% <50% studies reporting these TDF domains)

Red = Not reported TDF domains

Allocation of TDF domains for Group ONE and Group TWO participants in table 3.1 above was based on:

- Ensuring an equal number of TDF domains and modifiable determinants of adherence (items) in each group
- Assigning TDF domains to each group based on the frequency with which it is reported in the systematic review from chapter 2, the TDF domains were

divided into four categories: most frequently reported, frequently reported, least frequently reported and unreported, as presented in table 3.2 below.

Table 3.2: Frequency of TDF domains represented in the systematic review of modifiable determinants of medication adherence in bipolar disorder

	TDF Domains	**No. of Studies reporting the TDF domains**	**% of studies reporting the domain**
Most frequently reported (>50%)	Environmental context and resources	**39**	**71%**
	Belief about Consequences	**33**	**60%**
Frequently reported (>20% to <50%)	Knowledge	**22**	**40%**
	Social influences	**21**	**38%**
	Memory, attention and decision processes	**19**	**35%**
	Emotion	**13**	**24%**
	Intentions	**12**	**22%**
Less frequently reported (>10% <20%)	Social/professional role and identity	**9**	**16%**
	Beliefs about capabilities	**6**	**11%**
Least Frequent (>0%<10%)	Goals	**3**	**5%**
	Skills	**2**	**4%**
Not reported (0%)	Optimism, Reinforcement, Behavioural Regulation	**0**	**0%**

Colour codes: The colour of row/s indicates how frequently these TDF domains were reported as adherence determinant in the systematic review described in Chapter 2.

Blue = Most frequently reported (>50% of studies reporting these TDF domains)

Green = Frequently reported (>20% <50% studies reporting these TDF domains)

Amber = Less frequently reported (>10% <20% studies reporting these TDF domains)

Yellow = Frequently reported (>20% <50% studies reporting these TDF domains)

Red = Not reported TDF domains

Thus, participants in Group A were allocated to discuss one most frequently reported TDF domain ‘Environmental context and resources’; two frequently reported domains ‘Emotion’ and ‘Social influences’; one least frequently reported domain ‘Skills’. A similar distribution of TDF domains for participants in Group B is shown in table 3.1. This grouping was planned to give participants in both groups the right and equal amount of time to discuss each domain. It is expected that participants will take more time discussing the most frequently reported domain than for the least frequently reported. Three unreported TDF domains, ‘Optimism’, ‘Reinforcement’ and ‘Behavioural regulation’ were included in both groups to explore these domains with all participants. This is to ensure that whether these unreported domains were primarily missed in previous studies due to study design or whether they do not influence medication adherence in bipolar disorder or whether they were interpreted by participants in different ways so that they are mapped to another TDF domain. TDF domain ‘Skills’ was included in both groups as it was one of the least frequently reported domains. Additionally, adding ‘Skills’ to Group B means both groups have an equal number of TDF domains and number of determinants.

The sequencing of the TDF domain was planned for smooth conversation, i.e., starting with the most frequently reported domains mean most people are likely to have experienced most or some determinants on the list, which will make an initial conversation easy. Whilst unreported TDF domains were left at the end to provide more time and discussion.

3.2.3 Conduct of focus groups and interviews

I had initially planned to conduct face to face or online focus group discussions but due to COVID restrictions, only online focus groups were possible. In preparation for online focus groups, I confirmed the date and time of the focus group with participants, I posted the confirmation letter along with a £20 voucher and 7-page handouts (either Group 1 or Group 2). I confirmed the receipt of these at least a week before the focus group and I also trialled Skype conferencing with each of the participants to ensure no technical issues. I also called them 2-3 days before the focus group discussion to reconfirm the time and date. I sent a link to the online meeting 10minutes before (also to set as another reminder of the meeting) the online focus group meeting.

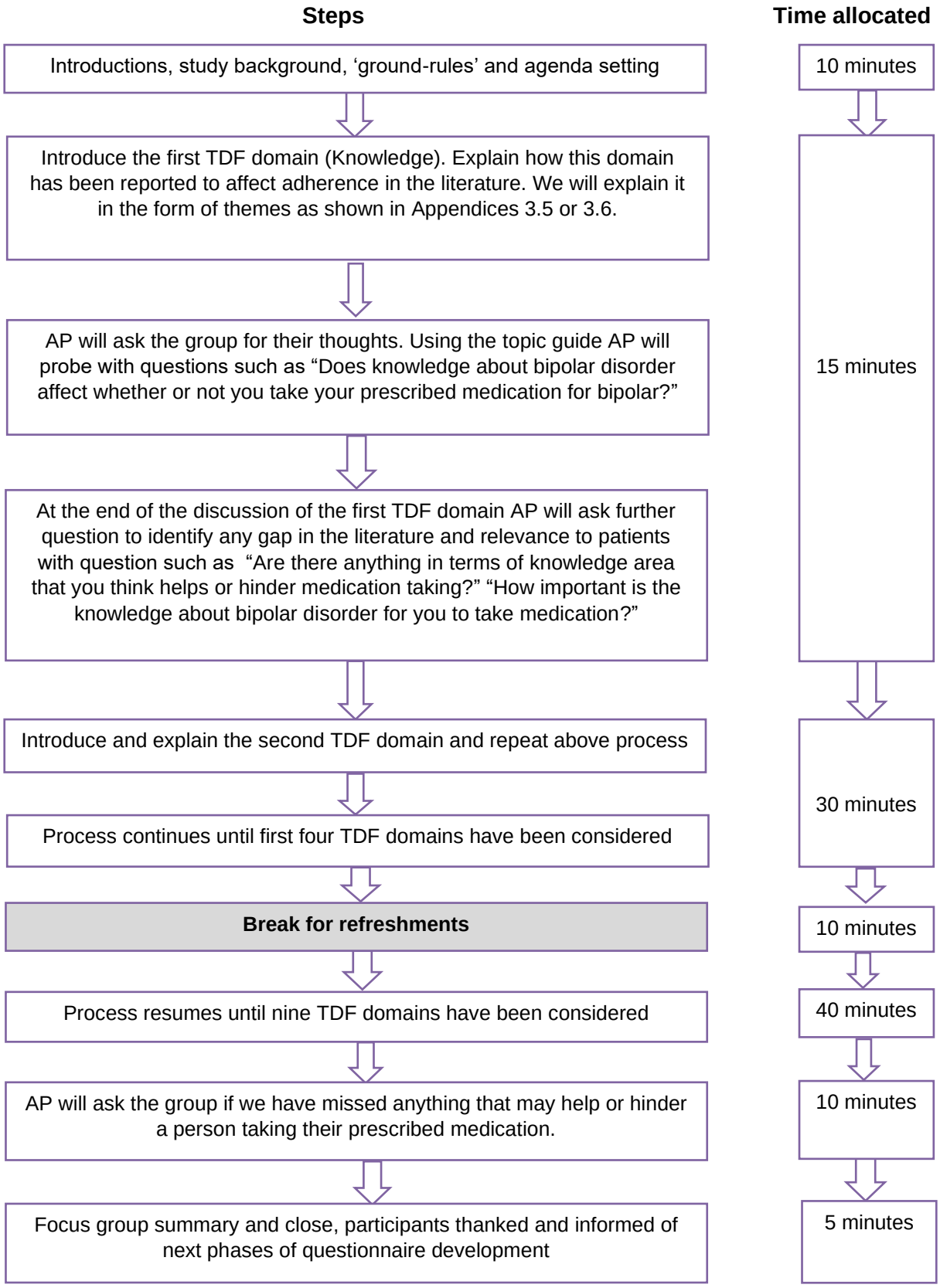
In preparation for telephone interviews, I confirmed the date and time of the interview and posted the confirmation letter along with a £10 voucher and 7-page handouts (either Group 1 or Group 2). I confirmed the receipt of these at least four days before the interview and I also called them a day before the interview to reconfirm the time and date.

The handouts sent to the participants in preparation for focus group discussions and interviews are available in Appendices 3.5 and 3.6. The handouts include a brief explanation of the TDF domain, the modifiable determinants of adherence within those domains and three specific questions that we will be discussing.

I practised mock interviews and focus group discussions with my UEA colleagues and supervisors.

I conducted the focus group discussions with a co-facilitator (SS/DB) using Skype. In the focus group, the researcher has less influence than in one-to-one interviews, allowing data and insights to be generated from a social context. AP telephone interviewed participants. Interviews lasted about an hour (35 to 75 minutes) on average and focus group discussions continued for about two hours with a short refreshment break in the middle. Both interviews and focus groups discussions were semi-structured. A topic guide (See Appendix 3.7) was used for focus groups and interviews to keep the discussion on track and on time. Figure 3.2 details the structure and time allocation for each TDF domain during focus group discussion. The same approach was followed for interviews.

Figure 3.2 Summary of focus group discussion structure



3.2.4 Data collection and analysis

Both focus group discussions and interviews were sound recorded. I transcribed the audio data verbatim for an interview. The rest of transcription was carried out by an NSFT professional transcriber. This transcribed data was inputted into NVivo 12 (103) for analysis.

I undertook the primary analysis of the data with regular input from DB, AD and JT. Transcribed data were analysed using NVivo 12 (103). A 'best fit' framework approach (187) was used to analyse the data. The priory identification of many key adherence determinants and their mapping to a framework makes the 'best fit' framework approach more suitable. At the same time, framework analysis is an established, transparent and rigorous method for qualitative data analysis. Additionally, the best fit approach provides us with the flexibility our study needs: a priory framework and prior identification of key constructs. The framework approach contains five distinct, inter-linked phases of data analysis (188,189):

1. Familiarisation – to become familiar with the focus groups and interviews data by listening to the audio or reading the transcripts
2. Identifying a thematic framework or coding – Identifying all the modifiable determinants of medication adherence within the text and coding them to relevant TDF domains
3. Indexing – Indexing all the modifiable determinants and their TDF domain
4. Charting - Rearranging the data according to the appropriate part of the thematic framework to which they relate and forming charts
5. Mapping and interpretation - using the charts to define concepts and develop themes

After reading the transcript, I extracted the chunk of text or paragraph where participants were expressing their thoughts on what was affecting their adherence. These texts were coded to the TDF domains as it was our priory framework. Another reviewer (AP, AD, DB and SS) double checked these coding. Any disagreement was resolved through discussion between the two reviewers or the involvement of the 3rd reviewer. These coding were then indexed, and a framework matrix was created. Based on all the determinants identified, key themes were generated.

Based on individual interviews and focus group discussions with patients and their families and friends, modifiable medication adherence determinants identified from the systematic review were refined, prioritised, and some new determinants not reported in previous literature were also identified. The prioritisation of the determinants was based on three key criteria:

- Direct causal relationship between the determinant and adherence (e.g., fear of side effects from Lithium stopped me from taking them in the first place)
- Sense of strength of determinants to influence adherence (e.g., I firmly believe that not taking medicines will lead me to hospitalisation)
- Strength of corroboration (e.g., not being listened to as a barrier to adherence was reported by the majority of participants)

In qualitative research, the researcher is also a part of the research process. Thus, researcher's experiences, knowledge and beliefs can influence and contaminate the research processes, data collection, interpretation and end result. This may lead to biased findings and inaccurate reflection of participant's views. In order to reduce such risk, the researcher need to self-critique and self-appraise their experiences and preconceptions that may influence research. The analytic attention to the researcher's role in qualitative research is termed reflexivity (177) which aim to promote objectivity in qualitative research. Reflexivity acknowledges that a total abstention of researcher's preconception is unlikely, and researchers are encouraged to be transparent thorough the research process.

As a practicing clinical pharmacist, I knew that I had preconceived ideas about determinants of adherence. For example, determinants related to TDF domain 'knowledge', 'environmental context and resources', 'beliefs about consequences' and 'skills' were predominant in my experience. However, to minimize the risk of my influence during participants discussion and data analysis I took following steps: 1) explored and identified my preconceived ideas about determinants of adherence 2) being attentive and fully focussed on participant's discussion and restrained myself from taking any position regarding adherence determinant and their importance 3) suspend my knowledge and experience during the discussion and analysis. Continuous acknowledgement of my own preconceptions and being mindful of their

influence on the research helped objectivity and robustness of the findings. An interesting example here is noteworthy to explain my reflexivity. As a devout meditator when a participant talked about mindfulness as a way of managing their bipolar disorder it resonated with me and I went to explore this further in the first interview despite not being explicitly relevant. However, after hearing the audio recording after the interview I became aware that it was my belief in meditation influencing the discussion and I was somehow trying to make a connection with adherence. In the subsequent interviews and focus group discussions, I was very mindful of such influence and avoided such recurrences.

Ethical Approval

The study protocol, patient information sheet, screening survey and consent form have undergone peer review via NSFT R & D. Ethical approval was received from Health Research Authority, England (REC reference:19/EE/0288), see Appendix 3.8.

3.3 RESULTS

We conducted 26 hours of interviews and four hours of focus group discussions involving 34 participants. Twenty-four participants were patients with bipolar disorder, and 10 participants were their family and friends. All participants were Whites, 23 British, and others from other European countries. Five out of 34 (14.7%) were 65 years or older. The telephone interviews and online focus group discussions took place in May and June 2020. Contrary to our initial anticipation of only six to eight interviews, most participants chose individual interviews instead of focus group discussions. Thus, we held only two focus group discussions but significantly more (n=26) interviews. Participants were mostly women representing over 80% (28 out of 34 participants). Patients' ages ranged from 28 to 76 years, and their family and friend ages ranged from 22 to 62. Participants' details are shown in table 3.3 below. Patients in the first focus group were aged 29, 62 and 66 years old and in the second focus group were 26, 31, 32, 45 and 49 years old.

Table 3.3: Demographic and other characteristics of participants

Description	Interview Participants				Focus Group Participants	
	Patients		Family & Friend		Patients	
	Group 1 (N = 8)	Group 2 (N = 8)	Group 1 (N = 5)	Group 2 (N = 5)	Group1 (N = 3)	Group 2 (N = 5)
Age range	28 to 66	28 to 76	22 to 62	22 to 62	29 to 66	26 to 49
Gender						
Male	2	2	1	1	0	0
Female	6	6	4	4	3	5
No. of Medications, Range (Median)	1 to 5 (3)	1 to 10 (3.5)	NA	NA	2 to 3 (3)	1 to 7 (5)
How often do you miss taking a prescribed medicine?						
Rarely	6	4	0	0	3	1
Sometimes	1	2	0	0	0	3
NA	1	2	5	5	0	1
Pay for prescriptions?						
Yes	6	2			0	0
No	2	6	NA	NA	3	5
How long have you had bipolar disorder? Range (Median years)	<1 year to 37 years (22.5)	<1 year to 55years (14. 5)	NA	NA	2 to 20 years (12)	2 to 14 years (6)
How often do you need somebody to help you with reading instructions or other written material from your doctor or pharmacy?						
Sometimes	3	5	NA	NA	1	2
Rarely	1	1			1	1
Never	4	2			1	2
Relationship with patient	NA	NA	Mother, Wife, Brother and Friend		NA	NA

A small number of participants in each focus group is worth explaining. Both focus groups had six to eight confirmed participants each. However, one participant sent an apology (text message) just a few hours before the first focus group meeting. She said she was feeling extremely nervous and anxious and didn't really want to participate,

but at the same time, she didn’t want to let me down. I assured her that it was absolutely fine if it is making her stressed and doesn’t want to participate as the patient’s wellbeing is of utmost importance. I offered her the option of the one-to-one interview on another date which she agreed. Another participant emailed me to apologise as her child is not well and won’t be participating. I offered her the opportunity to participate in the next focus group. A few participants didn’t join the meeting despite re-confirming their attendance a few days beforehand. Nearly double the number of participants may need to be confirmed for focus groups in the future to achieve the desired number of participants in this population.

Themes

We identified four key themes representing modifiable determinants of medication adherence in bipolar disorder: 1) The medication itself, 2) The practicalities, 3) How patients perceive themselves and their world, and 4) Working collaboratively. These four themes and the relevant modifiable determinants of medication adherence are presented in table 3.4 below.

No new themes were identified after 5-6 interviews in each group. There were very few noticeable differences between the adherence determinants reported by male and female participants despite very few male participants. Female participants were more expressive in terms of lack of support, medication interfering with life and preference for non-medicinal treatment. The role of families and friends in medication adherence was more pronounced in the families and friends' group than in the patient’s group.

Table 3.4: Theme of modifiable **determinants of medication adherence in bipolar disorder and their respective TDF domains**

Note: Green Italics = previously unreported or rarely reported, Bold = participants prioritised determinants, HCP = Healthcare Professionals

Theme 1: The Medication itself		
Facilitators	**Barriers**	**TDF Domains**
• **Acceptable formulation** • Not having to pay (e.g., >65 or other exemptions) • *Ways to minimise the cost of medication (e.g., NHS prepayment certificate)* • **Effective medication (Medication working/helping)**	• **Unacceptable formulations** • **Cost of medication or dossette box** • **Medication not working/helping** • **Pill burden / Higher number of prescribed medications** • **Higher dose frequency** • **Experience of Side effects**	Environmental context and resources
	• **Medication sedative effects interfering with life/job** • Medication reducing the quality of life	Goals
• **Decision to take medications if the benefit outweighs negative effects**		Memory, attention and decision processes
• **Belief that medication is/will be helpful**	• **Belief that It is unhealthy or unnatural to take medication**	Beliefs about consequences
• **Belief about Positive effect of medication, e.g., will keep me out of hospital** • ***Belief that not taking medication would lead to relapse or hospitalisation***	• **Belief that Mental health medications are harmful**	
	• Beliefs that medications make it harder to get well in the long term	
	• **Belief about Negative effects of medication, e.g., felt less creative, numb**	
• Understanding the reason behind why to take medications • Good understanding of how the medication works • Learning through experience that stopping medications is not a good idea	• **Not knowing the risks of stopping the medication** • **Not knowing the why medications were prescribed**	Knowledge
	• **Fear of addiction to medication**	Emotion
	• **Fear of side effects of medication**	
	• **Fear that the medication might alter personality, identity (**'Not being myself)	
	• Seeing other people having side effects	Social influences

Theme 2: The practicalities		
Facilitators	**Barriers**	**TDF Domains**
• **Having a job/routine that does not prevent taking medications** • **Being able to maintain a routine of medication taking** • ***Provision of online ordering of prescription and medications*** • ***Provision of medication delivery service*** • ***Provision of dossette box*** • ***Provision of easily accessible medicine information service Providing specific warnings related to the risk of stopping medications*** • *Not having to remember (e.g., CPN visits to inject)*	• **Irregular (or change of) daily routine or work schedule** • **Not having a daily regular routine** • **Chaotic lifestyle** • Difficulty accessing health service • Running out of medications and not being able to get them quickly	Environmental context and resources
• **Help to remember (putting medications in a common visible place)**	• **Forgetfulness** **Difficulty remembering**	Memory, attention and decision processes
• Family member managing medication (picking up from the chemist, putting in dossette box etc.) • **Family member reminding to take medications (e.g., text messages reminders)**		Social Influences

Theme 3: How patients perceive themselves and their world		
Facilitators	**Barriers**	**TDF Domains**
	• **Not accepting the need for treatment** • **Denial of illness or diagnosis/lack of insight into the illness** • denying illness severity • **Wanting to use different treatment** • ***Not wanting to take medications/chemicals*** • *Wanting to get a little bit manic*	Intentions
• ***Fear of getting unwell, relapse or hospitalisation*** • ***Fear of being sectioned or enforced medication*** • *HCPs addressing patient's Fear (emotion)*	• *Medication as an unwelcome reminder of the illness* • ***Fed up with taking medications*** • ***Feeling bothered that mood was controlled by medication***	Emotion
• Not Feeling stigmatised (I'm not ashamed)	• **Feeling stigmatised and wanting to conceal illness/medication** • *Strong dysfunctional belief that nobody wants to take medication as a barrier* • ***Reading (online, books) about negative things about medications***	Social Influences
• ***Medication being the top of the priority*** • ***Having a goal to be stable in mood*** • *Wanting to be able to function and look after the family*	• **Medication not being a priority**	Goals
• ***Identifies as someone who takes medication religiously*** • *Medications taking embedded in routine (just like brushing your teeth or putting on clothes)*	• *Seeing oneself as not wanting to be controlled by medications* • Patient seeing their role in self-adjusting the dose as the medication is not working as expected • Finding it hard to bring oneself to take medications • ***Perception that taking medications is a weakness***	Social/professional role and identity
• Having a good understanding of bipolar disorder	• Not knowing about bipolar disorder	Knowledge

Theme 4: Working collaboratively		
Facilitators	**Barriers**	**TDF Domains**
• Patient inherently trusting professionals • **Being involved in the decision about treatment choices and options** • Having autonomy and control/role over own's treatment	• **Not being involved in the decision about treatment choices and options** • **Prescriber not listening / lacks empathy**	Social/professional role and identity
• **Good relationship with prescriber** • Confidence/trust in prescriber due to prescriber's behaviour/approach/credibility • **Personal support from the healthcare service provider** • **Support from family and friends to take medication** • Positive and optimistic communication from HCPs. • Working together in partnership for recovery	• **Poor relationship with the prescriber** • Lack of trust in prescriber due to competence or credibility of prescriber • **Lack of personal support from HCPs** • **Opposition from family or friends or other HCPs** • Conflicting beliefs between patient and prescriber • Lack of real choice provided by prescriber other than medications • *Negative/pessimistic communication from HCPs* • ***Poor Communication (lack of info, unclear info, not asking for the patient about treatment, lack of communication between different HCPs) from HCPs*** • *Patient self-adjusting the dose as they are not getting help from HCPs*	Social Influences
	• **Lack of personalisation of treatment**	Environmental context and resources

I. The Medication itself

Characteristics of the medication itself were voiced by participants as a key factor influencing medication adherence. Both the actual experience of the medication and patients' perception of whether it may or may not work were prominent influencers of adherence.

> "So, I had tried other things uh a combination of olanzapine and venlafaxine, quetiapine um Lithium. I stopped them because they didn't work or help as I continue seeing things [hallucinating] and going manic…. but sodium valproate

worked …. it manages my symptoms and my bipolar, and so I take them regularly." 57-year-old male patient

"I believe the medication is going to help me, and I kind of want to make sure I keep taking them to help my quality of life." 28-year-old male patient

Experience of side effects, notably weight gain and sedation, was a common barrier to adherence. Often the severity of side effects and their impact on the individual patient determined whether patients' adherence was compromised. For example, one patient described how he continued taking his medication despite it causing chronic diarrhoea for over a year. In contrast, another patient explained that she stopped taking her medication because it made her feel numb and emotionally flat. Patients were therefore making decisions to take their medication based on whether they thought the positive effects of medications outweighed the negative effects.

In the absence of side effects experienced, emotions such as fear and worry about potential side effects such as the medication changing one's personality, 'not being myself' was a determinant of adherence.

"The only fly in the ointment is knowing about the side effects. Because then it takes away all your courage to take the medication." 66-year-old female

Participants expressed an overarching positive or negative attitude towards their medication which in turn supported adherence and non-adherence, respectively. Some participants believed that medication is or will be helpful in keeping them well and out of the hospital. Whilst others viewed medications as unnatural, unhealthy and even harmful.

Knowledge of why medications were prescribed and how they work were facilitators of adherence. Lack of knowledge about the risk of stopping medication was a barrier to adherence and led some people to stop taking their medication.

"um.. I think there isn't enough said about the risk of stopping it…..when I stopped it before…I wasn't fully warned of the consequences…it would have been nice if they'd warned me." 66-year-old female patient

Whether a patient is happy with the number of medications, medication regimen and formulation also determined adherence. For example, many patients preferred oral medication and would refuse injection, yet others preferred monthly injections as it relieves them from the need for daily medication and also relieves them from the cognitive burden to remember to take medication daily. Many patients also suggested that free or subsidised medication through UK National Health Service helped them take their medication without any financial worries.

II. The practicalities

Participants described how practical issues often affected their adherence. This barrier was most frequently described as forgetfulness which was exacerbated by the practicalities of things like the dose being in the middle of the day or changes in routine such as holidays or unusual work shifts. Participants also described how they sometimes forgot to order or collect their prescriptions or medications.

The underlying reason for the forgetfulness differed between participants; for some, it was driven by the demand; for others, it was purely not remembering or due to cognitive impairment such as impaired memory or attention; and yet for others forgetting to take medication was because it was not a priority. While many patients mentioned difficulty remembering to take medications as a barrier to adherence, some patients have put in place a system to make it easier to remember, e.g., putting medication on the dining table or bedside table. Many participants mentioned the Dossette box or pill organiser being very helpful for taking their medication. For some, the dossette box provided a routine and being able to check whether they had taken the dose for that day, while for others, it reduced the patient burden to sort out medications, e.g., popping out pills etc.

> "…. I am awful in the morning um… I get up and feed my cats. I do everything else, but my meds get forgotten." 26-year-old female patient

> "I think it's, dossette box, probably the single most useful aspect for taking medication, they are fantastic, invaluable. I mean, I actually think that the dosette

box should be part of the prescription actually." Wife of a patient with bipolar disorder

Patients' families or friends can play a significant role in improving medication adherence. A mother, who lives 30 miles away from her daughter, explained how she orders her daughter's medication from the pharmacy, sorts them out in a dossette box and then reminds her to take medication regularly.

"…you know I'm not blowing my own trumpet here but at the end of the day, if I didn't organise this, no, she wouldn't take them. She'd be all over the place, we check every morning we text cos I'm at work, so I text her it's like 'have you had your meds' and I get her to text me and tell me when she has taken them."

Some participants also stated that they have regular nurse visits to their residence to administer fortnightly or monthly antipsychotic injections. Such nurse-led medication administration helped them with medication adherence. It takes away the need to remember to take their medication daily and saves them the hassle of travelling to get prescriptions/medications, etc. Some participants mentioned how monitoring their mood and medication taking using smartphone Apps or using a chart on the wall helped them take their medication as prescribed.

Getting quick information about medication, e.g., whether one can reduce the dose if experiencing some side effects etc., was important to participants.

"I've done that all the time, self-adjust because I thought I can. The other trouble is you have to wait three weeks to see your doctor so um I thought that's ages that's ages but something like my illness you should be able to see someone straight away because three weeks you can be in a totally different, so I did adjust mine." 56-year-old female patient

III. How patients perceive themselves and their world

Patients' perception of themselves, bipolar disorder and its treatment influenced medication adherence.

Some patients expressed their dislike of being controlled by medication, and some did not take their medication because they saw taking medication as a sign of weakness or giving in.

> “Taking meds would make me feel very, very um weak, I suppose…like sort of giving in and weak.” 35 years old female patient

Patients who do not accept a bipolar diagnosis, who lack insight into the illness, who deny the severity of the illness or the need for medication and patients who felt bothered that their mood was being controlled by medication were more likely to be non-adherent.

> “My son did not want to take medication because he says that - he wasn’t ill, there’s nothing wrong with him, doctors got it wrong." *Mother of a son with bipolar disorder*

Patients who saw medication as an unwelcome reminder of the illness or fed up with taking medication often stopped or skipped their medication. Patients who viewed medication as a harmful chemical and would prefer non-medicinal treatment were often non-adherent.

> “I wanted a natural answer really. So, I took things like starflower oil and different things. I used to go to the health food shop and the chemist and all that...so I did take natural supplements and different things.” 56 years old female patient

Some patients described how they feel ashamed or embarrassed (e.g., to go to the pharmacy to pick up medication), while others expressed that they don’t feel any stigma. Whether patients felt stigmatised and wanted to conceal their illness and/or medication influenced medication adherence.

Patients’ view of medication is often a reflection of what they hear or read online, on social media etc. And some patients described how they are influenced by negative stories about medication in the media. Some patients did not take their medication because they believed that nobody wants to take medication, and thus, viewing that not wanting to take medication is the norm.

> “They’re toxic, pharmaceuticals are toxic, nobody wants to take medication, do they?” 56 years old female patient

Patients with a good understanding of bipolar disorder and its treatment tend to adhere to their prescribed regimen and vice versa. A 28-year-old male patient discussed the importance of understanding bipolar and its impact on adherence:

> “So, every few years, I would have an episode when I was much younger, about 23, 24. I refused to take medication because I didn’t know what was going on. Now, having understood bipolar, I know how important it is to take medications, I sort of take it a bit more seriously.”

Another patient questioned why she needed to go on medication for something like this as she said she didn’t have much knowledge about what bipolar disorder was. Some patients explained that having knowledge of bipolar disorder helps them realise the reasoning behind taking the medication regularly.

Patients who are fearful of getting unwell, relapse or hospitalisation, being sectioned if they don’t take their medication tend to have good adherence. Other patients saw taking medication itself as rewarding as they saw positive effects of medications such as improved quality of life. Some participants see medication taking as a journey and described how they learn through the experience of non-adherence and its consequences which later motivated them to take their medications regularly.

> “I’m too scared to not take my medication and end up hospitalised again…I just take it because I’m just fearful that if I don’t take it what will happen.” 24 years old female patient

Whether patients see medication taking as a priority or not affected medication adherence. Some patients see medication taking as their top priority to remain well and stable and identify themselves as someone who takes their medication religiously.

> “My medication is very important to me coz it helps me out in so many other ways of my life sort of thing, um, and I don’t think at any point there will be anything that can take a priority over my medication, to be honest.” 28 years old male patient

For others, taking medication is embedded into a daily routine so profoundly that they see medication taking as a part of the routine, like brushing their teeth.

Some patients adjusted their dose without consulting healthcare professionals because the medication has not been working to their expectations, and they feel they can tweak the dose.

IV. Working collaboratively

Patients, their family and friends and healthcare professionals working together facilitated medication adherence and vice versa. Working collaboratively was primarily described in terms of patients' involvement in their treatment decisions, availability of personal support, financial or social reward, the relationship between patients and healthcare professionals, conflicting beliefs between patients and healthcare professionals, lack of personalisation of treatment and communication.

Whether patients are being offered treatment choices and whether treatment decisions were made in partnership with patients influenced medication adherence.

> "…in my experience, you don't get a lot of involvement in how you're treated … you're not really treated as a person with an opinion or any rights…it does make you feel like it's something that's been imposed upon." 54-year-old male patient

Some patients complained that there was a lack of real choice apart from medication to manage their bipolar disorder. They suggested that healthcare professionals need to work with patients and offer broader treatment options based on their preferences.

Personal support was described in as psychological support, such as providing assurances about medication and practical support, such as sorting out medication. Support or lack of it influenced medication adherence. A mother explains how her daughter is unlikely to be taking her medication without her working with her daughter and providing practical support:

> "If I didn't organise her medication, no, she wouldn't take them. She'd be all over the place."

Participants saw monitoring of medication adherence by healthcare professionals as an encouragement to take their medications. On the contrary, lack of personal support from healthcare professionals, making patients feel like the “system doesn't give a toss”, discouraged patients from taking their medications. Some patients self-adjusted the dose of their medication as they were not getting any help from healthcare professionals on time.

Some participants suggested that some sort of financial, e.g., vouchers or social reward e.g., personal care and attention, can facilitate medication adherence. But others stated that any such reward is often short lived and unsustainable.

> “Any incentive scheme is short lived cos after a while people won’t be motivated by anymore, these things are always short term” Brother of a patient with bipolar disorder

Participants explained how the relationship between patients and healthcare professionals was very important for medication adherence. Participants discussed how feeling being listened to and understood and feeling like an equal partner in the treatment is critical for a good relationship. Similarly, healthcare professionals who are accessible, trustworthy, empathetic, friendly, approachable and non-judgemental are more likely to have a good relationship. As expected, a good relationship facilitated adherence and vice versa.

> “It’s important to have a good relationship because when you lose the trust of the patient the likelihood is they won’t take any meds.” 35-year-old female patient

Poor relationship with healthcare professionals was discussed in terms of not being listened to, rushing during the appointment and not showing interest in the patient, not being friendly and approachable, not being honest and open about medication, not looking at patient’s problems holistically, lack of engagement, information and empathy. Some patients explained that their relationship with healthcare professionals was dependent upon whether they had confidence in them, and this affected their decision on whether to take their medications.

Some patients mentioned how relationships can deteriorate and adherence can be compromised due to conflicting beliefs between healthcare professionals and patients.

For example, some symptoms of hypomania led patients to be very energetic and productive which they enjoyed but healthcare professionals saw it as symptoms to be subdued. Some patients said that they wanted to try and reduce the dose, but healthcare professionals are not interested in their views. A 66-year-old lady described how her homeopath's view conflicted with mental healthcare professionals and her homeopath often discouraged her from taking her medications.

Communication plays an important role in encouraging or discouraging medication taking. Negative, pessimistic, and poor communication from healthcare professionals was described as a barrier to medication adherence. A mother described how her son absolutely refused to go on antipsychotic injection because healthcare professionals had not communicated well with him:

> "When he was in the hospital, that's what they decided and said he needs to go on a depo [long-acting injection]. And he was just absolutely horrified he said, 'I never consented to this' and the way at that meeting we had, they almost had a smirk about it saying, 'no you don't consent to this'. I just couldn't believe it and they didn't put that very well to him at all. That was absolutely oh my goodness, it weighed so heavy on him."

This patient took the matter to the mental health tribunal and won the case, so he did not go on the antipsychotic injection.

Most of the determinants of adherence described by patients and their families and friends overlapped. There were, however, few notable differences. Medication's interference on the way of life and influence of side effects on medication adherence was more pronounced in the patients' group than in the family and friends' group. This is logical and reasonable as patients are the ones with lived experience. On the other hand, family and friends saw their role in supporting medication adherence far more critical than patients although some patients explained how they would not have been taking their medication if it was not for the support of their family and friends.

Mapping of the determinants to TDF domains

Table 3.4 presents the determinants of adherence and their corresponding TDF domains. Determinants were presented as barriers or facilitators. Some facilitators are the opposite of barriers, such as beliefs about positive effects of medication is described as a facilitator of adherence whereas beliefs about negative effects of medication as a barrier. In other cases, facilitators are described as a BCT to overcome the barrier, such as forgetfulness being presented as a barrier and facilitator being putting medication in a common visible place like a bedside table which would fall under BCT 'Restructuring the physical environment' (80). Determinants in *italics (green)* are rarely reported in the literature and those in the bold text are the ones that were prioritised by our participants.

Exploring previously under-reported determinants in addition to well-established determinants has provided us with a more comprehensive list of adherence determinants in bipolar disorder. Prioritisation of the determinants from the perspectives of patients and their families and friends will help us which determinants need more focus and resources. More importantly, mapping these determinants to the TDF domains will help develop healthcare profession friendly adherence support tool with evidence based BCTs.

3.4 Discussion

Many modifiable determinants we found in our study are frequently reported in the literature (20,39,63). So, we will unpick some of the determinants that were unreported or less recognised or the determinants which are more nuanced or subtler than previously reported. Historically, determinants of adherence are reported without differentiating between what is modifiable vs what is not (20,39,63). For example, age and ethnicity cannot be modified whereas knowledge about medication can (76)**.** We focused on modifiable determinants of adherence in this study as these determinants can be targeted in adherence interventions to improve adherence. Some differences between male and female participants reported determinants are likely to be due to the smaller number of male participants. Nonetheless, the difference was not

significant as the difference was more in the magnitude of expression rather than an absence of those determinants in male participants.

The reported relationships between non-adherence and characteristics of the medication itself are inconsistent. There are some reports of increased regimen complexity such as multiple medicines/multiple daily doses, the experience of negative side-effects and sub-optimal efficacy adversely affecting adherence, yet there are also reports of them having no effect on adherence (17,27,128,141). The narratives offered by study participants offer some explanation for this inconsistency as there is a complex interplay between the characteristics of the medication itself and the value that the patient attributes to the medication's ability to improve their overall wellbeing. This complexity is in turn, reflected in the two TDF domains of 'Environmental context and resources' or 'Memory, attention and decision processes' being the driving force of the non-adherence. In these circumstances, the prescriber is required to facilitate the patient in balancing the pros and cons of adhering to the medication. This activity will contribute to deciding whether adherence may be facilitated by changing the environmental context, e.g., prescribing a different medication, or whether the patient's expectations of medication in terms of complexity, side effects and efficacy may be unachievable and therefore require re-shaping.

Furthermore, in circumstances where concerns regarding the efficacy and side effects are voiced by patients, it is essential to distinguish between patient dissatisfaction primarily driven by their experience of the medication and dissatisfaction driven by beliefs about what may happen. In the former, where possible, a change of medication may be warranted whilst the latter requires exploration of the patient's ideas and concerns before any change is considered. This is reflected in mapping these determinants to either 'Environmental context and resources' for the former or 'Beliefs about consequences' for the latter.

Education is a frequently cited component of medication adherence interventions (190). Whilst knowing how the medication works and why it is important is an enabler of adherence, the absence of this knowledge was not voiced as a barrier. However, insufficient knowledge about the negative consequences of suddenly stopping medication oneself was a barrier to adherence. Given that excessive information provision can both compromise recall by the patient and the patient prescriber

relationship (191,192), prescribers may wish to prioritise ensuring that patients have a clear understanding of the harms associated with treatment cessation without medical advice.

Forgetting to take medication is a widely reported adherence barrier and this study has revealed that under the umbrella of 'forgetting', there was a difference in its antecedents. For some, it was the environment not being conducive to remembering whilst for others, it was a conscious prioritisation decision. Establishing the antecedents is essential to selecting the most appropriate behaviour change techniques given that a conscious decision relates to motivational factors including, 'beliefs about consequences' and 'Goals' TDF domains. In contrast, an unconducive environment may be addressed by targeting 'Environmental context and resources' domain. The conflicting evidence regarding the effectiveness of reminders to improve medication adherence (193,194) may be explained by this insight provided in our study of different antecedents of forgetfulness. The mainstay of current practice such as text messages or other reminders, pill boxes and education (21,85), is not targeting different antecedents leading to forgetfulness. Furthermore, the distinct antecedents of forgetting have not been recognised in previous systematic reviews of adherence barriers (39,63,165).

The influence of other people on the ability and motivation of patients to adhere was demonstrated by the practical support offered by family and friends to undertake the activities needed to adhere such as collecting prescriptions. In the absence of existing practical social support, guiding patients to access pharmacy provided services such as repeat prescription collection and delivery and technology such as reminder apps may address this barrier to adherence.

Timely access to information to aid a patient's decision making regarding whether to adhere to their prescribed medication directions was important. This emphasises the high level of involvement that patients expect in decision making regarding their medication. The absence of timely information may therefore lead to patients adjusting their medication dosing without first securing expert advice. Adherence intervention often comprises education, however, there is a clear distinction between general education about medications for bipolar disorder and the tailored advice desired by patients to inform their decision regarding medication adherence. Less than half of UK

mental health trusts provide patient medication helplines (195); universal provision of such a service may address this barrier (195).

There have been national and global efforts to address the long-held stigma associated with mental health problems; for example, the World Health Organization led ‘World mental health day’, National Alliance on Mental Illness led ‘Stigma free’ campaign and UK Mental Health (Discrimination) Act 2013. However, the negative connotations of mental health problems remain present. The resulting negative association with taking medications for a mental health problem is a barrier to adherence such as being an unwelcome reminder of having a diagnosis of bipolar disorder. Similar findings have been reported with medication for physical health problems as taking medicines is a reminder of otherwise asymptomatic conditions such as hypertension and therefore generating negative emotions such as anxiety about having a diagnosed physical health condition (46). In contrast, we have mapped this determinant to social influence in recognition of it being driven by the stigma of a bipolar disorder diagnosis. This deeply ingrained stigma also manifested as patients choosing treatments other than medication. Healthcare professionals should therefore be aware that patients may benefit from being supported to reframe how they perceive their diagnosis and medication. Potentially relevant BCTs to address this determinant are ‘Framing/reframing’, ‘Social Comparison’ and ‘Comparative imagining of future outcomes’ (80).

Fear is often portrayed in the literature as one of the barriers to adherence, such as fear of the negative effects of medication (39,63,165). The fear expressed by our study participants, however, had a dual effect whereby fear of relapse or hospitalisation because of non-adherence was a facilitator of adherence. Thus, our study shows that some fear can motivate patients to adhere. Where patients had a bad experience of previous non-adherence, a reminder of such events using BCTs like ‘anticipated regret’ or ‘imaginary punishment’ may help patients stick to medication taking routine (80).

Social influences are well established determinants of medication adherence (39,63,165). Our study shows that patient’s perception of the social norms can affect motivation to take their medications, particularly if it is perceived that taking medication for mental health is not normal. In such a situation, patients would be better served by

healthcare professionals trying to understand the patient's viewpoint, discussing some factual information (BCT such as 'Credible sources' or 'Social comparison') and then negotiating a mutually agreeable and clinically appropriate action plan. Prescribing medication in haste without such negotiated plan is unlikely to be helpful in this context.

Shared decision making and treatment choices affect adherence (113), however, involvement in decision making and treatment options are personal choices. Our study shows that while patient involvement may be very important for many patients, for some patients' decision making and treatment choices could present a great burden. For some patients, too many choices and options make it harder as they do not consider themselves experts in medication. So, for some, less is more - giving some basic info and limited option rather than comprehensive lists of options may work better. Thus, healthcare professionals need to tailor information to patient's needs and preferences. It is, however, clear that patients should not feel that the medications are being imposed upon them, a clear barrier to adherence. The impact of effective collaboration between healthcare professionals and patients on medication adherence is well known (39,63,165) (113); however, the impact of such collaboration between patients and their family and friends may be underappreciated. Considering the significant influence of patients' families and friends in managing medication in mental health patients, their role should not be underestimated. Patients' families and friends may be an untapped resource to improve adherence.

Strengths and Limitations

One of the key strengths of this study is the use of a comprehensive behaviour change framework, the TDF, to guide the discussion during focus groups and interviews. This enabled the identification of previously unreported modifiable adherence determinants. Another strength is the focus on modifiable determinants of medication adherence, thus providing the patients and healthcare professionals with some salient pointers that they can work together to improve adherence. Refinement and prioritisation of the modifiable determinants provided a better understanding of those determinants and those needing more attention.

The lack of patients' families and friends' views on medication adherence determinants was a clear gap in previous studies. This study bridges this gap. Families and friends of patients are an untapped resource that could be utilised to improve adherence.

The lack of ethnic diversity among participants is a limitation. Stigma, denial of illness and medication may be more prominent in an ethnic minority group. However, these determinants were shown to be important in this study. A very few male participants may underrepresent male patient's perspectives of determinants but the difference in the determinants was mostly in the magnitude and not in substance.

Norfolk county has relatively higher proportion (24.6%) of older (65 and over) population compared to England's national average (18.5%) (196). Thus, recruiting participants from Norfolk only could have led to higher proportion of older participants taking part in this qualitative research and consequent dominance views from older population. However, the study participants were broadly spread out in the age groups and over 65 represented 14.7% of total participants.

It is also noteworthy that NSFT used to provide medication information service to patients and public up until 2016 when the service was discontinued. This may have influenced some participants view on importance of such service on adherence. Participants with previous positive experience of the service may have been more vocal about the need of such service. But, provision of information and their influence on medication adherence is evident in the literature (15,39,165).

CHAPTER FOUR

Development of

Collaborative Medication Adherence in Bipolar disorder Questionnaire (C-MABQ)

4.1 Introduction

Chapter 3 lists the prioritised modifiable determinants of medication adherence in bipolar disorder based on the focus group discussions and interviews with patients and their families and friends. In this chapter, I will describe the development of a tool to identify an individual's determinants of medication adherence underpinned by a comprehensive behaviour change framework. This tool/questionnaire is called 'Collaborative Medication Adherence in Bipolar disorder Questionnaire (C-MABQ)'.

The magnitude of the problem of non-adherence, its clinical and financial implications have been previously discussed in Chapter 1. One of the key challenges to successfully addressing non-adherence is identifying an individual's modifiable determinants (barriers and facilitators) of adherence and providing tailored support based on their determinant of adherence as described in Chapter 1. However, no gold standard tool exists for identifying and addressing determinants of medication adherence in the mental health population. Currently available validated adherence questionnaires in bipolar disorder and other mental health conditions, their clinical use and their limitations are discussed in Chapter 1. Existing adherence questionnaires focus on the nature of the behaviour (non-adherence), e.g., frequency and magnitude, rather than the determinants of non-adherence. Additionally, there is an absence of comprehensive behavioural theory underpinning the development of most questionnaires despite this being critical for the development of any behaviour change intervention (48,52).

The premise behind C-MABQ for identifying an individual's determinants of medication non-adherence is to inform the development of an individualised intervention to improve adherence that is tailored to address these specific determinants.

Development of preliminary C-MABQ statements

Formulation of statements for a questionnaire is a critical part of designing an effective questionnaire since it can affect how respondents answer the questions and thus can affect the validity and reliability of the questionnaire (197). For example, responses to questions are influenced by the words used in the questions, the structure and tone of questions, readability, word counts and response options (197,198).

The BRUSO Model recommends that statements should be (197):

I. **B**rief – Statements should be brief and simple. It is often recommended that each statement should be less than 20 words and should have no more than three commas.
II. **R**elevant – Every statement and words in that statement has costs associated with it such as the cost of developing, testing, administering and analysing. Thus every word and every statement should only be included if they are relevant.
III. **U**nambiguous - Statements should be clear without any words that are unfamiliar or have multiple meanings. They should be easily understood by the general public with no more than a middle school education.
IV. **S**pecific – Statements should be specific enough to provide the answer that the question is trying to elicit but not too specific that many patients are excluded from answering the question.
V. **O**bjective – Statements should be unbiased and non-leading.

Similarly, font size and style can affect appeal, engagement and how easy it is to read; Sans serif font style (such as Helvetica, Verdana, Arial, Calibri) is considered objective, simple, straightforward, sensible and a common choice for reading (199,200). Moreover, ordering the statements in a questionnaire is also very important (197). In general, it is recommended that the first question should be relevant to the central topic, easy to answer, engaging, applicable to and answerable by most respondents, closed and not sensitive (201). Similarly, ordering the section or group of statements should follow their relevance, ease, interest and a smooth progression (201). Sensitive questions are better placed latter part of the questionnaire but not the last one (201).

Turning the modifiable determinants of adherence from Chapter 3 into statements that are well understood, interpreted correctly and in the same way by all patients requires multiple stakeholder input.

Consultation with stakeholders such as healthcare professionals and experts in the area, who will be evaluating patients' responses to C-MABQ, will not only ensure the relevance of C-MABQ statements to adherence but will enhance the face and content

validity (97). Face validity is testing if the questionnaire, at face value, appears to measure what it claims to measure whereas content validity refers to whether statements on an adherence questionnaire fairly represent most determinants of adherence (202). It is recommended that the questionnaire should be evaluated by five to seven experts in the area (97). Evaluation of questionnaires by patients is critical for developing effective questionnaires and to test face validity (97). A cognitive interview is a validated method to evaluate respondents' understanding of the questionnaire, how they retrieve information to answer the question, how they decide to answer and can their response actually match how they intend to answer (203). Thus, the aim of the consultation with healthcare professionals and cognitive interviews with patients is to refine the C-MABQ so that it is relevant, easily understood and answered.

Thus, in this chapter, I will explain the development of the C-MABQ, through the process of consultation with experts in behavioural medicine and healthcare professionals and cognitive interviews with patients.

4.2 Methods

The development of C-MABQ involved the following three steps:

I. Develop preliminary C-MABQ statements based on the prioritised modifiable determinants of adherence as listed in Chapter 3. Discuss these statements with the experts in behavioural medicines and agree the first draft of C-MABQ called C-MABQ v1.
II. Consult C-MABQ v1 with healthcare professionals and make any changes necessary to C-MABQ v1. The amended C-MABQ v1 is called 'C-MABQ v2'.
III. Conduct cognitive interviews with patients using C-MABQ v2 and make any changes necessary to generate the final C-MABQ.

4.2.1 Development of C-MABQ v1

Formulating preliminary statements

I generated preliminary statements for C-MABQ v1 capturing the prioritised modifiable determinants of medication adherence in bipolar disorder listed in Chapter 3. If the adherence determinant included more than one concept, I developed at least one

statement per concept. For example, forgetfulness is described as forgetting to take medications and forgetting to pick up prescriptions or medications from doctors or pharmacies. So, I created two statements to capture both concepts. Additionally, I created more than one statement for some determinants capturing just one concept if that determinant can be expressed in different ways. These multiple statements for the same determinant provided options to experts in behavioural medicine for choosing an appropriate statement. While developing these statements, I followed the BRUSO model for statement generation; I avoided acronyms, jargon, long and complex questions, complex terms/concepts, double negatives and double-barrelled statements (197,204,205). I used a mixture of both positively and negatively phrased statements to reduce the risk of acquiescent response bias, whereby respondents tend to respond to each statement in a similar way. Such combination of the positive and negative phrases was also recommended by patients and relatives' representatives on our research advisory board.

Refining and selecting from preliminary statements and developing response options

These preliminary statements were then discussed together with AD (Psychologist with previous experience of developing adherence scales), CG (Psychologist with expertise in patient related outcome measures) and DB (Professor in behavioural medicine) in group meetings. We held three separate 1 to 2 hours meetings where we discussed and considered each statement and potential response options. Some preliminary statements were amended, and appropriate statements were chosen from multiple statements covering the same determinant. AD, CG and DB also checked and agreed to the mapping of the C-MABQ v1 statements to the TDF domains.

4.2.2 Consultation with healthcare professionals to evaluate face and content validity

I consulted with healthcare professionals for their feedback on C-MABQ v1 based on their experience of consulting patients and prescribing medication for bipolar disorder. The eligibility criteria for healthcare professionals to take part in this consultation were:

- Currently working in mental health settings AND
- Have at least one year of experience working in mental health settings AND

- Involved in front line care of patients with bipolar disorder

See Appendices 4.1 for Participants Information Sheet, 4.2 for the screening form and 4.3 for a consent form. We recruited healthcare professionals from NSFT who met the above criteria. Each consultation involved a 15-minute phone conversation to clarify what specific information (see below) was being sought from them. Following the phone conversation, I asked them to complete Microsoft Excel Spreadsheet with their responses at their convenience. The spreadsheet contained a brief introduction:

"Following statements are based on the barriers and facilitators of medication adherence in bipolar disorder. These barriers and facilitators were identified through literature review, interviews and focus group discussions with patients with bipolar disorder and their families and friends. We would be very grateful if you can complete this survey and provide your honest feedback. In a way, we are trying to sense check these statements with you and to see if we have missed any barriers or facilitators of adherence."

After this brief introduction, the spreadsheet included the determinants of adherence and their corresponding statements (C-MABQ v1) with the following three specific questions related to each statement (Questions I to III) and one question related to each section (Question IV) and one broad question to explore any determinants not reported in Chapters 2 and 3 (Question V).

I. As a determinant of medication adherence, does this statement make sense to you? Does the statement cover the adherence determinant listed?
II. Is the statement clear and unambiguous to you?
III. Do you have any other comments about this statement?
IV. Are you happy with the order of the statements in each section? Or is there any statement that is out of place?
V. Are there any other determinants of adherence we may have missed?

Based on the findings of this consultation, C-MABQ v1 was amended. This amended C-MABQ v1 is called C-MABQ v2. Face validity was subjectively measured based on the responses to first four questions above (I to IV). If the participants responded that the statement did not make sense or needed clarification or suggested amendment to make it unambiguous or any other comments to improve the statement, then the

feedback would have been incorporated and the statements resent to the participants for further feedback. If there was no or minimal change suggested, then face validity was considered to have been established. Similarly, based on response to Question V, content validity was assumed if no additional determinants were suggested or suggested but discarded due to irrelevance or inapplicable.

4.2.3 Cognitive interviews with patients to evaluate face and content validity

I conducted cognitive interviews with patients using C-MABQ v2. Patients were recruited from NSFT who met the following criteria (See Appendix 4.4 for participant screening form):

- Diagnosis of bipolar disorder and
- Taking medication for bipolar disorder and
- Able to provide consent

Patients recruited for cognitive interviews were either those who expressed interest in participating in focus groups and interviews but could not take part or those referred by participants in focus groups and interviews. Participant information sheet, Appendix 4.5, provided more details regarding the study to potential participants. Patients who provided consent (see Appendix 4.6 for consent form) to participate in the cognitive interviews were sent a copy of C-MABQ v2 before the interview. The purpose of cognitive interviews was to identify any difficulties in understanding and responding to the C-MABQ v2 statements. At the beginning of the interview, I explained the purpose of the interview. During the interview, I asked them to read aloud each statement and respond verbally. Then I asked if they understood the statement if there was anything confusing about the statement, how they reached the response decision etc. See Appendix 4.7 for the procedure for cognitive interviews for more details. I also asked participants whether any presentation features needed altering, e.g., font style, size, colour, etc. Based on the cognitive interview findings, necessary refinements to C-MABQ v2 were made to produce the final C-MABQ.

Face and content validity were measured subjectively based on responses from patients. The C-MABQ v2 is considered to have face validity if patients understood and interpreted the questions correctly, responded without any difficulty and minimal or no changes were suggested during cognitive interviews. Similarly, content validity

of C-MABQ v2 was considered to have established if no new determinants was identified during cognitive interviews.

The final C-MABQ was evaluated for word frequency count and readability score using app.readable.com and app.grammarly.com. A readability score is a number that describes how easy it will be for someone to read written text (206). There are many different methods of calculating readability scores and different methods can give different results (206). Based on Flesch–Kincaid reading ease score, higher readability scores indicate better readability (206). Although readability score will differ based on the audience, it is generally recommended to aim Flesch–Kincaid reading ease score of 60 or more or a Flesch–Kincaid reading grade level of 8 (easy to read by 11-12 years old) or less for patient health information (206,207).

Ethical Approval

Ethical approval was received from Health Research Authority, England (REC reference:19/EE/0288).

4.3 RESULTS

4.3.1 Development of C-MABQ v1

Formulating preliminary statements

I formulated 75 statements based on the prioritised modifiable determinants of adherence - see appendix 4.8 for the complete list of preliminary statements, their corresponding determinants and the TDF Domains. Many of the determinants have more than one statement; for example, four statements were generated for determinant ‘1.4 Not knowing the risks of stopping medication’ (see Table 4.0 below). These variations often represented situations where it was unclear if the determinant should be negatively or positively phrased for ease of reading and what language would best represent the determinant.

Refining and selecting from preliminary statements and developing response options

Out of the 75 statements, 51 statements were selected. These 51 statements were refined and re-ordered as C-MABQ v1 as shown in table 4.1 after discussion with AD,

CG and DB. Where multiple items were developed for a determinant, the version was selected because it fully captures the determinant, is direct, simpler and easier to understand and is presented as natural conversation. For example, the negative phrasing in statement 4 below (bold) was selected because it was more natural, easier to understand and is more direct.

Table 4.0: An example of prioritised determinant and proposed statements to capture that determinant

1.4 Not knowing the risks of stopping medication	5. I am unsure about the risks of stopping my medications. OR 6. I understand very well the risks of stopping my medications. OR 7. I don't know what would happen if I stop taking my medications. OR 8. I know that I will become unwell if I stop taking my medications.

We agreed on a five-point Likert scale response option as it offers more precision than a three-point Likert scale (197) and less burden to participants in processing response options than a seven-point Likert scale whilst providing a similar level of information (197).

We agreed on three five-point Likert scale response options: Easy/Difficult, Agree/Disagree and Acceptable/Unacceptable. This decision was based on which response option would best reflect the adherence determinants. For example, when checking with the patients if they felt they were listened to by their healthcare team, we used the agree-disagree scale. Whereas asking about sticking to the routine of medicine taking was best fitted with the response option easy-difficult scale. Furthermore, the number of medicines as a determinant was best asked as an acceptable-unacceptable response option because acceptability to the individual patients was the important factor rather than the number of medicines per se.

We divided the structure of the questionnaire into three sections based on their response options: 1) Easy/Difficult section, 2) Agree/Disagree section, and 3) Acceptable/Unacceptable section and their ordering. We put the 1st section at the beginning of the questionnaire as they are relatively simple, easy to answer and applicable to most. The first question is about remembering to take medications which

is one of the most common barriers to adherence. Furthermore, the first section is short and cognitively easy. The order and structure of the statements were organised to flow smoothly within each section.

Table 4.1: C-MABQ v1

Please put a cross (X) to the answer that best reflects you.

Section ONE Statements	Very Easy	Easy	Neutral	Difficult	Very Difficult
1. Remembering to take my medicines is					
2. Remembering to collect my medicines from the doctors or pharmacy is					
3. Sticking to a medicine taking routine is					
4. Obtaining medicines advice from my healthcare team is					

Please put a cross (X) to the answer that best reflects you.

Please notice the different response options.

Section TWO Statements	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
5. I am unsure of how and when my prescriber would like me to take my medicines.					
6. I don't understand why I was prescribed my medicines.					
7. I do not recognise myself as someone with bipolar disorder.					
8. I don't need medicines for my condition.					
9. I don't want to take my medicines for my condition.					

10. I prefer to use treatments other than what my doctor prescribes.					
11. I believe that mental health medicines are harmful.					
12. I have read or heard things that make me doubt my medicines.					
13. Medicines are being imposed upon me.					
14. I don't like the idea of my mood being controlled by medicines.					
15. I am unsure about the risks to my health from stopping my medicines.					
16. I don't want people to know that I have this condition.					
17. My healthcare team listens to me.					
18. My healthcare team is there for me when I need them.					
19. I have a good relationship with my prescriber.					
20. My friends and family are supportive of my mental health.					
21. People judge me because of my illness.					
22. People around me do not like me taking my medicines.					
23. I believe that I will become unwell if I stop taking my medicines.					
24. In terms of my health, the positive effects of my medicines outweigh any negative effects.					

25. I believe that taking my medicines keeps me well.					
26. I need to continue to take my medicines no matter what my mood is like.					
27. I have ways to help me remember to take my medicines at the right time.					
28. I have a set routine to help me take my medicines at the right time.					
29. Taking my medicines as prescribed is a top priority for me.					
30. Other things take priority over my medicines.					
31. My medicines make it difficult for me to get on with my life.					
32. My medicines get in the way of my life.					
33. I have practical problems with collecting my prescriptions or medicines.					
34. I worry about getting addicted to my medicines.					
35. I worry about the side effects of my medicines.					
36. I worry about being sectioned if I do not take my medicines as prescribed.					
37. I worry that I may harm myself or others if I do not take my medicines as prescribed.					
38. I fear of not being myself if I take my medicines.					
39. Getting unwell and hospitalised because of my condition really frightens me.					

40. I am fed up with taking medicines to control my condition.					

Please put a cross (X) to the answer that best reflects you.

Please notice the **different response options**.

Section THREE Statements	Totally Acceptable	Acceptable	Neutral	Unacceptable	Totally Unacceptable
41. The extent to which my medicines are working is					
42. The side effects I'm getting from my medicines are					
43. The amount of support that I am getting from my friends and family to take my medicines is					
44. In my culture, a diagnosis of mental health is					
45. In my culture, mental health medicines are					
46. My involvement in decisions about my treatment is					
47. The prescription cost for me is					
48. The number of medicines prescribed for me is					
49. The type of medicines prescribed for me is (For example: tablets, capsules, liquids, injections)					
50. The doses (amounts) of the medicines prescribed for me are					
51. The number of times a day I have to take my medicines is					

4.3.2 Consultation with healthcare professionals to evaluate face and content validity

Six healthcare professionals; two psychiatrists, two psychiatric nurse independent prescribers and two pharmacist independent prescribers; were recruited for consultation of C-MABQ v1.

Following consultation with healthcare professionals following changes were made to C-MABQ v1 statements:

- Response option ‘Neutral’ in section one and ‘Totally Acceptable’ in section three were changed to ‘Neither easy nor difficult’ and ‘Perfectly Acceptable’ respectively.
- Term ‘Condition’ was changed to mental health condition in statements 8, 9, 16, 39 and 40.
- Term ‘Healthcare team’ was changed to ‘mental health team’ in statements 4, 17 and 18.
- Term ‘prescriber’ was changed to ‘mental health team’ in statement 19.
- Term ‘illness’ was changed to ‘mental health condition’ in statement 20

Further changes to C-MABQ v1 are presented in table 4.2 below together with changes after cognitive interviews. Apart from changes suggested, the healthcare professionals agreed that the statements represented the determinant of adherence and the statements were unambiguous suggesting good face and content validity.

Although healthcare professionals thought the list of determinants is comprehensive, some suggested additional determinants of adherence: not liking the effects of their mood being artificially flattened or controlled, low mood, substance misuse, knowing which medications are for bipolar disorder, being able to talk to the healthcare team about side effects, knowing where to find good quality information about my medications and side effects.

4.3.3 Cognitive interviews with patients to evaluate face and content validity of C-MABQ v2

Seven patients, four females and three males aged 27 to 69, were recruited for the cognitive interviews. Overall, all patients understood and interpreted most of the C-MABQ v2 statements and responded as they intended suggesting good face validity.

The presentation, layout, font size, colour and style were well received, with no change recommended. Patient recommended changes to the C-MABQ v2 statements are shown in table 4.2 below.

Table 4.2: Changes made to C-MABQ statements after consultation with healthcare professionals and cognitive interviews with patients

Changes to C-MABQ v1 after consultation with healthcare professionals	Changes to C-MABQ v2 after cognitive interviews with patients
3. Sticking to medications taking routine is (alternative suggested "taking your medications at the same time every day is")	Original was preferred by patients.
4. ~~Obtaining~~ Getting medications related advice from my ~~healthcare~~ mental health team is	
5. I am unsure of how and when my prescriber would like me to take my medications.	5. I don't know how and when my healthcare professional would like me to take my medications.
6. I don't understand why I ~~was~~ am prescribed my medications.	
10. I prefer to use treatments other than what my ~~doctor~~ mental health team prescribes.	10. I prefer to use treatments other than ~~what my mental health team prescribes~~medications
12. I have read or heard things that make me ~~doubt~~ not want to take my medications.	
13. I feel that my ~~M~~medications ~~are being~~have been imposed upon me.	
15. I am unsure about the risks to my mental health from stopping my medications. (OR - I am unsure what would happen to my mental health if I stopped my medications.)	15. I don't know (unsure) what would happen to my mental health if I stopped taking my medications.
17. My mental health ~~healthcare~~ team listens to me.	17. I feel that my mental health team listens to
24. In terms of my physical and mental health, the positive effects of my medications outweigh any negative effects.	
31. My medications make it difficult for me to get on with my life.	The majority preferred statement 31 against 32 and everyone interpreted correctly.
36. I worry about being sectioned (detained under Mental Health Act) if I do not take my medications as prescribed.	

38. I fear of not being myself (what does it mean for patients) if I take my medications.	Understood and interpreted correctly as fear of medication making them feel like zombies, blunted and emotionless than before taking medication.
39. Getting unwell and being hospitalised because of my mental health condition really frightens me.	
41. The extent to which my medications are working to improve my mental health is	
44. In my culture, ~~a diagnosis of~~ mental health diagnosis is	
45. In my culture, taking mental health medications ~~are~~is	
46. The amount of ~~M~~my involvement in decisions about my treatment is	
48. The number of medications prescribed for my~~e~~ mental health condition is	
49. The type of medications prescribed for me is (For example: tablets, capsules, liquids, injections)	49. The type of medications (For example: pills, injections) prescribed for me is ~~(For example: tablets, capsules, liquids, injections)~~

Statements 31 and 32 represented same concepts but were checked with patients for their preferred statement. Four patients preferred statement 31 over 32 and others did not have any preference, so we chose statement 31 for the final C-MABQ which now has a total of 50 statements – referred to as 'C-MABQ' from here onward. Given the minimal recommended changes, there are no consistent messages regarding the required refinements. It is notable that the two statements 5 and 15, initially phrased as 'unsure' were recommended to be changed to 'don't know'. Statement 10 sought to emphasise a difference between prescribed medication and remedies that the patient obtains from alternative sources. The recommended phrasing from participants was that anything that is not prescribed is not perceived as a medication.

The final C-MABQ statements, their reordering as recommended by healthcare professionals and patients (see red text statement which has been reordered) and their corresponding TDF domains are presented in table 4.3 below. See Appendix 4.9 for the full final C-MABQ with instructions, response options and scoring method.

Table 4.3: C-MABQ final statements and corresponding TDF domains

C-MABQ final Statements	TDF domains
1. Remembering to take my medications is	Memory, attention and decision processes1
2. Remembering to collect my medications from the doctors or pharmacy is	Memory, attention and decision processes2
3. Sticking to medications taking routine is	Memory, attention and decision processes3
4. Getting medications related advice from my mental health team is	Environmental context and resources1
5. I don't know how and when my healthcare professional would like me to take my medications.	Knowledge1
6. I don't understand why I am prescribed my medications.	Knowledge2
7. I don't recognise myself as someone with bipolar disorder.	Intentions1
8. I don't need medications for my mental health condition.	Intentions2
9. I don't want to take medications for my mental health condition.	Intentions3
10. I prefer to use treatments other than medications.	Intentions4
11. I believe that mental health medications are harmful.	Beliefs about consequences1
12. I have read or heard things that make me not want to take my medications.	Social influences1
13. I feel that my medications have been imposed upon me.	Social/professional role and identity1
14. I don't like the idea of my mood being controlled by medications.	Social/professional role and identity2
15. I don't know what would happen to my mental health if I stopped taking my medications.	Knowledge3
16. I don't want people to know that I have a mental health condition.	Social influences2
17. People around me do not like me to take my medications.	Social influences3
18. I feel that my mental health team listens to me.	Social influences4
19. My mental health team is there for me when I need them.	Social influences5
20. I have a good relationship with my mental health team.	Social influences6
21. My friends and family are supportive of my mental health.	Social influences7
22. People judge me because of my mental health condition.	Social influences8

23. I believe that I will become unwell if I stop taking my medications.	Beliefs about consequences2
24. I have a set routine to help me take my medications at the right time.	Memory, attention and decision processes4
25. Taking my medications as prescribed is a top priority for me.	Goals1
26. In terms of my physical and mental health, the positive effects of my medications outweigh any negative effects.	Memory, attention and decision processes5
27. I believe that taking my medications keeps me well.	Beliefs about consequences3
28. I have ways to help me remember to take my medications at the right time.	Memory, attention and decision processes6
29. I need to continue to take my medications no matter what my mood is like.	Knowledge4
30. Getting unwell and being hospitalised because of my mental health condition really frightens me.	Emotion1
31. I worry that I may harm myself or others if I do not take my medications as prescribed.	Emotion2
32. Other things take priority over my medications.	Goals2
33. My medications make it difficult for me to get on with my life.	Goals3
34. I have practical problems with collecting my prescriptions or medications.	Environmental context and resources2
35. I worry about getting addicted to my medications.	Emotion3
36. I worry about the side effects of my medications.	Emotion4
37. I worry about being sectioned detained under the Mental Health Act if I do not take my medications as prescribed.	Emotion5
38. I fear of not being myself if I take my medications.	Emotion6
39. I am fed up with taking medications to control my mental health condition.	Emotion7
40. The extent to which my medications are working to improve my mental health is	Environmental context and reosures3
41. The side effects I'm getting from my medications are	Environmental context and reosures4
42. The amount of support that I am getting from my friends and family to take my medications is	Social influences9
43. In my culture, a mental health diagnosis is	Social influences10
44. In my culture, taking mental health medications is	Social influences11
45. How much I am involved in the decisions about my treatment is	Social/professional roles and identity3

46. The prescription cost for me is	Environmental context and reosures5
47. The number of medications prescribed for my mental health condition is	Environmental context and reosures6
48. The type of medications (For example: pills, injections) prescribed for me is	Environmental context and reosures7
49. The doses (amounts) of the medications prescribed for me are	Environmental context and reosures8
50. The number of times a day I have to take my medications is	Environmental context and reosures9

Note: Red statements are reordered as recommended by healthcare professionals.

The total number of words in a statement ranged from 6 to 20 words (median of 11 words and mean of 10.5 words). Nine (18%) statements have less than nine words, 29 (58%) statements have less than 12 words and 40 (80%) statements have less than 15 words. The final 50-item C-MABQ had a Flesch-Kincaid reading ease test score of 63.7 as per app.readable.com and 66 as per app.grammarly.com, indicating good readability that should be understood by 13 to 15 years old.

4.4 Discussion

This chapter presents the final C-MABQ comprising 50 statements with good face and content validity, appropriate word count per statement and good readability. The minimal required changes during the cognitive interviews afford some confidence in the rigorous development process of the items. The re-phrasing of statements from 'unsure' to 'I don't know' is supported by the literature. The Likert scale offers a continuum representing the strength of agreement which is best applied to a definitive statement such as 'I don't know' rather than a statement which in itself is imprecise such as 'unsure' (197).

Evaluation of questionnaires by experts is recommended as a part of testing face and content validity (97). Thus, initial discussions with experts in behavioural medicines and later consultation with healthcare professionals fulfil this recommendation. No formal calculations of the face and content validity were carried out; the responses from the healthcare professionals to the questions show the face and content validity

of C-MABQ. There were some new determinants of adherence suggested by healthcare professionals, however, they were not added to C-MABQ. Some of the new recommended determinants were already covered by C-MABQ v1 statements but in slightly different wording. For example, ‘not liking the effects of their mood being artificially flattened or controlled’ is covered by statements ‘14. I don’t like the idea of mood being controlled by medications’, and ‘being able to talk to the healthcare team about side effects’ is covered by statement ‘4. Obtaining medicines advice from my healthcare team is (easy/difficult)’. Other new determinants were deemed not modifiable such as low mood or substance abuse, in the context of this study.

It is generally recommended to keep sentences to 15 words on average and not longer than 25 words (198,208,209). Furthermore, readers find sentences of 8 words or less very easy to read; 11 words, easy; 14 words fairly easy; 17 words standard; 21 words fairly difficult; 25 words difficult and 29 words or more, very difficult (198,208,209). Readers understand more than 90% of what they are reading when average sentence length is 14 words (208). Considering none of the statement has more than 20 words and vast majority of the statements have less than 15 words, the final C-MABQ can be considered relatively easy to read and understand.

In addition to the length of the statement readability score also takes into account of the difficulty of the words and word syllables (207). However, general recommendation of Flesch–Kincaid reading ease score of ≥ 60 can be difficult to achieve, and many patients related health information including commonly used health-related quality of life surveys such as Short-Form Health Survey failed to meet such readability score (207,210). Overall readability score of the final C-MABQ and average number of words per statement in C-MABQ shows good readability and comprehension.

Strengths and Limitations

One of the key strengths of this study is the multidisciplinary approach in developing C-MABQ. The involvement of key stakeholders; namely healthcare professionals who will be using the responses to inform tailored support and patients who will be completing the questionnaire; ensures its face and content validity. Mapping of C-

MABQ statements to the TDF domains is unique to this study in the field of mental health medication adherence. This mapping allows each determinant to be linked to appropriate BCTs to provide tailored support to patients in future studies.

C-MABQ statements were based on the prioritised determinants of adherence in Chapter 3 and thus may have excluded some of the determinants important to some patients. However, questionnaires should not be too long to avoid significant burden on respondents and to keep respondents interested and engaged. Thus, there will always be some level of trade-off. Using patients with bipolar disorder and their families and friends to prioritise the determinants identified in the literature should have helped us strike the right balance. Calculation of face or content validity index to evaluate face and content validity instead of subjective evaluation would have added robustness to the study. However, the consultation and cognitive interviews aimed to refine the C-MABQ, and thus subjective assessment was sufficient. Additionally, specific questions were used during all consultations and cognitive interviews, which add the scientific rigour required to fulfil the aim of the study.

CHAPTER FIVE

Evaluation of Collaborative Medication Adherence in Bipolar disorder Questionnaire (C-MABQ)

5.1 INTRODUCTION

Chapter 4 described the development of C-MABQ. In this chapter, I will focus on the evaluation of the psychometric properties of C-MABQ with patients with bipolar disorder. C-MABQ was developed through a rigorous method as described in Chapter 4 and is underpinned by a comprehensive behaviour change framework described in Chapter 1. Each C-MABQ statement covers one of the 9 TDF domains: 'Environmental resources', 'Belief about consequences', 'Knowledge', 'Social influences', 'Intentions', 'Social/professional role and identity', 'Goals', 'Emotions', 'Memory, attention and decision processes'. Any questionnaire developed needs to undergo rigorous testing to ensure it is valid and reliable (97,211). Chapters 2, 3 and 4 involved questionnaire development. This chapter is dedicated to the 3rd stage of questionnaire development to evaluate C-MABQ for dimensionality, validity, and reliability (97).

Dimensionality refers to the test of the number of dimensions (212) in a scale. A unidimensional scale contains a single dimension, whereas a multidimensional scale contains more than one dimension. Validity is the extent to which the scale actually measures what it purports to measure (213). There are different types of validity measures: face validity, content validity, construct validity, and criterion validity. See chapter 3 for face and content validity. Criterion validity is the extent to which an individual's scores on a scale/subscale are correlated with other measures that have previously been used to measure the behaviour of interest, e.g., adherence (213). Construct validity tests if the scale measures the behaviour of interest and not something else (213). However, more recently, construct validity is seen as a unifying form of validity for scales, subsuming both content and criterion validity and central to establishing the overall validity of the scale (214). Reliability refers to the consistency of the scale, which can be across items (internal consistency reliability) or consistency over time (test-retest reliability) (213).

Adherence questionnaires have historically been evaluated using Factor Analysis for dimensionality and validity and Cronbach's alpha for consistency (87,211,215) .

Factor analysis is a statistical method that examines the number of factors (set of variables with similar pattern of responses) in a questionnaire and how these factors are explained by the items (105). Factor analysis can be divided into two types:

exploratory factor analysis and confirmatory factor analysis. In exploratory factor analysis, the number of possible underlying factors are explored based on the observed variables. Exploratory factor analysis is often used to reduce a large number of items into a small number of factors that explains the latent (hidden or unobserved or not directly measurable) trait such as adherence (105). On the other hand, confirmatory factor analysis examines a predetermined number of factors based on theory, evidence, or another method. Confirmatory factor analysis is a statistical technique used to verify the factor structure of a set of observed variables (105). Correlations between the factors and the observed items are described by factor loading. While factor analysis does test dimensionality of a questionnaire, it is unable to investigate item level diagnostics as offered by Item Response Theory (IRT) (211,215,216), such as whether items are scalable, locally independent, monotonous, and whether items meet invariant item ordering criteria (See Method section for details of each of these terms). These criteria are important for the construct validity and for the scale's total score to be meaningful (211,216). Cronbach's alpha is a measure of the coefficient of internal consistency and explains how closely related items are in the questionnaire (217). Internal consistency describes the extent to which all the items in a test measure the same construct, and hence it is connected to the inter-relatedness of the items within the test (217). It is considered to be a measure of scale reliability (217). Cronbach's alpha is appropriate if items in the scale are unidimensional, but this should be tested and not assumed (211). In addition, it is recommended to use several other indices of reliability such as Gamma, Lambda to avoid relying on a single measure of reliability (218,219).

Over the last few decades, IRT has gained popularity in the psychometric evaluation of questionnaires. IRT is a collection of measurement models that attempt to explain the connection between observed item responses on a scale (such as C-MABQ items) and an underlying construct (such as non-adherence) (214). IRT models are mathematical equations describing the association between latent variables (such as non-adherence) and the probability of a particular response to an item, using a nonlinear monotonic function (see Method section for more details) (214). IRT can be broadly divided into parametric IRT and non-parametric IRT. Parametric IRT is more stringent compared to non-parametric IRT in the sense that the relationship between the latent trait (unobserved characteristic such as non-adherence), and the probability

of a correct response, i.e., the item response function, need to follow a predetermined specific shape, for example, S shape (211,216). This can lead to the exclusion of items not meeting item response function shape and thus lower the number of items in the final questionnaire, compromising other aspects of questionnaire performance such as reliability or content validity (215). Mokken Scale Analysis (MSA) is a non-parametric IRT where item response function does not have to follow any specific shape other than it should be non-decreasing (211,216). The relationship between the latent trait and the item responses is represented with item response function in non-parametric IRT (216). According to MSA, if item sets (group of items in a scale or subscale) meet properties of unidimensionality, local independence and monotonicity (see method section for these terms), then the set of items can measure differences in the degree of adherence between patients (211). Scales meeting the Mokken Scale criteria is considered to have construct validity (216). However, construct validity can also be measured using convergent and discriminant validity (211).

Criterion validity can be investigated using subjective measures such as self-reported adherence scales and objective measures such as pill count. Both subjective and objective measures of adherence have their own merits and limitations (see Chapter 1 for more details). Six adherence scales validated in bipolar disorder and number of questions in each of those scales are described in Chapter 1. Subjective measure for criterion validity should be brief to minimise patient burden. Such measure should also have been validated in other studies in similar health condition. Compared to other adherence scales, Medication Adherence Report Scale - 5 (MARS-5) is completed by patients, relatively short and easy to answer, have been validated in multiple studies and is used to measure medication adherence (87). Objective measures such as patients' blood level of medication are commonly referred to as the gold standard of medication adherence measures (10). As per NICE guideline in the UK, all Lithium patients need to have regular (3 to 6 monthly) blood tests to check their blood Lithium level (7). Thus, this readily available objective measure is preferrable for criterion validity. Other objective measures such as pill count and medication event monitoring system which are more intrusive can discourage patients to participate in the research leading to recruitment difficulties. However, blood Lithium level only provides a snapshot of whether a patient took Lithium over the last five to seven days (220) and thus, does not guarantee the patient's adherence a week before or in the future. Also,

the awareness of the blood test itself can lead to white coat adherence i.e., patients taking Lithium just a week or so before the blood test (14).

RESEARCH AIM AND OBJECTIVES

The research aimed to evaluate the psychometric properties of C-MABQ. The objectives were to:

- Identify and extract C-MABQ items set that meet Mokken Scale criteria called C-MABQdmm (C-MABQ Double Monotonicity Model)
- Evaluate criterion validity of C-MABQdmm by
    a. Measuring the correlation between MARS-5 and C-MABQdmm
    b. Comparing mean score of C-MABQdmm between high and low adherence patients based on their blood Lithium level
- Evaluate construct validity of C-MABQdmm by measuring the correlation between the subscales of the C-MABQdmm and Brief Illness Perception Questionnaire (BIPQ) items
- Test internal consistency using Cronbach's alpha, gamma and lambda coefficients
- Evaluate test-retest reliability using intra-class correlation coefficient

5.2 METHODS

5.2.1 Study Design, Settings and Sample Size

A survey design was used for testing C-MABQ. A questionnaire survey is a common approach for testing the validity and reliability of a questionnaire (221). Patients were recruited from NHS mental health settings in Norfolk County in England.

The sample size for questionnaire evaluation studies varies from 100 to over 1000 participants (97,222,223). Some suggest 2 to 10 participants per item on the survey, with the C-MABQ having 50 items, this means 100 to 500 participants, while others propose that 300 to 500 participants are good or very good (97,222,223). So, the plan was to recruit 350 to 600 participants to allow for analysis of 300 to 500, allowing for

incomplete or un-usable returned questionnaires. The purposive sampling (total population sampling) technique was used for this survey. Survey invitations were sent to all potential patients on the NSFT Lithium monitoring database via email or post.

The recommendation for the sample size for test-retest reliability also varies. A recent systematic review found the median sample size to be 44 in the included studies (224). Terwee et al. recommend a sample size of at least 50 (225). Consensus based Standards for selection of health Measurement Instrument suggest a sample size of ≥ 100 patients is very good, and 50 - 99 patients are adequate (222). One hundred fifty patients who responded to the first survey were randomly selected, using the random number generator www.random.org, and invited to complete the survey for the second time.

The period between the repeated administrations should be long enough to prevent recall, though short enough to ensure clinical change has not occurred (224). A recent systematic review found that the median time interval between test and retest is 14 days (224). A 1-2 weeks' time interval is commonly recommended in the literature (222,224,225). Thus, a second survey invitation was sent 1 - 2 weeks after receiving the first completed survey.

5.2.2 Recruitment and Data Collection

NSFT has a Lithium monitoring system, which retains the record of all patients on Lithium in Norfolk; sends regular blood tests reminders and maintains the Lithium blood level results for all patients on the system. All potentially eligible and reachable patients (n = 835) on the database were invited to participate in the survey via email or post. Patients were offered a £5 voucher to complete the survey. The patient's eligibility criteria are described below.

Inclusion criteria:

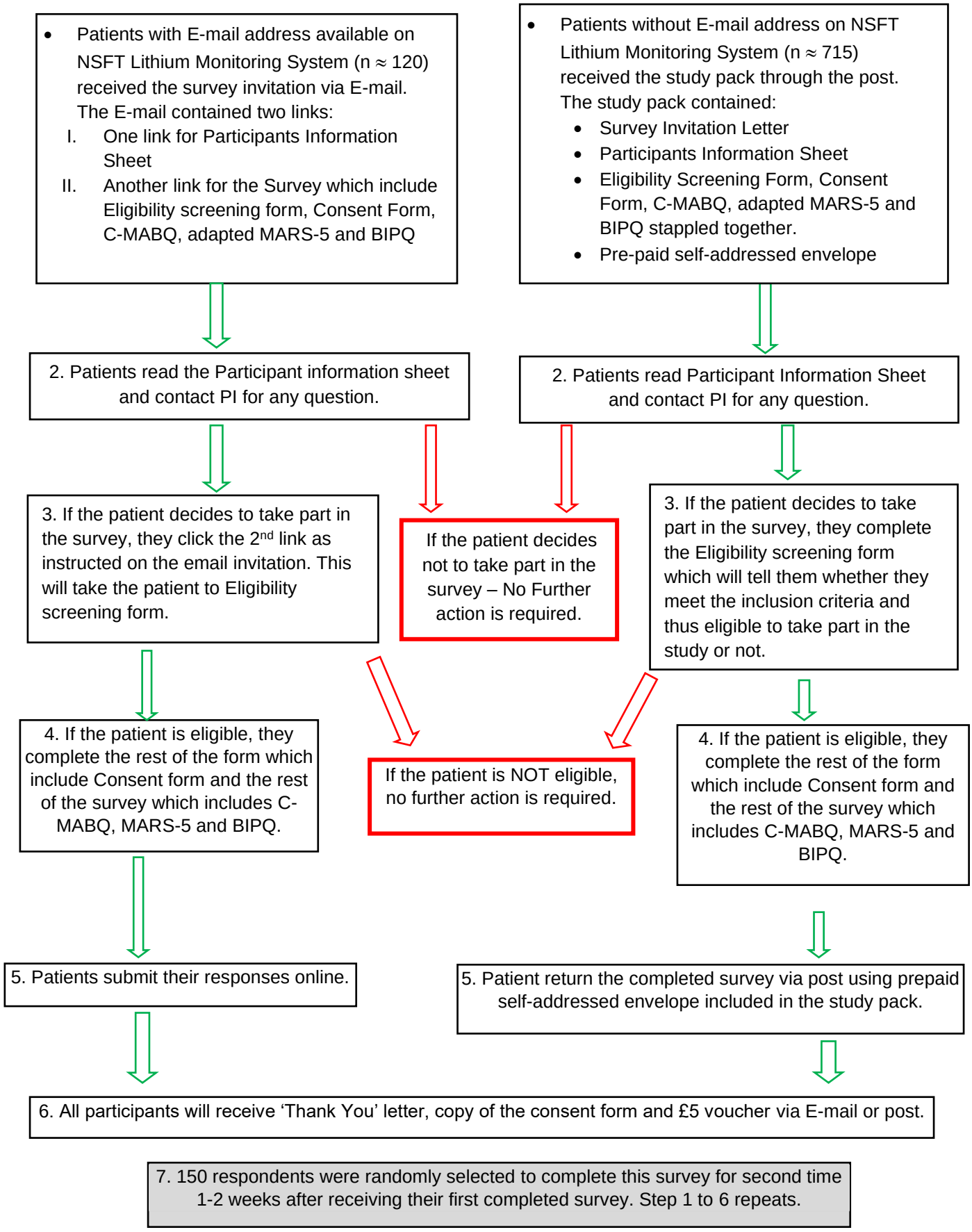
- Adults, >18 years old
- Patients from Norfolk and Suffolk County in the UK
- Currently prescribed Lithium for bipolar disorder
- Prescribed Lithium for more than four months

Exclusion criteria:

- Unable to read English
- Unable to provide informed consent

Details of the recruitment, materials contained in the study pack, survey invitation via post or emails and patient survey completion process are described in figure 5.1. Informed consent was obtained from the participants on paper or electronically. See Appendices 5.1 for Survey Invitation Letter, 5.2 for Survey Invitation Email, 5.3 for Participants Information Sheet, 5.4 for Participant eligibility screening form, 5.5 for Survey Consent Form, 5.6 for Survey Invitation Letter for completing the survey second time, 5.7 for Reminder letter to potential participants who have not responded to the first survey invitation, 5.8 for Reminder email to potential participants who have not responded to the first survey invitation, 5.9 for Reminder email to potential participants who have not responded to the first survey invitation and 5.10 for Thank You Letter to participants. The online survey was built on Microsoft Form.

Figure 5.1: Patient Survey Completion process



Based on the literature, the following strategies were implemented to improve the response rate to the survey (226,227):

- Personalised letters and emails
- A sticker with a photo of a £5 voucher was stuck on each envelope as incentive
- Incentive on email with a subject heading “Please complete this survey and receive £5 voucher”
- Monetary incentives of £5 voucher to complete the survey
- First-class outward mailing
- Recorded delivery
- Stamped return envelope
- Single-sided questionnaire
- QR codes to complete the survey online on both postal and email survey invitations
- Reminders were sent if a response was not received within four weeks of sending the first survey invitations

Data related to the following details were collected: patient’s eligibility, consent, demographics details (name, gender, date of birth, address, e-mail, phone number), survey response and patient’s latest blood Lithium level. Data for patients who completed the survey online was exported in MS Excel Spreadsheet. For patients who completed the survey on paper, the data was entered onto an MS Excel Spreadsheet manually.

5.2.3 Data analysis

C-MABQ scoring

C-MABQ has 50 items divided into three sections based on three different response options. All sections have five-point Likert style response options (see Appendix 4.9).

- Section ONE contains four statements, and each has the response option: Very Difficult, Difficult, Neither Difficult nor Easy, Easy, Very Easy.
- Section TWO includes 35 statements with response options: Strongly Disagree, Disagree, Neither Disagree nor Agree, Agree, Strongly Agree.

- Section THREE contains 11 statements with response options: Totally unacceptable, Unacceptable, Neutral, Acceptable, Perfectly Acceptable.

Each response was scored one to five in such a way that the presence of facilitator or absence of barrier was the lowest score, and the presence of barrier was the highest score. For example:

Section TWO Statements	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I feel that my medications have been imposed upon me.	1	2	3	4	5
I feel that my mental health team listens to me.	5	4	3	2	1

The higher score means that the patient has more barriers to medication adherence and thus more likely to be non-adherent and vice versa. Therefore, a higher score is indicative of lower adherence. A detailed scoring sheet is provided in Appendix 4.9.

Analysis

Free open-source software 'R' (228) was used for the data analysis. The analysis aimed to ensure only parsimonious, functional, and internally consistent items are ultimately included to reduce the participant's burden and to minimise the resource required to collect and analyse the responses (97). Parsimony refers to ensuring the questionnaire is short and simple with only necessary items with high predictive power or explanatory. Functional items are items that are correlated with each other, discriminate between individual cases, underscore a single or multidimensional domain, and contribute significantly to the construct (97).

Data analysis included eight key steps as listed below:

1. Check basic descriptive statistics of each item on C-MABQ
2. Perform Mokken Scale Analysis:
    A. Investigate dimensionality and the number of subscales
    B. Investigate which items within each subscale meet Mokken Scale Double Monotonicity Model (DMM) criteria, i.e., local independence,

monotonicity and invariant item ordering. Subscales and the items set meeting the Mokken Scale Double Monotonicity Model criteria is called C-MABQdmm, as mentioned earlier, and will be analysed further in Steps 3 to 8.

3. Conduct confirmatory factor analysis to test C-MABQdmm
4. Examine the internal consistency reliability and properties of C-MABQdmm
5. Compute total scores and score statistics of C-MABQdmm
6. Examine the correlation between C-MABQdmm, MARS total scores and Adherence defined by patient's blood Lithium level for criterion validity
7. Examine the correlation between C-MABQdmm and BIPQ items for convergent and discriminant validity
8. Check test-retest reliability of C-MABQdmm by calculating the intra-class correlation coefficient between 1st and 2nd survey responses

STEP 1: Descriptive Statistics

First, response frequencies of each item were checked. Other descriptive statistics such as mean, median and standard deviation of each item were calculated. Descriptive statistics were used to investigate:

- Out-of-range values
- Representation of all response options
- Associations between items
- Missing Data

Any item with less than 5% variation, i.e., items where less than 5% of patients endorsed response options 1 and 2 or 4 and 5 combined, were deleted (211). Items with <5% variation are least likely to differentiate between adherent and non-adherent patients. Negatively correlated items were deleted in a stepwise manner, i.e., the item having negative correlation with most other items was deleted, then the next most negatively correlated item was excluded and so on until there were no negatively correlated items. Missing data were investigated in terms of the proportion of missing per item, whether the missing was at random and imputed missing data using the median value for that item.

STEP 2: Mokken Scale Analysis (MSA)

Compared to parametric IRT, the MSA has less strict statistical assumptions, e.g., normal distribution of the latent trait and the shape of item characteristics curves (215,229). MSA has two broad parts: An Automated Item Selection Procedure (AISP) and an Investigation of the assumptions of the Non-parametric IRT (NIRT) model (230).

A) Investigation of dimensionality and the number of subscales

Scalability coefficients (Hi, Hij, H where i and ij are items) indicate the degree to which individual item (Hi), pairs of items (Hij), and the items set in the subscale (H) that can be used for ordering individuals on a latent continuum, i.e., adherent to non-adherent (216). These coefficients are used to evaluate the fit of data to the Mokken Scale (216). AISP is an algorithm that divides the items into scalable and unscalable items at various levels of scalability coefficients. AISP also checks for dimensionality, to establish whether the scale/questionnaire is unidimensional or multidimensional. In MSA, items belonging to the same Mokken Scale should have an item scalability coefficient (H) greater than some positive lower bound value, as a rule of thumb H > 0.3 (231). A Mokken scale is a set of items which positively correlate with each other, have an item scalability coefficient > lower bound Hi (generally recommended > 0.3) and scale total H is greater than 0.3 (216). AISP selects a group of items meeting these requirements (216). AIPS produce a table with items in the rows and whether the item is scalable or not on the column. At certain Hi value, lower bound Hi value is set at 0.3 for this study, unscalable items will be shown as 0. The scalable items will be shown as 1 or 1, 2, 3 etc., depending on the number of dimensions/subscales remaining item sets represent. If the column in lower bound Hi of 0.3 scalability coefficient shows just 0 and 1, then the whole items set is unidimensional, and the items set makes one scale. However, if it shows 0, 1, 2, 3 etc., then it means the items set is multidimensional and corresponding numbers indicate the number of dimensions/subscales. However, each of those subscales is unidimensional, i.e., all the items in that subscale measure the same underlying attribute represented by the latent trait (adherence) (216).

The scalability coefficient for the item set or scale/subscale (H), also known as the homogeneity coefficient, for each Mokken Scale/subscale are also presented in the

output of the AISP function in R (216). Homogeneity is the degree to which items in the scale/subscale are alike or represent the same dimension. As a general rule of thumb, a scale with 0.3 > H < 0.4 considered weak, 0.4 > H < 0 .5 moderate and H > 0.5 strong (230).

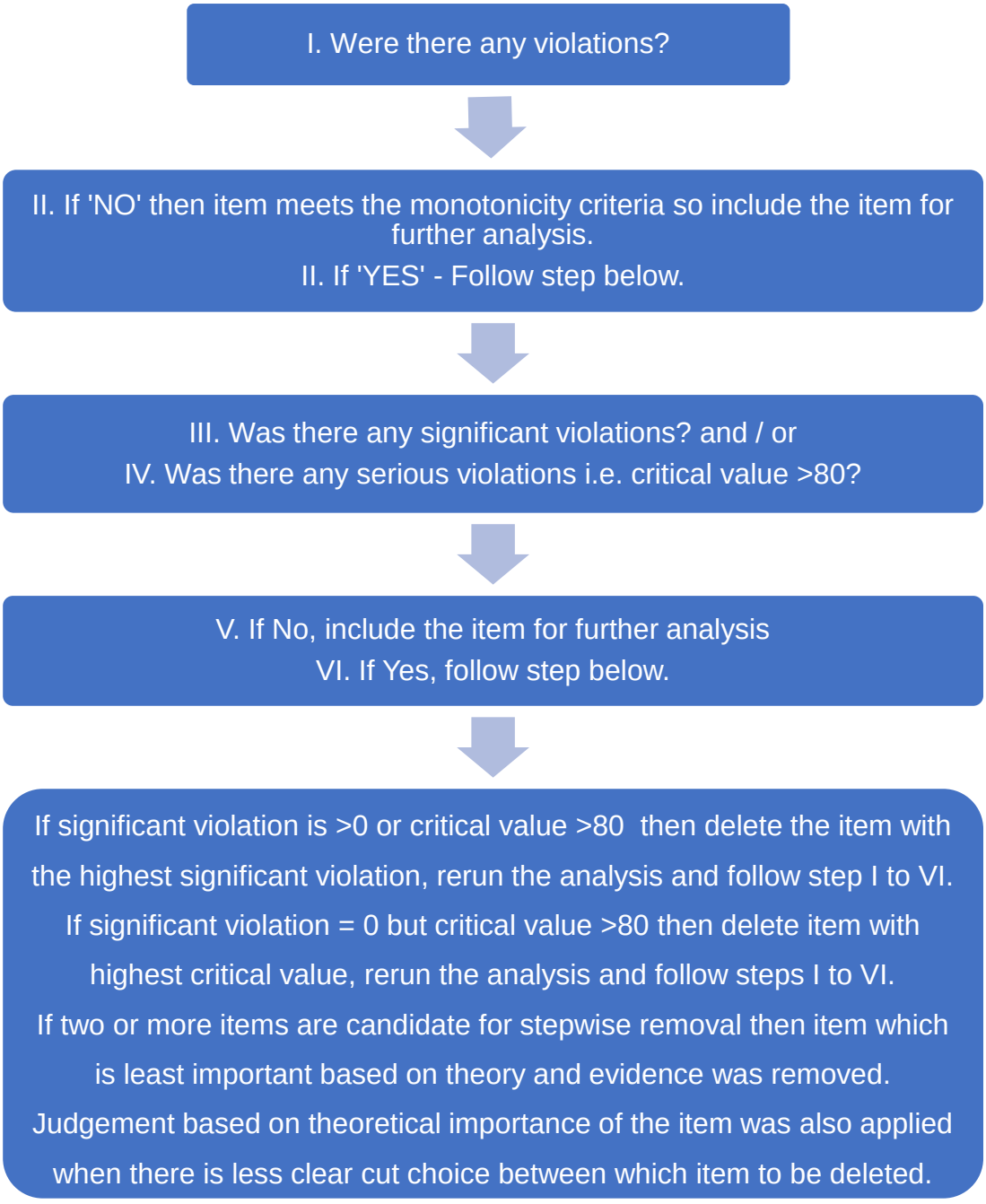
B) Investigation of Mokken Scale Double Monotonicity Model criteria

Local independence: The assumption of local independence implies that the respondent's response to any item is not influenced by their response to previous or subsequent items on the questionnaire but only dependent on the respondent's latent trait, i.e., items in the questionnaire are only correlated through the latent trait of respondents and nothing else (216). Local independence is investigated using conditional association, i.e., association is only due to their latent trait between the items in the subscale. This is implemented in the 'R' (Ref) function 'check.ca' and the results are reported as TRUE/FALSE values. To fulfil the criteria of local independence all values should be TRUE. If any of the items show up as FALSE, these items were separated and put through AISP to see if these items are scalable into one or more different subscales as discussed earlier.

Monotonicity: The criterion of monotonicity specifies that the probability of response to a higher-level response option (e.g., strongly agreeing to a barrier to adherence) should be constant or increasing (but should not be decreasing) as the respondent's latent trait (e.g., adherence) is decreasing (229). Monotonicity was investigated using the rest score group method to check if any item violates the assumption of monotonicity, with the 'check.monotonicity' function in R (211,228). Rest score is the total raw score excluding the item under investigation, where each rest score should have a fixed minimum number of members (216). As higher the barrier (expressed by patients with higher response option of 4 or 5 to an item) the rest score for rest of the items should increase or remain constant to satisfy the monotonicity criteria. Since C-MABQ is a polytomous questionnaire, the assumptions of monotonicity were investigated both at the item level and the level of item response categories. The rest score for items was plotted against the mean item responses, and item step response functions for each item were plotted to check monotonicity within the response option categories. Then monotonicity is evaluated using graphs and statistics (216). The

result of monotonicity is presented in a table and graph. The tabular results show a number of statistics, including the total number of violations of monotonicity by the item, number of statistically significant violations, and an overall index of fit of the item represented by critical value (216). Monotonicity for each item was checked using the following criteria as shown in figure 5.2 (211,215,216):

Figure 5.2: Steps in checking monotonicity criteria



High critical values indicate poor items, and as a rule of thumb, critical value > 80 is considered serious (i.e., item unlikely to fit monotonicity criteria), whereas critical value < 40 is likely to be due to fluctuations in the data and likely non-consequential whereas 40 > critical value < 80 indicate evidence of a violation is unclear (211,216) (215). This study considered critical value of 80 or below as an acceptable level. So, all items were kept for further analysis if there were no significant or serious (i.e., critical value <= 80) violations. Violations or not of monotonicity criteria was also displayed visually by item step response function where lines are horizontally increasing or remaining constant but not decreasing.

Items or item sets meeting the criteria of unidimensionality, local independence and monotonicity are known as the Mokken Scale Monotone Homogeneity Model and can be scaled, and respondents can be ordered according to their latent trait (216,232). However, in Monotone Homogeneity Model, the ability parameters (a theoretical value that represents a person's capability or probable performance on a task such as taking medication) of respondents cannot be estimated numerically, and respondents are rather ordered according to their latent trait using the true score (216,232).

Invariant Item Ordering (IIO): Items or item sets in the Mokken Scale Double Monotonicity Model (DMM) also meet the criteria of IIO in addition to the three criteria of the Monotone Homogeneity Model which are unidimensionality, local independence and monotonicity. IIO implies that the item response functions of items in the scale or subscales may coincide or touch but should not intersect with each (216,232). IIO allows items to be ordered according to their difficulty or strength of determinants of adherence i.e., in addition to ordering respondents according to their latent trait (Monotone Homogeneity Model), DMM also orders items according to their difficulty or strength of determinants (216,232). If the subscale items cannot be ordered in the same way for all the respondents across the latent trait continuum or across different gender/ages etc., then different scores will give us very little meaning. Thus, for the total score to be useful and meaningful, the IIO criteria need to be met, i.e., subscales should meet Mokken Scale DMM criteria (216,232).

IIO test results are shown in a table similar to the results of monotonicity. The result is interpreted in the same way using the steps described in Figure 5.2. IIO can also be

checked visually by item step response function plots for each item pair. The items set from C-MABQ fulfilling DMM criteria is called C-MABQdmm (C-MABQ Double Monotonicity Model), as mentioned earlier, and each unidimensional subset of the items are called subscale 1, subscale 2 and so on.

Outliers or aberrant or idiosyncratic response patterns were checked using Guttman error (211,216). If there are data entry errors or other possible reasons for aberrant response patterns or if the outliers affect the results, then analysis can be rerun without the outliers (211,216).

STEP 3: Confirmatory Factor Analysis

Confirmatory factor analysis is carried out to provide a complementary perspective on the dimensionality of the item set and the model fit of C-MABQdmm (211). Confirmatory factor analysis provides us with valuable information regarding the fit of the data to C-MABQdmm. Results that align with the C-MABQdmm can be considered as enforcing the findings and show construct validity (i.e., results do not depend on the method used) (211). In contrast, if large deviations are seen in the results, then this implies that the MSA findings are not robust and varies depending on the analytical method used. The results are produced graphically with confirmatory factor analysis diagrams and as output text. The fit statistics and parameter estimate for the C-MABQdmm were checked. Model fit indices above recommended thresholds of Tucker-Lewis index (TLI) and Comparative Fit Index (CFI) >0.95; Root Mean Square Error of Approximation (RMSEA) <0.06; chi-squared P-value <0.05) and factor loading in the expected ranges (>0.30 or 0.40) suggest a model fit (211).

STEP 4: Internal consistency reliability and properties

Internal consistency is the degree to which the set of items in the subscale co-vary relative to their sum score or the consistency of patient's responses across the items on a subscale (213). In general, all the items on the subscale are supposed to reflect the same underlying construct, so respondents' scores on those items are correlated with each other (213). Internal consistency reliability indices can be represented by Cronbach's alpha, Guttman's lambda6, beta and omega. It is often recommended to

calculate and present multiple indices of internal consistency reliability as some argue that traditional Cronbach's alpha alone may not represent internal consistency well (211,233). Thus, different measures of internal consistency reliability, including Cronbach's alpha, are presented.

STEP 5: Total scores and score statistics

Total scores for each subscale of C-MABQdmm and summary statistics are presented. The frequency and distribution of each subscale were calculated, and a histogram of each subscale was plotted. This is to provide an overview of the C-MABQdmm including the mean and range of total scores for each subscale. This also provides a visual representation of total score distribution (e.g., normal distribution) which determines test statistics (such as Spearman or Pearson's correlation coefficient) to be used for further analysis.

STEP 6: Examine the criterion validity

C-MABQdmm, the final item sets meeting Mokken Scale criteria were tested against the adapted Medication Adherence Rating Scale - 5 (MARS-5) (Appendix 5.11) (15) (234,235) and blood Lithium level for criterion validity. Correlation between subscales scores of C-MABQdmm and MARS-5 total score and adherence based on blood Lithium level were checked for criterion validity.

MARS-5 was chosen as it is simple, short, and quick to complete without increasing any significant burden to participants. In addition, MARS-5 has been validated in bipolar disorder and has been correlated with blood Lithium levels in some studies (87,236). The terms "medicines" and "doctor" in MARS-5 were changed to "mental health medications" and "mental health professional", respectively, to make it more relevant to this study. Approval for the change and the use of adapted MARS-5 in this study was obtained from the relevant author.

MARS-5 contains five statements:

I. I take less than instructed
II. I stop taking it for a while

III. I miss out a dose
IV. I alter the dose
V. I forget to take it

It asks participants to rate the frequency with which they engaged in each of these statements on a five-point scale, where 5 = never, 4 = rarely, 3 = sometimes, 2 = often and 1 = always (235). Scores for each item are summed to give a total score, with higher scores indicating higher levels of reported adherence (235). However, to align with the C-MABQ scoring system, MARS-5 were reverse scored (i.e., never = 1 and always =5 and so on). So, a higher score means lower adherence and vice versa in both questionnaires. Correlation between total scores of each subscale of C-MABQdmm and MARS-5 total score was checked.

The study used the latest blood Lithium level routinely collected by the healthcare team for patient care. The quoted reference range for blood Lithium level varies from 0.4 to 1.0mmol/L to 0.8 to 1.0 mmol/L (7,10,16,220,237-239). In an informal survey of prescribers in the NSFT, a vast majority (>80%, n=36) stated that their normal target Lithium level in their patients is 0.4 to 1mmol/L in adults =>65 years old and 0.5 to 1mmol/L in <65 years old. So, the respondents in this survey were divided into two groups: 1) High Adherence group (patients aged => 65 with Lithium level =>0.4 mmol/L or patients aged <65 with Lithium level =>0.5mmol/L) and 2) Low Adherence group (patients aged => 65 with Lithium level <0.4 mmol/L or patients aged <65 with Lithium level <0.5mmol/L). T-test was used to measure the difference in mean of C-MABQdmm subscales scores and C-MABQdmm total scores between the high adherence group and low adherence group.

STEP 7: Investigate the convergent and discriminant validity

Scale meeting Mokken Scale criteria such as C-MABQdmm are considered to have met construct validity (216). However, construct validity was also checked by investigating convergent and discriminant validity. Each subscale of C-MABQdmm carried a distinct concept of adherence determinants such as social influence or memory. These concepts were tested against items in the adapted BIPQ (Appendix 5.12) (240), a MARS-5 item where each item carried a specific meaning.

BIPQ contains eight dimensions of illness perceptions: consequences (the extent to which illness affects one's life), timeline (the expected duration of illness), personal control (the extent to which one perceives control over one's illness), treatment control (the extent to which one perceives treatment controls illness), identity (the number of symptoms associated with illness), coherence (the extent to which one understands the illness), concern (the extent of concerns about the illness), and emotional response (the extent of emotional distress attributed to the illness). The term "illness" in BIPQ was changed to "mental illness" to make it more relevant to the study and its focus. Approval for the change and the use of adapted BIPQ in this study was obtained from the relevant author. For convergent validity C-MABQdmm subscale was expected to be at least moderately associated (i.e., $r > 0.3$) (241-243) with conceptually related constructs of BIPQ items. And for discriminant validity, the C-MABQdmm subscale was expected to have medium to nonsignificant associations (i.e., $r < 0.3$) (241-243) with BIPQ items that are conceptually different.

MARS-5 covers both intentional non-adherences, e.g., taking less than instructed or missing the dose, as well as unintentional such as forgetfulness. Convergent and discriminant validity of C-MABQdmm subscales was also tested against MARS-5 items like the BIPQ item above. C-MABQdmm subscale representing concepts similar to unintentional non-adherence in MARS-5 was expected to have moderate or strong association while dissimilar concepts were expected to have medium to the non-significant association (241-243).

STEP 8: Check test-retest reliability

The test-retest reliability, also known as the coefficient of stability, is used to assess the degree to which the participants' performance is repeatable, i.e., how consistent their sum scores are across time (97). Intraclass correlation coefficient (ICC) was used to measure the test-retest reliability between first and second surveys. Koo et al. suggest ICC < 0.5 as poor, between 0.5 and 0.75 as moderate, between 0.75 and 0.9 as good and > 0.90 is excellent reliability (244). But Fleiss defined ICC value between 0.4 and 0.59 is considered as fair, 0.60 and 0.74 as good, and > 0.75 as excellent and this was supported by Cicchetti (245). So, Fleiss and Cicchetti's ICC reference range were used to make inference from ICC calculation.

ETHICAL AND REGULATORY COMPLIANCE

The study protocol, patient information sheet, screening survey and consent form were peer reviewed by NSFT Research Department colleagues. South West Central Bristol Research Ethics Committee provided a favourable ethical opinion to the study, and the study was approved by the Health Research Authority UK (Research Ethics Committee Ref number 21/SW/0078, Project ID: 297357). The letter from the Research Ethics Committee and approval letter from the Health Research Authority UK are provided in Appendices 5.13 and 5.14, respectively.

5.3 RESULTS

Survey data for first and second survey are provided separately to this thesis. Additional R analyses are provided in Appendix 5.15. Tables 5.1 and 5.2 provide participant flow and characteristics respectively. Overall, the response rate was just under 44%. Only patients who responded to 80% or more items, who provided consent and who were eligible to participate were included in the analysis. 89.5% in the first survey and 97% responses in the second survey were usable for the analysis. The majority of respondents were over 51 years old.

Table 5.1: First and second survey invitation, response rate and valid responses

First Survey	**Number of patients**
Potentially eligible and reachable patients	835
Total responded (% Response rate)	363 (43.5%)
Ineligible patients who returned the survey	22 (4.8%)
Consent form not completed	4 (1.2%)
Eligibility not completed	2 (0.6%)
Unusable responses (<80% questions completed)	10 (3.1%)
Total included for analysis	325 (89.5%)
Second Survey	**Number of patients**
Number of patients invited to take part	150
Total responded (% Response rate)	104 (69.33%)
Unusable (<80% questions completed)	3 (3%)
Total included for analysis	101 (97%)

Table 5.2: Participant's demographics and survey response time		
Descriptions	**1st Survey**	**2nd Survey**
Age (in Years)		
Range	20 to 89	27 to 85
Mean	61	60
Median	62	62
Age 20 to 30	8 (2.5%)	3 (3%)
Age 31 to 40	23 (7.1%)	6 (5.9%)
Age 41 to 50	33 (10.1%)	11 (10.9%)
Age 51 to 64	114 (35.1%)	42 (41.6%)
Age =>65	147 (45.2%)	39 (38.6%)
Gender		
Female	194 (59.7%)	63 (62.4%)
Male	131 (40.3%)	38 (37.6%)
Days between survey invitation and completion		
Range	0 to 73	0 to 37
Median	4	4
Days between reminders and survey completion		
Range	0 to 59	NA
Median	4	NA

Note: No reminders were sent to 2nd survey participants.

5.3.1 Descriptive summary

C-MABQ items response frequencies were checked to see if the items show sufficient variation to be able to differentiate respondents on the determinant of adherence represented by each item. Each item is nominated with 'Q' at the beginning for the question, a number in the middle for the item/question number in C-MABQ and letter/s at the end for the TDF domain that the item represents. For example, Q3M is 3rd question in C-MABQ representing the TDF domain 'Memory, attention and decision Processes'. See appendix 5.15 for item labels and corresponding C-MABQ questions. The frequencies of endorsing individual response options are presented in table 5.3.

Table 5.3: Distribution of response frequencies and missing responses									
C-MABQ Items	**Brief description of the item** (Note: meds = medications)	**Response Options**					**% 1 to 3 combined**	**% 4 to 5 combined**	**No. missing**
		1	**2**	**3**	**4**	**5**			
Q1M	1. Remembering to take	122	106	64	25	8	89.85	10.15	0
Q2M	2.Remembering to collect	108	108	61	38	7	85.23	13.85	3
Q3M	3.Sticking to routine	111	118	63	24	8	89.85	9.85	1
Q4EN	4.Getting Advice	32	56	130	52	37	67.08	27.38	18
Q5K	5.Knowing when to take	138	79	62	25	14	85.85	12	7
Q6K	6.Knowing why prescribed	183	79	22	26	14	87.38	12.31	1
Q7I	7.Not recognising as bipolar	118	76	54	49	25	74.31	22.77	3
Q8I	8.Don't need meds	190	89	22	13	7	92.62	6.15	4
Q9I	9.Don't want to take	146	79	49	30	18	84.31	14.77	3
Q10I	10.Prefer non-medicines	141	102	59	15	8	92.92	7.08	0
Q11B	11.Believe meds are harmful	110	86	70	46	13	81.85	18.15	0
Q12S	12.Read negative about meds	111	109	56	34	14	84.92	14.77	1
Q13R	13. Feel meds were imposed	145	104	47	23	5	91.08	8.62	1
Q14R	14.Don't like mood controlled by meds	110	98	56	50	9	81.23	18.15	2
Q15K	15.Not knowing what happen if meds stopped	85	48	31	94	67	50.46	49.54	0
Q16S	16.Don't Want people Know	62	59	86	83	35	63.69	34.31	0
Q17S	17. People don't like me taking meds	181	85	42	13	2	94.77	4.62	2
Q22S	22.People judge me	52	87	95	71	18	72.00	27.38	2
Q32G	32.Other things take priority over meds	113	149	39	14	8	92.62	6.77	2
Q33G	33.Meds get in the way	87	137	55	36	9	85.85	13.85	1

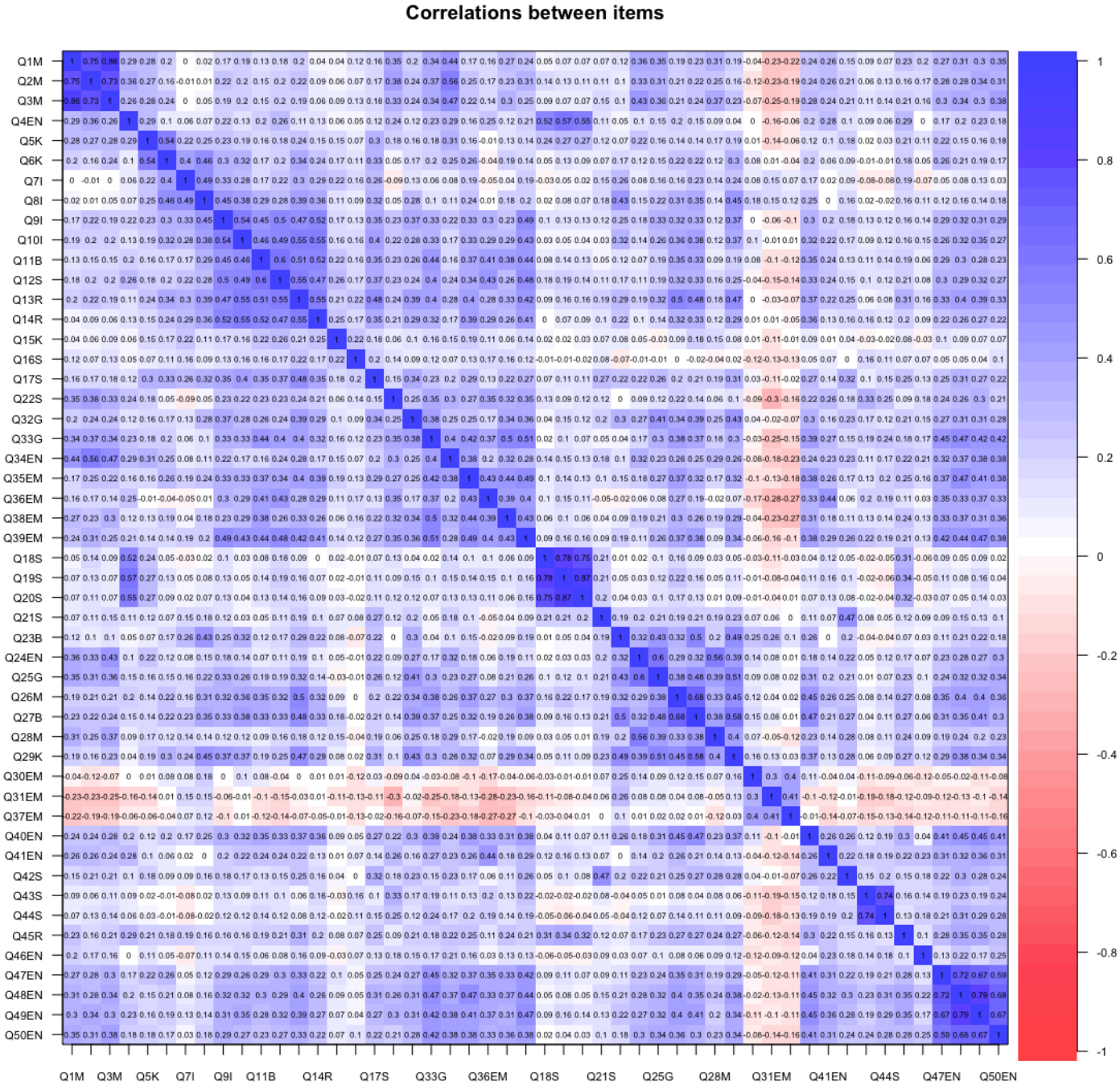
Q34EN	34. Have practical problem to collect meds	123	117	40	29	14	84.15	13.23	2
Q35EM	35.Worry of addiction	101	106	61	42	13	82.46	14.92	2
Q36EM	36. Worry of side effects	41	78	63	94	46	54.00	43.08	3
Q38EM	38. Fear of not being myself	75	97	78	53	21	74.92	22.77	1
Q39EM	39.Fed up taking meds	67	98	68	57	34	71.69	28	1
Q18S	18.Mental Health Team listens to me	33	98	102	36	36	71.69	22.15	20
Q19S	19.Mental Health Team there for me	36	91	91	48	43	67.08	28	16
Q20S	20. Have good relationship with Mental Health Team	38	86	96	38	44	67.69	25.23	23
Q21S	21.SupportiveFamily	106	145	38	23	11	88.92	10.46	2
Q23B	23.Will be unwell if I stop meds	148	128	35	8	5	95.69	4	1
Q24EN	24.Have routine to take meds	139	148	21	11	5	94.77	4.92	1
Q25G	25.Meds a priority	146	126	39	7	6	95.69	4	1
Q26M	26.Positive of meds outweigh negative	103	152	53	10	5	94.77	4.62	2
Q27B	27.Meds keep me well	119	171	26	6	2	97.23	2.46	1
Q28M	28.Have ways to remember to take meds	89	166	45	18	3	92.31	6.46	4
Q29K	29. Know need to continue meds	146	156	19	1	2	98.77	0.92	1
Q30EM	30.Fear of hospitalisation	153	100	45	16	10	91.69	8	1
Q31EM	31.Worry of harming	61	85	54	55	68	61.54	37.85	2
Q37EM	37.Worry of detention	61	82	72	59	50	64.15	33.54	1
Q40EN	40.Meds effective	96	179	33	6	7	94.77	4	4
Q41EN	41.Side effects	31	128	117	37	9	84.92	14.15	3
Q42S	42.Support from family	107	136	61	9	8	93.54	5.23	4

Q43S	43.Acceptability of diagnosis	46	160	71	35	7	85.23	12.92	6
Q44S	44.Acceptability of meds	57	170	72	18	2	92.00	6.15	6
Q45R	45.Involvement in meds decisions	49	173	68	17	10	89.23	8.31	8
Q46EN	46.Prescription cost	112	77	107	8	11	91.08	5.85	10
Q47EN	47.Number of meds	61	186	50	17	7	91.38	7.38	4
Q48EN	48.Type of meds	66	204	41	6	4	95.69	3.08	4
Q49EN	49.Doses of meds	68	187	47	12	4	92.92	4.92	7
Q50EN	50.Frequency of meds	87	199	28	2	6	94.62	2.46	3

Response variance for the 11 Items in red text was very low with < 5% of people choosing options 4 and 5 combined. These 11 items were removed for MSA as these items are least likely to differentiate between adherent and non-adherent patients or provide very little information regarding adherence. Moreover, further analysis of these items shows that most of these items did not meet MHM or DMM criteria such as scalability, local independence, monotonicity, or invariant item ordering. The inclusion of these items produced a complex scale with 7 subscales (cumbersome for daily clinical practice), poorer model fit and very poor internal consistency.

The highest missing data are for items Q4E, Q18S and Q20S where 5% to <8% of respondents didn't answer, and all questions were related to mental health team. These missing data were from respondents who were managed by their GPs and did not have a mental health team. However, this amount of missing data for these items is unlikely to impact the results as all these items have a good distribution of the respondents across the response scale. Missing data were imputed using the median value for that item.

Figure 5.3: Heat plot of correlations between item scores



Twelve items were negatively correlated with other items. A heat plot of inter-item correlations is shown in Figure 5.3 above. Thus, a stepwise deletion of item/s with reinvestigation of the correlation matrix after each deletion was carried out for removal of all negatively correlated items as below:

I: Removed Q30EM, Q31EM, Q37EM, which were negatively correlated with most items.

II: Removed Q44S, which was negatively correlated with seven other items.

III: Removed Q43S, which was negatively correlated with six other items.

IV: Removed Q7I and Q46EN, which were both negatively correlated with five other items. Q46EN is also unscalable.

V: Removed Q16S, which was negatively correlated with four other items. In addition, Q16S is unscalable.

VI: Removed Q5K, Q6K, Q21S, Q28M as they have a negative correlation with Q36EM, which is a theoretically critical item. In addition, Item Q21S is similar to Q42S and violated MHM criteria, item Q5K and Q28M are unscalable, and item Q6K does not meet IIO criteria.

After removing these 12 items, the remaining items did not have a negative correlation with any other items. Thus, 27 out of 50 C-MABQ items were included for further investigation after removing 11 low variance items and 12 negatively correlated items.

5.3.2 Mokken Scale Analysis (MSA)

Investigation of Scalability and Dimensionality

Table 5.4 presents the result of the AISP. It shows items scalability (0 = unscalable and >0 scalable) at various levels of scalability coefficient. At recommended lower bound Hi of 0.3, it shows that four items (Q8I, Q15K, Q32G and Q42S) are unscalable, 5 items (Q4EN, Q18S, Q19S, Q20S and Q45R) form one scale, which is called Subscale 1 from here onwards and remaining 18 items form 2nd scale called Subscale 2 from here onwards.

Table 5.4: Dimensionality at various levels of scalability coefficient

C-MABQ Items	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65
Q8I	2	0	0	0	0	0	0	0	0	0	0
Q15K	2	0	0	0	0	0	0	0	0	0	0
Q32G	1	1	0	0	0	0	0	0	0	0	0
Q42S	1	0	0	0	0	0	0	0	0	0	0
Q4EN	1	1	1	1	1	1	1	1	1	0	0
Q18S	1	1	1	1	1	1	1	1	1	1	1
Q19S	1	1	1	1	1	1	1	1	1	1	1
Q20S	1	1	1	1	1	1	1	1	1	1	1
Q45R	1	1	1	1	1	0	0	0	0	0	0
Q1M	1	1	2	2	2	2	2	2	2	2	2
Q2M	1	1	2	2	2	2	2	2	2	2	2
Q3M	1	1	2	2	2	2	2	2	2	2	2
Q9I	1	1	2	2	3	3	3	4	0	0	0
Q10I	1	1	2	2	3	3	3	3	0	0	0
Q11B	1	1	2	2	3	3	3	3	3	3	0
Q12S	1	1	2	2	3	3	3	3	3	3	0
Q13R	1	1	2	2	3	3	3	3	4	0	0
Q14R	1	1	2	2	3	3	3	3	4	0	0
Q22S	1	1	2	2	2	0	0	0	0	0	0
Q33G	1	1	2	2	2	3	5	6	0	0	0
Q34EN	1	1	2	2	2	2	2	2	0	0	0
Q35EM	1	1	2	2	3	4	0	0	0	0	0
Q36EM	1	1	2	2	3	3	4	5	0	0	0
Q38EM	1	1	2	2	0	4	5	6	0	0	0
Q39EM	1	1	2	2	3	3	3	4	0	0	0
Q41EN	1	1	2	2	4	5	4	5	0	0	0
Q47EN	1	1	2	2	4	5	0	0	0	0	0

The homogeneity values (H) and standard error (SE) of all items in Subscale 1 and that for Subscale 1 total are shown in table 5.5A. Similarly, table 5.5B shows the homogeneity values (H) and standard error (SE) value for items in Subscale 2 and Subscale 2 total. Based on the homogeneity value, Subscale 1 is strong but Subscale 2 is weak. Only items Q1M and Q3M have Homogeneity value (H) <0.3, however, as the estimated values were above 0.295 (0.299 & 0.296, respectively), these items were kept for further investigation.

Table 5.5A: MSA Subscale 1: Item homogeneity values

Items	Item H	se
Q4EN	0.539	(0.040)
Q18S	0.654	(0.035)
Q19S	0.697	(0.024)
Q20S	0.688	(0.027)
Q45R	0.367	(0.062)
Subscale 1 Total	0.601	(0.031)

Table 5.5B: MSA Subscale 2: Item homogeneity values

Items	Item H	SE
Q1M	0.299	(0.031)
Q2M	0.320	(0.033)
Q3M	0.301	(0.032)
Q9I	0.351	(0.031)
Q10I	0.341	(0.032)
Q11B	0.366	(0.030)
Q12S	0.384	(0.030)
Q13R	0.373	(0.030)
Q14R	0.314	(0.032)
Q22S	0.311	(0.032)
Q33G	0.402	(0.031)
Q34EN	0.296	(0.033)
Q35EM	0.343	(0.032)
Q36EM	0.370	(0.031)
Q38EM	0.327	(0.034)
Q39EM	0.427	(0.027)
Q41EN	0.314	(0.034)
Q47EN	0.345	(0.041)
Subscale 2 Total	0.345	(0.021)

Investigation of Local Independence

All the items in Subscale 1 met the criteria for local independence, as shown in table 5.6A below. The full results of local independence are shown in Appendix 5.15.

Table 5.6A: MSA Subscale 1: Local independence test
(TRUE = locally independent, FALSE = locally dependent)

Item	Result
Q4EN	TRUE
Q18S	TRUE
Q19S	TRUE
Q20S	TRUE
Q45R	TRUE

However, seven items (Q1M, Q2M, Q3M, Q14R, Q22S, Q34EN, Q41EN) of Subscale 2 did not meet the criteria of local independence as shown in table 5.6B. The remaining 11 items of Subscale 2 were locally independent, as shown in table 5.6C.

Table 5.6B: MSA Subscale 2: Local independence test

Item	Result
Q1M	FALSE
Q2M	FALSE
Q3M	FALSE
Q9I	TRUE
Q10I	TRUE
Q11B	TRUE
Q12S	TRUE
Q13R	TRUE
Q14R	FALSE
Q22S	FALSE
Q33G	TRUE
Q34EN	FALSE
Q35EM	TRUE
Q36EM	TRUE
Q38EM	TRUE
Q39EM	TRUE
Q41EN	FALSE
Q47EN	TRUE

Table 5.6C: MSA Subscale 2 after removing locally dependent items: Local independence test

Item	Result
Q9I	TRUE
Q10I	TRUE
Q11B	TRUE
Q12S	TRUE
Q13R	TRUE
Q33G	TRUE
Q35EM	TRUE
Q36EM	TRUE
Q38EM	TRUE
Q39EM	TRUE
Q47EN	TRUE

Seven items (Q1M, Q2M, Q3M, Q14R, Q22S, Q34EN, Q41EN) not meeting the criteria of local independence were put through the AISP algorithm to see if these items are scalable into different Subscale. The result of AISP is shown in table 5.6D. Item Q14R and Q41EN were unscalable, so both items were excluded from further analyses. The remaining five items (Q1M, Q2M, Q3M, Q22S and Q34EN) were scalable at Hi = 0.3, unidimensional and called Subscale 3 from here onwards.

Table 5.6D: AISP of Subscale 2 items not meeting Local Independence criteria

Item	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6
Q14R	0	0	0	0	0	0	0	0	0	0
Q41EN	1	1	1	0	0	0	0	0	0	0
Q1M	1	1	1	1	1	1	1	1	1	1
Q22S	1	1	1	1	1	0	0	0	0	0
Q2M	1	1	1	1	1	1	1	1	1	1
Q34EN	1	1	1	1	1	1	1	1	0	0
Q3M	1	1	1	1	1	1	1	1	1	1

All five items in Subscale 3 were locally independent, as shown in table 5.6E below.

Table 5.6E: MSA Subscale 2: Local independence test

Item	Result
Q1M	TRUE
Q2M	TRUE
Q3M	TRUE
Q22S	TRUE
Q34EN	TRUE

Investigation of Monotonicity

Tables 5.7A, 5.7B and 5.7C show the results of the monotonicity test of Subscale 1, 2 and 3, respectively. As shown, none of the items in the three subscales violated monotonicity criteria: none of the items show significant or serious violations. So, all items continued for further analysis of IIO. Monotonicity is also displayed visually by item step response functions plot in figure 5.4 for Subscale 1. See Appendix 5.15 for Item Step Response Function plots for Subscales 2 and 3 and more detailed results of monotonicity test.

Table 5.7A: MSA: Subscale 1: Monotonicity check

Item	Homogeneity	No. of violations	Maximum violation	Sum of all violations	No. of significant violations	Critical value
Q4EN	0.54	0	0.00	0.00	0	0
Q18S	0.65	0	0.00	0.00	0	0
Q19S	0.70	0	0.00	0.00	0	0
Q20S	0.69	0	0.00	0.00	0	0
Q45R	0.37	3	0.04	0.12	0	31

Figure 5.4: Item Step Response Function plot of Subscale 1 items

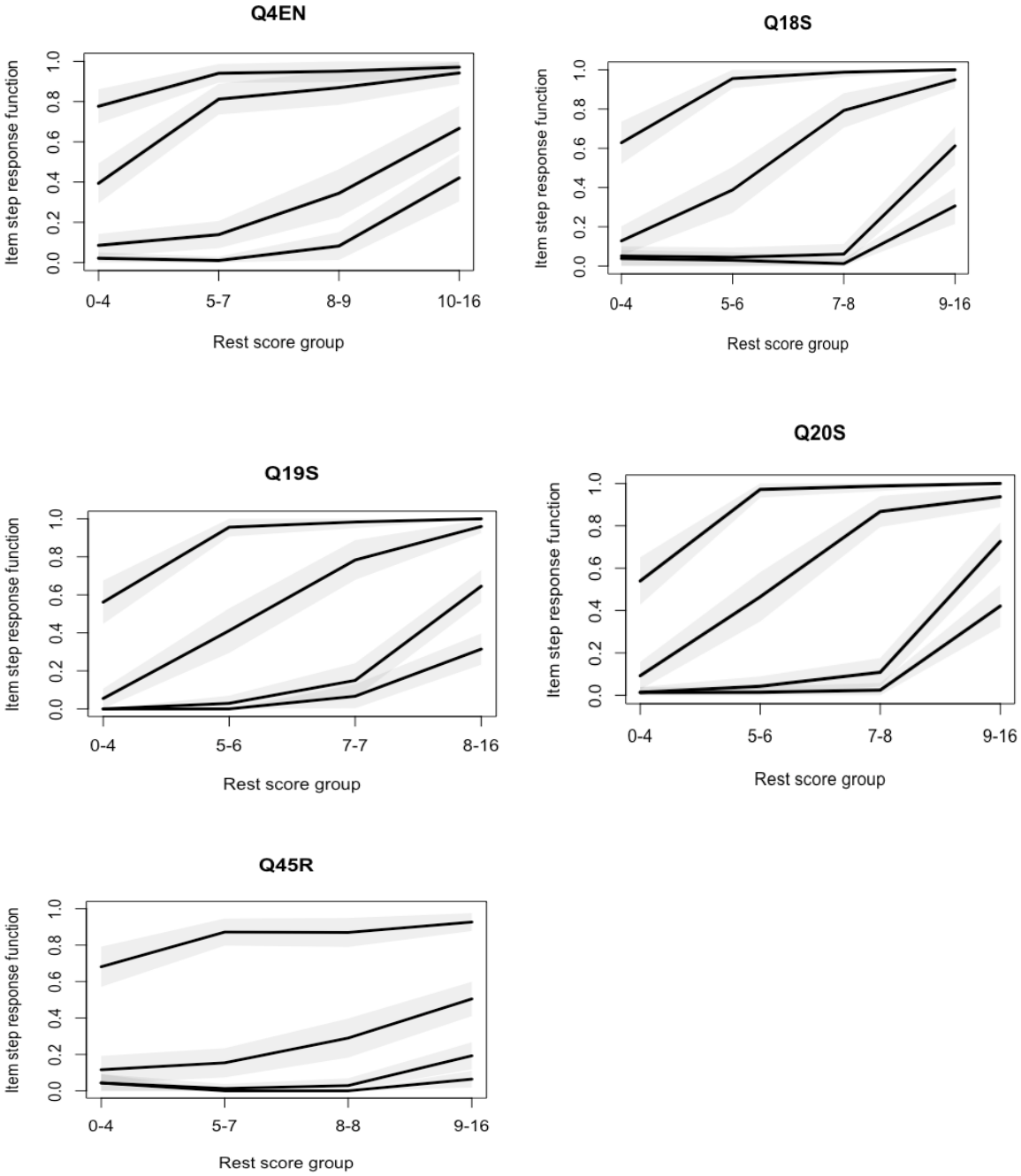


Table 5.7B: MSA: Subscale 2: Monotonicity check

Item	Homogeneity	No. of violations	Maximum violation	Sum of all violations	No. of significant violations	Critical value
Q9I	0.41	0	0.00	0.00	0	0
Q10I	0.41	0	0.00	0.00	0	0
Q11B	0.45	0	0.00	0.00	0	0
Q12S	0.46	1	0.05	0.05	0	8
Q13R	0.43	0	0.00	0.00	0	0
Q33G	0.43	0	0.00	0.00	0	0
Q35EM	0.40	1	0.03	0.03	0	5
Q36EM	0.42	1	0.03	0.03	0	6
Q38EM	0.36	1	0.04	0.04	0	12
Q39EM	0.49	1	0.04	0.04	0	4
Q47EN	0.37	0	0.00	0.00	0	0

Table 5.7C: MSA: Subscale 3: Monotonicity check

Item	Homogeneity	No. of violations	Maximum violation	Sum of all violations	No. of significant violations	Critical value
Q1M	0.61	0	0.00	0.00	0	0
Q2M	0.63	0	0.00	0.00	0	0
Q3M	0.61	0	0.00	0.00	0	0
Q22S	0.36	1	0.06	0.06	0	16
Q34EN	0.47	0	0.00	0.00	0	0

Scales or subscales meeting above three criteria, i.e., unidimensionality, local independence and monotonicity, are called Mokken Scale Monotone Homogeneity Model. Following 21 items met Monotone Homogeneity Model criteria:

- Subscale1 (n=5): Q4EN, Q18S, Q19S, Q20S and Q45R
- Subscale2 (n=11): Q9I, Q10I, Q11B, Q12S, Q13R, Q33G, Q35EM, Q36EM, Q38EM, Q39EM and Q47EN
- Subscale 3 (n=5): Q1M, Q2M, Q3M, Q22S and Q34EN

Some consider that these three criteria of the Monotone Homogeneity Model are sufficient for many applications of NIRT; however, for the total score to be meaningful and to place respondents in order by items in the subscale, the items need to meet further criteria of non-intersection of IIO (216). Thus, these 21 items were tested for IIO criteria.

Investigation of Invariant Item Ordering (IIO)

IIO tests, using the 'check.iio' function in R for each subscale, are shown in the tables below. Items with number of significant violations >0 and critical value > 80 are considered to violate the IIO criteria. Any item violating IIO criteria was removed in a stepwise manner as described in the method section. However, for space preservation, only the first and the last IIO test results are presented in the tables below; hence some homogeneity and critical values on the paragraph below and tables may vary. Each iteration results and visual display of item step response function plots for each item pair are available in Appendix 5.15.

- Subscale1: As seen in table 5.8A below, item Q45R has the highest number of significant violations so this item was removed. IIO test was rerun after removing item Q45R. Then items Q4EN and Q19S have one significant violation each, but Q4EN has the lowest homogeneity and highest critical value, so removed this item. Remaining 3 items show no significant or serious violations of IIO.
- subscale2: Item Q47EN has six violations and the highest number of significant violations, so Q47EN was removed. Q11B has four violations with critical value 90, so this item was removed. There were no further significant or serious for remaining 9 items.
- subscale3 - Q34EN has five violations with critical value 173, so this item was removed. Analysis was carried out with the remaining four items. But Q22S was a misfit; it has the lowest homogeneity value in the scale and lowest loading factor in confirmatory factor analysis. Removing Q22S improved internal consistency reliability indices, confirmatory factor analysis model fit and t-test. So, this item was also removed.

The first IIO test results are shown in tables 5.8A to 5.8C and the last IIO test results are shown in tables 5.8D to 5.8F.

Table 5.8A: MSA: Subscale 1: First IIO test results

Item	Homogeneity	No. of violations	Maximum violation	Sums of all violations	No. of significant violations	Critical value
Q4EN	0.54	2	0.27	0.47	0	117
Q19S	0.70	3	0.35	0.87	1	190
Q20S	0.69	3	0.33	0.78	1	176
Q18S	0.65	2	0.25	0.49	0	102
Q45R	0.37	2	0.35	0.68	2	166

Table 5.8B: MSA: Subscale 2: First IIO test results

Item	Homogeneity	No. of violations	Maximum violation	Sums of all violations	No. of significant violations	Critical value
Q36EM	0.42	0	0.00	0.00	0	0
Q39EM	0.49	2	0.38	0.66	0	71
Q38EM	0.36	2	0.38	0.66	0	80
Q11B	0.45	2	0.35	0.60	1	84
Q35EM	0.40	4	0.33	0.96	1	103
Q33G	0.43	2	0.33	0.57	0	65
Q12S	0.46	5	0.33	1.28	1	111
Q47EN	0.37	6	0.35	1.79	3	155
Q9I	0.41	1	0.30	0.30	0	52
Q10I	0.41	1	0.16	0.16	0	27
Q13R	0.44	1	0.16	0.16	0	26

Table 5.8C: MSA: Subscale 3: First IIO test results

Item	Homogeneity	No. of violations	Maximum violation	Sums of all violations	No. of significant violations	Critical value
Q22S	0.36	0	0.00	0.00	0	0
Q2M	0.63	2	0.18	0.34	0	63
Q3M	0.61	2	0.16	0.28	0	55
Q34EN	0.47	5	0.30	0.93	0	173
Q1M	0.61	1	0.30	0.30	0	64

Table 5.8D: MSA: Subscale 1: Last IIO test results with IIO compliant items only						
Item	Homogeneity	No. of violations	Maximum violation	Sums of all violations	No. of significant violations	Critical value
Q19S	0.85	1	0.15	0.15	0	63
Q20S	0.84	0	0.00	0.00	0	0
Q18S	0.79	1	0.15	0.15	0	66

Table 5.8E: MSA: Subscale 2: Last IIO test results with IIO compliant items only						
Item	Homogeneity	No. of violations	Maximum violation	Sums of all violations	No. of significant violations	Critical value
Q36EM	0.42	0	0.00	0.00	0	0
Q39EM	0.49	2	0.30	0.59	0	66
Q38EM	0.36	2	0.30	0.59	0	77
Q35EM	0.41	2	0.17	0.31	0	44
Q33G	0.42	1	0.13	0.13	0	25
Q12S	0.45	3	0.17	0.44	0	55
Q9I	0.41	0	0.00	0.00	0	0
Q10I	0.42	0	0.00	0.00	0	0
Q13R	0.43	0	0.00	0.00	0	0

Table 5.8F: MSA: Subscale 3: Last IIO test results with IIO compliant items only						
Item	Homogeneity	No. of violations	Maximum violation	Sums of all violations	No. of significant violations	Critical value
Q2M	0.76	0	0	0	0	0
Q3M	0.82	0	0	0	0	0
Q1M	0.82	0	0	0	0	0

Thus, a total of 15 C-MABQ items met the Mokken Scale DMM criteria as described in table 5.9 below.

Table 5.9: C-MABQdmm (15-item C-MABQ) - Three Subscales and respective items meeting Mokken Scale DMM criteria

Subscale 1 items (n = 3)
Q18S. I feel that my mental health team listens to me.
Q19S. My mental health team is there for me when I need them.
Q20S. I have a good relationship with my mental health team.
Subscale 2 items (n = 9)
Q9I. I don't want to take medications for my mental health condition.
Q10I. I prefer to use treatments other than medications.
Q12S. I have read or heard things that make me not want to take my medications.
Q13R. I feel that my medications have been imposed upon me.
Q33G. My medications make it difficult for me to get on with my life.
Q35EM. I worry about getting addicted to my medications.
Q36EM. I worry about the side effects of my medications.
Q38EM. I fear of not being myself if I take my medications.
Q39EM. I am fed up with taking medications to control my mental health condition.
Subscale 3 items (n = 3)
Q1M. Remembering to take my medications is
Q2M. Remembering to collect my medications from the doctors or pharmacy is
Q3M. Sticking to medications taking routine is

Subscale 1 contains items representing the TDF domain ‘Social Influence’ as a determinant of adherence. Items in Subscale 2 are related to TDF domains ‘Intentions’, ‘Social/professional role and identity’, ‘Goal’ and ‘Emotion’ as the determinant of adherence. Similarly, Subscale 3 include items representing the TDF domain ‘Memory, attention and decision processes’ as the determinant of adherence.

These three subscales comprising 15 items in table 5.9 are called the C-MABQdmm or 15-item C-MABQ from here onwards. These items were further analysed to investigate model fit as per confirmatory factor analysis, internal consistency reliability, criterion validity, convergent and discriminant validity and test-retest reliability. There

were seven outliers based on Guttman's error calculations, but their exclusion did not affect the MSA results, so further analysis was carried out with these outliers.

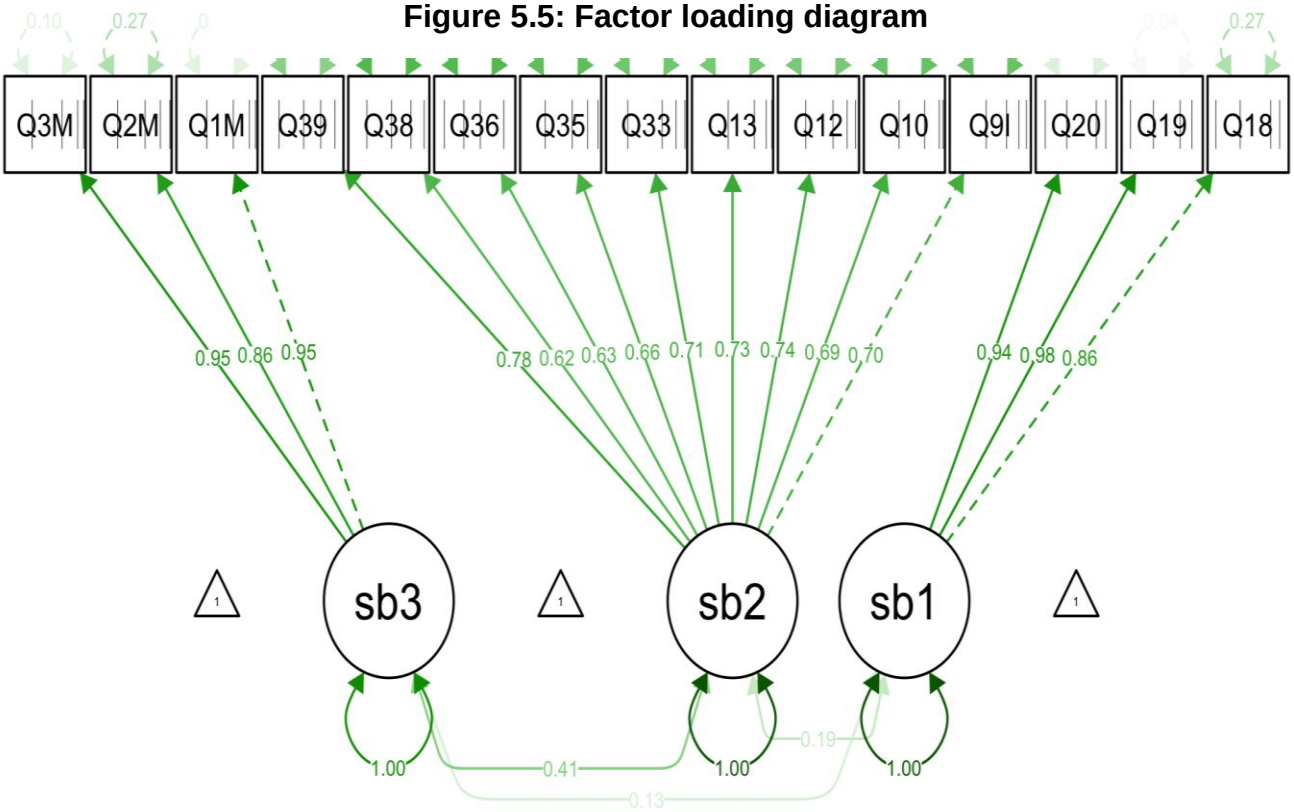
5.3.3 Confirmatory Factor Analysis

Confirmatory factor analysis was carried out on the C-MABQdmm model to provide a complementary perspective on the dimensionality of the item sets. The fit statistics and the parameter estimate for the model are presented in table 5.10 below. As described in the method section, the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root mean Square Error of Approximation (RMSEA) are all within the recommended values. Thus, the results of confirmatory factor analysis suggest a good model fit and enforce the C-MABQdmm model and structure derived from MSA. The diagram showing factor loading (0.62 to 0.98) in Figure 5.5 suggest very good or excellent factor loading.

Table 5.10: Results of Confirmatory factor analysis of C-MABQdmm model (See Appendix 5.15 for full result)

Description	**Standard**	**Robust**
Number of observations = 325	-	-
User Model versus Baseline Model: • Comparative Fit Index (CFI) • Tucker-Lewis Index (TLI)	 0.997 0.996	 0.988 0.986
Root Mean Square Error of Approximation: • RMSEA • 90% CI – lower • 90% CI – upper	 0.059 0.047 0.070	 0.074 0.063 0.085
Standardised Root Mean Square Residual: • SRMR	 0.061	 0.061

Figure 5.5: Factor loading diagram



5.3.4 Internal Consistency Reliability

The estimated Cronbach's alpha and Omega for each subscale representing internal consistency reliability are displayed in table 5.11 below. The results show that all three subscales have good internal consistency reliability, with all three indices showing a greater than the usually recommended threshold of 0.7 (211).

Table 5.11: Internal Consistency Reliability indices of each subscale (See Appendix 5.15 for more details)

Scale	Cronbach's alpha [95% CI]	Omega [95% CI]
Subscale1	0.92 [0.91 - 0.94]	0.93 [0.91 - 0.95]
Subscale2	0.85 [0.83 - 0.87]	0.85 [0.82 - 0.88]
Subscale3	0.91 [0.89 - 0.93]	0.91 [0.89 - 0.94]

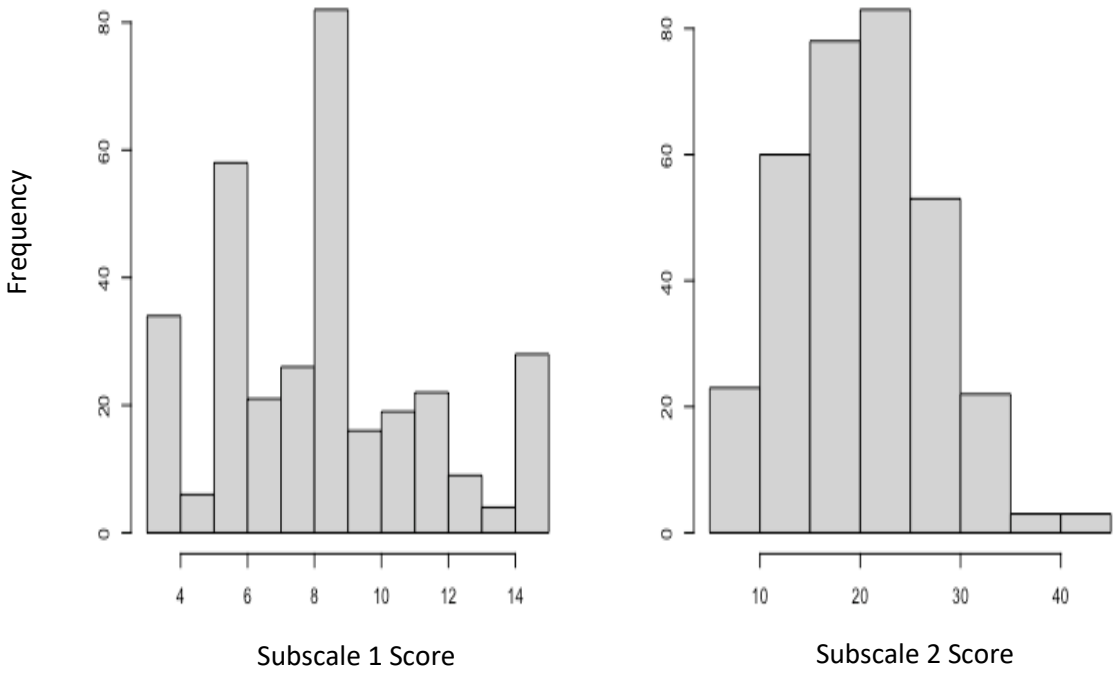
5.3.5 Subscales scores and score statistics

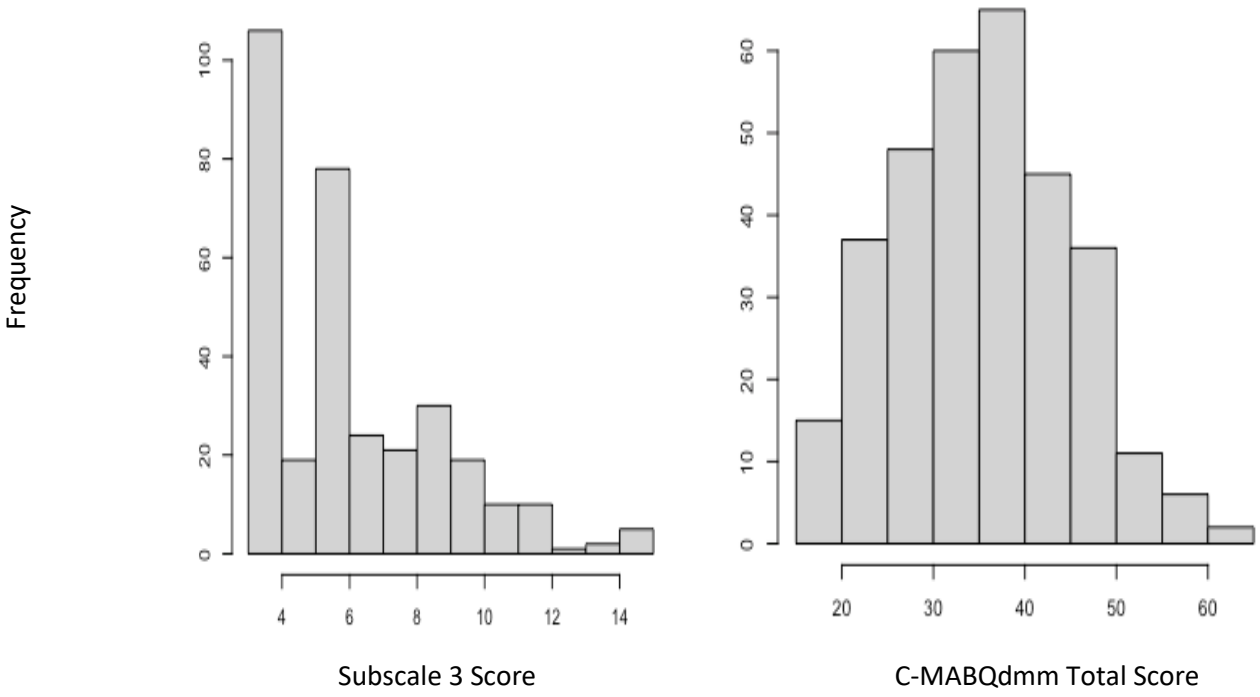
Total scores for each subscale are computed, and descriptive statistics are presented in table 5.12 below. Distributions of the scores are shown graphically in Figure 5.6.

Table 5.12: Descriptive statistics total scores of each subscale

	Mean	Standard deviation	Minimum score	Maximum score	Range
Subscale 1 score	8.63	3.24	3	15	12
Subscale 2 score	20.76	4.96	9	43	34
Subscale 3 score	4.28	2.91	3	15	12

Figure 5.6: Histogram of each subscale score and C-MABQdmm total scores





5.3.6 Criterion Validity

The correlation between the total scores of each subscale, C-MABQdmm whole scale (i.e., 15-item C-MABQ) and MARS-5 total scores are shown in table 5.13 below. There was a moderate, statistically significant positive correlation between Subscale 3 and MARS-5 total scores as well as C-MABQdmm total score and MARS-5 total scores. Subscales 1 and 2 have a statistically significant, weak correlation with MARS-5.

Table 5.13: Correlations between C-MABQdmm Subscales total scores, C-MABQdmm total scores and MARS-5 total scores

	Correlation coefficient with MARS total scores
Subscale 1 score	0.11*
Subscale 2 score	0.25***
Subscale 3 score	0.38***
C-MABQdmm Total Score	0.32***

*Note: *** indicates $p < 0.001$ and * indicates $p < 0.05$*

The relationship between subscales total scores and MARS total scores is also presented graphically with the best fit line in Figures 5.7 to 5.9 below.

Figure 5.7: Graph plot of Subscale 1 total score and MARS total score

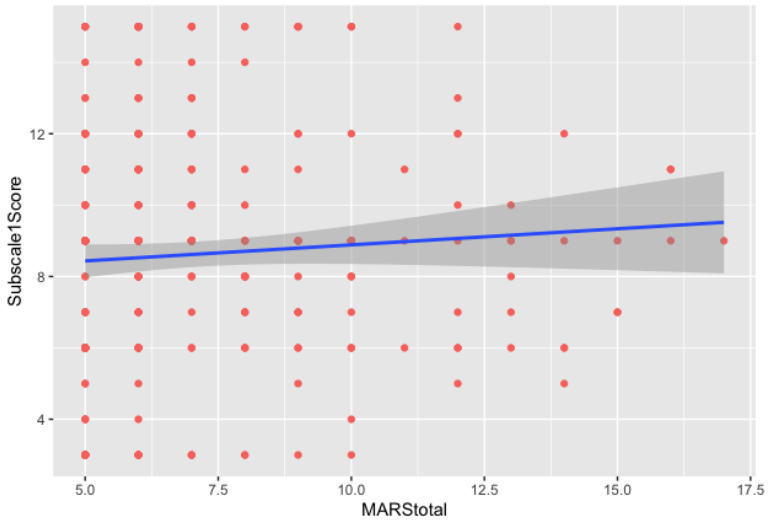


Figure 5.8: Graph plot of Subscale 2 total score and MARS total score

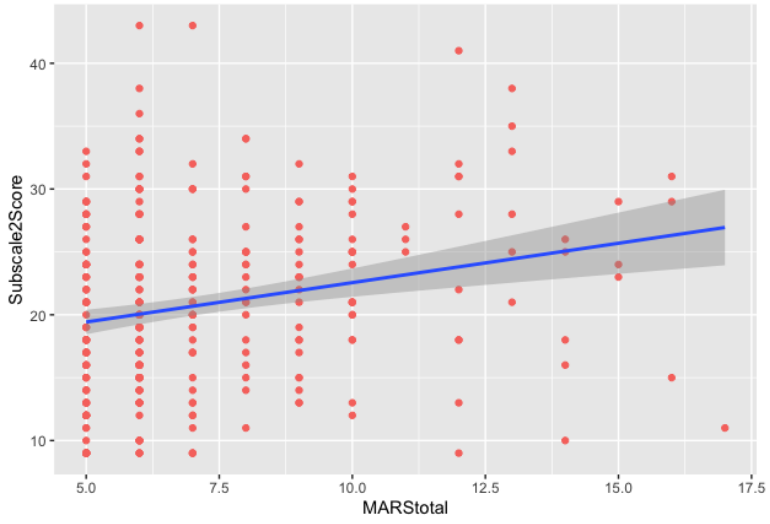


Figure 5.9: Graph plot of Subscale 3 total score and MARS total score

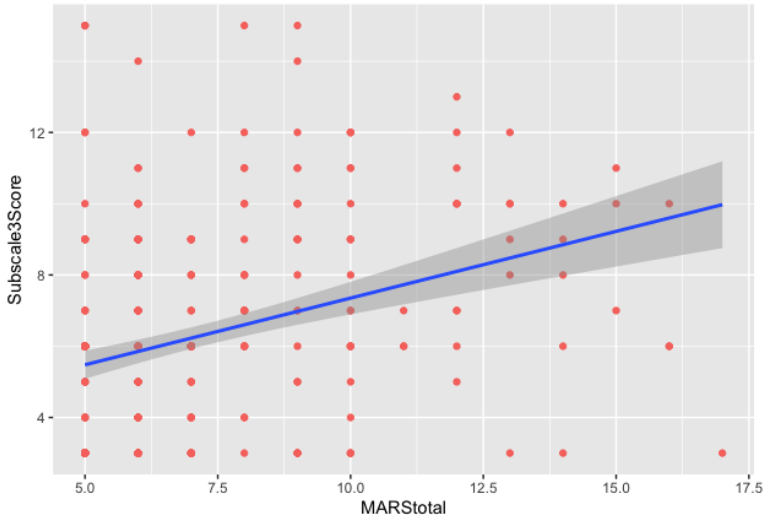
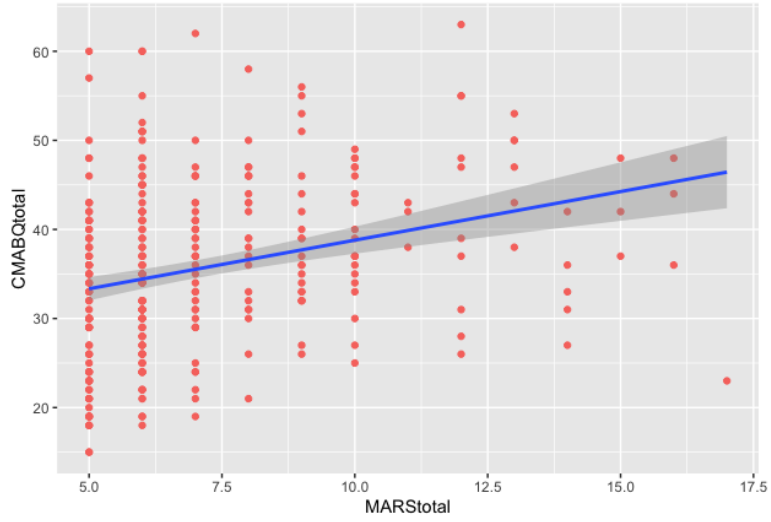


Figure 5.10: Graph plot of C-MABQdmm total score and MARS total score



The above results suggest the criterion validity of Subscale 3 and C-MABQdmm as a whole scale against the medication adherence scale MARS-5.

Criterion validity was also tested against binary adherence level measured by the patient's blood Lithium level. Blood Lithium levels ranged from 0 to 1.02 mmol/L amongst all patients with a median of 0.59 mmol/L. Blood Lithium level within 90 days from the survey completion date was available for around 90% of patients. As described in the method section, patients were divided into two groups, the high adherence group and low adherence group, based on the patient's age and their latest blood Lithium level. The

mean score of each subscale of C-MABQdmm and total C-MABQdmm between these two groups was compared using a t-test. The mean score of MARS-5 between these two groups was also tested. The results of the t-test are displayed in tables 5.14A to 5.14C below.

Table 5.14A: Welch Two Sample T-test results with a mean difference in each subscale scores between high and low adherence group (See Appendix 5.15 for more details)

C-MABQdmm Subscale1 total score	
Mean in group 0 (High Adherence Group)	8.63
Mean in group 1 (Low Adherence Group)	8.63
The difference in the mean	0.00
95% CI for the mean difference	-0.85 to 0.84
p-value	0.9912
C-MABQdmm Subscale 2 total Score	
Mean in group 0 (Good Adherence Group)	20.66
Mean in group 1 (Poor Adherence Group)	21.21
The difference in the mean	-0.55
95% CI for the mean difference	-2.62 to 1.52
p-value	0.6015
C-MABQdmm Subscale 3 total Score	
Mean in group 0 (Good Adherence Group)	6.29
Mean in group 1 (Poor Adherence Group)	6.19
The difference in the mean	0.10
95% CI for the mean difference	-0.79 to 0.99
p-value	0.8211

Table 5.14B: Welch Two Sample T-test results with a mean difference in C-MABQdmm total scores between high and low adherence group

C-MABQdmm total Score	
Mean in group 0 (Good Adherence Group)	35.59
Mean in group 1 (Poor Adherence Group)	36.04
Difference in the mean	-0.45
95% CI for the mean difference	-3.25 to 2.35
p-value	0.7507

Table 5.14C: Welch Two Sample T-test results with a mean difference in MARS-5 total scores between high and low adherence group

MARS-5 total Score	
Mean in group 0 (Good Adherence Group)	7.08
Mean in group 1 (Poor Adherence Group)	7.39
Difference in the mean	-0.31
95% CI for the mean difference	-1.10 to 0.49
p-value	0.4428

C-MABQdmm subscale scores mean is expected to be higher in the low adherence group (Group 1) than in the high adherence group (Group 0), i.e., lower the C-MABQdmm subscale score lower the barriers to adherence and thus higher the adherence. The mean difference in total scores for Subscale 1 between the high and low adherence groups was negligible. As expected, the subscale 2 scores mean was 0.55 higher in the low adherence group than the high adherence group. The mean difference for Subscale 3 was small -0.1. The mean C-MABQdmm total score was 0.45 higher in the low adherence group compared to the high adherence group. The figure increased to 0.98 when seven outliers based on Guttman's error and seven patients with blood Lithium levels not available within 6 months of survey completion date were removed for the t-test. So, although statistically not significant at p=0.05, the mean differences in a total score for C-MABQdmm, Subscale 2 among low adherence and high adherence group were in the right direction.

Similarly, the MARS-5 total score was expected to be higher in the low adherence group and vice versa. Table 5.14C shows that the mean MARS-5 total score was 0.31 higher in the low adherence group compared to the high adherence group; however, this was not statistically significant.

None of the differences was statistically significant with p values ranging from 0.34 to 0.94. Thus, the study could not establish criterion validity of both MARS-5 and C-MABQdmm against adherence based on the patient's blood Lithium level.

5.3.7 Convergent and discriminant validity

Table 5.15 displays the correlation coefficient between each subscale score and scores of BIPQ items and the first MARS-5 item. Items in each subscale of C-MABQdmm are described in table 5.9.

Subscale 1 includes items representing the TDF domain 'Social Influence' as a determinant of adherence. This concept is not covered by any BIPQ items or MARS-5 items, and thus, no correlation or only a weak correlation (or $r < 0.3$) was expected between Subscale 1 and any BIPQ and MARS-5 items. Table 5.15 second column shows $r < 0.2$, indicating discriminant validity.

Subscale 2 is a bit more complex as it covers multiple concepts and unsurprisingly, we can see $r > 0.3$ for many BIPQ items in column 2 of table 5.15. Subscale 2 includes items that cover the TDF domains 'Intentions', 'Social Influence', 'Social/professional role and identity', 'Goals' and 'Emotion'. As expected, the highest correlation is between Subscale 2 and BIPQ item 4 (How much do you think your treatment can help your mental illness?) as many items in Subscale 2 relate to the patient's own view and emotions about medication. BIPQ item 7 is about knowledge of the illness, and the first MARS-5 item M1 is about forgetfulness both of which are weakly correlated, i.e., $r < 0.3$ to Subscale 2.

Subscale 3 captures the concept of difficulty in remembering and maintaining a routine of medication and includes items representing the TDF domain 'Memory, attention and decision processes'. The first MARS-5 item M1 asks patients how often they forget to take medication. Thus, as expected, r is > 0.3 between Subscale 3 and M1. But r is <0.3

between Subscale 3 and unrelated BIPQ items B2, B3, B4 and B4. The correlation coefficient between Subscale 3 and B1, B5 and B8 are >0.3. Medication taking is a part of the illness, and taking medication often reminds patients of their illness; thus, such correlation is not unexpected.

Table 5.15: Correlation between C-MABQdmm subscales, BIPQ and MARS-5

	Subscale 1 score	Subscale 2 score	Subscale 3 score
B1 -How much does your mental illness affect your life? (Consequences)	0.10	0.36	0.42
B2 - How long do you think your mental illness will continue? (Timeliness)	0.05	-0.07	0.10
B3 - How much control do you feel you have over your mental illness? (Personal Control)	-0.15	-0.33	-0.27
B4 - How much do you think your treatment can help your mental illness? (Treatment Control)	-0.17	-0.47	-0.27
B5 - How much do you experience symptoms from your mental illness? (Identity)	0.04	0.29	0.32
B6 - How concerned are you about your mental illness? (Concern)	0.09	0.30	0.24
B7 - How well do you feel you understand your mental illness? (Understanding)	-0.10	-0.24	-0.31
B8 - How much does your mental illness affect you emotionally? (e.g., does it make you angry, scared, upset, or depressed?) (Emotional response)	0.17	0.34	0.34
M1 - I forget to take them	0.10	0.17	0.37

5.3.8 Test-retest reliability

Results of Intra-class Correlation Coefficient (ICC) calculation to measure test-retest reliability of each subscale is displayed in table 5.16 below. A two-way mixed effect model and absolute agreement definition were selected to calculate ICC for test-retest reliability as recommended (244) (245). Based on Fleiss's definition (245) Subscale 1 has excellent test-retest reliability, and Subscale 2 and 3 has good test-retest reliability. C-MABQdmm as a whole i.e., 3 subscales with 15 items together, had good test-retest reliability.

Table 5.16: Test-retest reliability using ICC

Subscales	ICC	95% CI	Significance
Subscale 1	0.76	0.63 to 0.84	<0.001
Subscale 2	0.59	0.39 to 0.72	<0.001
Subscale 3	0.69	0.54 to 0.79	<0.001
C-MABQdmm	0.74	0.61 to 0.82	P <0.001

5.4 DISCUSSION

The study presents a 15-item adherence questionnaire comprising three subscales that met the Mokken Scale Double Monotonicity Model, thus showing construct validity. Construct validity of C-MABQdmm was also demonstrated through convergent and discriminant validity. The 15-item C-MABQ (C-MABQdmm) has a good model fit with very good to excellent factor loading, thus reaffirming the construct validity of C-MABQdmm. Criterion validity of the 15-item C-MABQ could not be established against blood Lithium level however, it was established with MARS-5. The 15-item C-MABQ has strong internal consistency and good test-retest reliability.

According to the ABC taxonomy of medication adherence, non-adherence may occur during the phase of initiation, implementation or persistence (246). Adherence determinants may differ in these three phases e.g., patient's view of the benefit of treatment is mostly influential in medication adherence during initiation and persistence of treatment (247). Non-adherence in the form of non-initiation was not relevant in this

sample as the study only recruited patients already established on Lithium for at least four months. Similarly, the study did not include patients who have discontinued Lithium. This provides some explanation for why those adherence determinants mostly influential in initiation and persistence may not have been relevant in this sample and thus very few patients reporting these determinants. Additionally, issues with medication form (e.g., pills, liquids, or injections), dose and frequency of medication are likely to have been resolved within the first few weeks or months of prescribing medications. And thus, these determinants may not have been relevant in our sample.

Negatively correlated items are often due to negatively phrased statements and thus resolved by reverse coding. However, unlike the majority of items which are positively correlated with each other, 12 items were positively correlated with some items but negatively correlated with many others. This discrepancy may be due to the items being misunderstood and thus answered incorrectly. The cognitive interviews with patients did not indicate such problems, however, these items may need refinement through more qualitative work with patients. It is also likely that these items were not present as a determinant of adherence in this sample and thus their answers may be unrelated to adherence. Nonetheless, when MSA was carried out by including these items, most of them were unscalable or did not meet Mokken Scale criteria so they would have been excluded.

Patient's experience and perception of their healthcare professionals represented by Subscale 1, affect their medication adherence accordingly. Social influences are known determinant of medication adherence in mental health in general as well as in bipolar disorder (18,39,165,247). However, social influence in the literature was mainly described as family or social support to take medication (39,247). Moreover, none of the validated adherence scales in bipolar disorder capture social influence as a determinant of adherence (87). Subscale 1 of 15-item C-MABQ presents social influences as determinants of adherence at a granular level.

Subscale 2 covers five TDF domains mostly dominated by 'Emotion' domain. While the experience of side effects is frequently reported adherence determinant albeit inconsistently (39,63,165), emotional aspect of potential side effects are rarely reported not only in physical health but also in mental health (18,53). As described in Chapters 2 and 3, the TDF domain 'Emotion' is an important determinant of medication

adherence in bipolar disorder. Thus, a lack of this domain in other adherence scale raise question on content validity. ‘Intentions’ domain is also significantly under-represented in the literature and underappreciated by healthcare professionals (18,39). As described in Chapter 1, the intention is critical for performing a behaviour such as medication taking. Moreover, the treatment option other than medications, when clinically appropriate should be considered for holistic approach to mental health treatment. Influence of media (TV, newspaper, social media etc.), shared decision making and practical difficulties (e.g., too sedated on medication to go to work) on medication adherence is recognised in the literature. However, mapping these determinants to the TDF domain mean relevant tailored BCTs can be implemented to improve adherence.

Most frequently reported practical determinant of adherence is encapsulated in Subscale 3. Forgetting to take medication is a frequently cited determinant of medication adherence in the literature but is underappreciated by healthcare professionals (18,39,247). Nonetheless, many adherence scales validated in bipolar disorder do ask about forgetfulness, but they generally have three key limitations. First, most adherence scales mainly focus on the magnitude of forgetfulness to take medication and ignore other similar but important determinants such as forgetfulness to collect medication or sticking to medication routine (18,47). Secondly, most scales ask direct questions, such as how often you forget to take medication, which may introduce reporting bias. Subscale 3 of the 15-item C-MABQ captures all important concepts related to forgetfulness and mapping these items to the TDF domains further strengthens its clinical utility.

The 15-item C-MABQ with these three Subscales is Mokken Scale DMM compliant demonstrating construct validity (216). Construct validity is also shown by convergent and discriminant validity test. The structure of 15-item C-MABQ derived from MSA is reinforced by confirmatory factor analysis.

A moderate correlation between 15-item C-MABQ total score and MARS-5 total score suggest criterion validity (243). Subscale 3 also shows criterion validity against MARS-5 with statistically significant moderate correlation. Subscale 1 and 2 shows statistically significant but only weak correlation with MARS-5 total score. This may be explained by key differences between the two scales. MARS-5 contains four items

covering intentional non-adherence (altering the dose, stopping for a while, missing a dose and taking less than instructed) and one item representing unintentional non-adherence (i.e., forgetting to take medication) (235). MARS-5 provides a very short adherence questionnaire, thus reducing respondents' burden, but this comes at the cost of compromised content validity. MARS-5 does not include any items covering social influences or emotional aspects predominant in the 15-item C-MABQ. In addition, MARS-5 measures the magnitude of adherence and not the determinants of adherence. The 15-item C-MABQ, on the other hand, focuses on identifying determinants of adherence as these determinants influence not only current medication adherence but also future adherence. Medication adherence is a dynamic process where past or present adherence does not necessarily mean future adherence and vice versa (30). Moreover, C-MABQdmm covers multiple dimensions of intentional and unintentional non-adherence, thus strengthening its content validity.

Difficulty in demonstrating criterion validity of the 15-item C-MABQ and its subscales against blood Lithium level merit some explanation. Monitoring blood level of medication is often considered the gold standard for checking medication adherence. However, there are many limitations and identifying non-adherence using medication blood level is not as simple as often believed. Firstly, the range of medication blood level, or Lithium level in our case, varies significantly. For example, a marketing authorisation document such as a summary of product characteristics of Lithium recommend a minimum blood Lithium level of 0.5 mmol/L in adults and 0.4mmol/L in the elderly and those <50 kilogram (248). NICE guideline and British Association of Psychopharmacology guideline advocate a minimum blood Lithium level of 0.6mmol/L (10,21). Yet others suggest 0.8mmol/L is required for optimum efficacy (239,249). Secondly, effective lower blood Lithium level is individualistic, i.e., for some patients, 0.4mmol/L may be sufficient to manage their bipolar disorder while others may need 0.8mmol/L in clinical practice. Thirdly, blood Lithium level depends on many variables such as whether the blood was taken at the right time (i.e., 11 to 13 hours post-dose), dose of Lithium, dietary changes and co-medications. Thus, it can be very difficult to accurately identify non-adherence based on blood Lithium levels. Moreover, blood Lithium level tells us about patient's adherence during the immediate past only, i.e., Lithium adherence during 5 to 7 days before the blood test. Thus, adherence based

on blood Lithium level is no proof that patients were taking Lithium > 7 days before the blood test, nor does it indicate patients will take Lithium in the future. Notwithstanding the limitation of other objective measure of adherence and hence longstanding complexities and difficulties in accurately identifying non-adherence, future study may benefit from using different objective measure of non-adherence such as medication event monitoring system.

The 15-item C-MABQ aimed to identify what may be helping or hindering patients from taking their medication as prescribed. This is critical for providing tailored adherence support to patients. For example, even if the patient is shown to be adherent based on blood Lithium level (not discounting the complexities described above) but if the patient is experiencing the barriers identified through 15-item C-MABQ (e.g., fed up taking medication), then their adherence is likely to be compromised in the future even if they are currently adherent. Thus, the difficulties individual patients are experiencing to take their medications should be addressed to prevent non-adherence as recommended by NICE (21). Unlike other adherence scales validated in bipolar disorder, which mainly focus on measuring the magnitude of adherence, 15-item C-MABQ is designed and aimed to support these NICE principles of adherence. And since each item is mapped to the TDF domains, which are linked to BCTs as described in Chapter 1, 15-item C-MABQ provides the foundation for developing patient-tailored adherence interventions. Any patient scoring 4 or 5 (i.e., presence of a barrier) on any of the 15-item C-MABQ items requires support to address that determinant regardless of the patient's current adherence status since it is causing the patient difficulty.

The feasibility of the use of the 15-item C-MABQ in clinical practice need to be explored in future study.

Strength and Limitation of the Study

The 15-item C-MABQ is underpinned by a comprehensive behaviour change framework as recommended by NICE, the World Health Organization and the UK General Medical Council. To my knowledge, this is the first adherence scale developed in the field of mental health underpinning such a comprehensive

framework. In chapter 1, I discussed the lack of theory and limitation of individual behavioural theory and why comprehensive behaviour change framework such as TDF is critical to developing patient-tailored support. Thus, it provides a foundation to guide healthcare professionals to choose appropriate BCTs based on the patient's individual determinant of adherence.

Focussing on patients with bipolar disorder who are prescribed Lithium for at least four months reduced the heterogeneity in the sample. But this comes at the cost of generalisability as the study excluded patients during the treatment initiation. Thus, the 15-item C-MABQ may not be representative of adherence determinants during treatment initiation. However, bipolar disorder requires long-term maintenance treatment, so it is likely to be useful in the vast majority of patients taking Lithium. Blood Lithium level is considered a good objective adherence measure and thus, focussing on patients taking Lithium allowed blood Lithium level to be used for the criterion validity. However, as discussed earlier, blood Lithium level has many limitations and may not be as accurate and reliable measure of adherence as generally considered.

The study participants were from Norfolk, a county with a relatively older (65 years old or over) population compared to the whole of England, 24.6% vs 18.5% (196). Furthermore, around one third of patients prescribed lithium in the UK are 65 years old or over (250) compared to 45.2% of survey participants in this study. This may limit the generalisation of the study findings.

The reliability and validity of 15-item C-MABQ in patients taking medication other than Lithium may need to be tested in future research.

CHAPTER SIX

DISCUSSION

Discussion

This chapter synthesises the key findings, strengths and limitations, implications for clinical practice and research.

6.1 KEY FINDINGS

Behaviour change theories help explain the observed behaviour through proposing determinants of the behaviour. Such understanding is essential for any behaviour change intervention. Chapter 1 describes different behaviour change theories and their relevance to medication adherence. Understanding behaviour change theory has helped me appreciate the complexities and difficulties in changing behaviour and made me more empathetic towards patients. The systematic review described in Chapter 2 provided a comprehensive list of modifiable determinants of adherence in bipolar disorder some of which are not previously reported in the literature and underappreciated by healthcare professionals such as determinants within the 'Emotion' and 'Intentions' domains of the TDF. The systematic review, thus, added new knowledge to the field. Using the TDF facilitated condensing hundreds of determinants into easily comprehensible groups (the TDF domains) to structure the focus group and interview discussions described in Chapter 3. Discussions with patients with bipolar disorder and their families and friends further enhanced my understanding of reasons why some patients struggle to take medication as prescribed, and some choose to deviate from the prescribed directions. The discussions also allowed the target audience to refine and prioritise the determinants identified in Chapter 2. For systematic investigation of an individual's determinants of adherence, C-MABQ developed from the prioritised determinants in Chapter 3, showed good face and content validity and good readability as reported in Chapter 4. Chapter 5 detailed the evaluation of C-MABQ and reported 15-items C-MABQ showing construct validity, criterion validity with an adherence scale, strong internal consistency reliability and good test-retest reliability.

The funding of my fellowship to develop the C-MABQ has contributed towards addressing the historical failure to afford mental health, the same level of investment as physical health conditions (251,252). It aligns with national efforts to prioritise mental health and to bring it on par with physical health. In 2011, A cross-government mental health outcomes strategy document titled 'No health without mental health' was

published in England to prioritise mental health. Following that, parity of esteem, the principle of giving mental health equal priority to physical health in terms of access to service and treatment, quality and research, was enshrined in the UK health and social care act 2012 (252). A questionnaire similar to the C-MABQ, called the 'Identification of medicines adherence barriers questionnaire' exists for physical health conditions thus the development of the C-MABQ is a step towards parity of esteem. Furthermore, a lack of behaviour change theory in mental health medication adherence research is striking compared to physical health medication despite the recognition of its importance (48,52,79). So, the use of the TDF to develop C-MABQ support the principle of parity of esteem and gives mental health medication adherence same opportunity as physical health medication adherence.

Practical barriers to adherence

The key practical barriers to adherence in this sample are encapsulated in Subscale 3 and Q33G of the 15-item C-MABQ which are related to difficulty remembering to take medication, difficulty in collecting medication, sticking to a medication-taking routine and medication interfering with daily activities. However, most adherence scales and adherence interventions only focus on the first barrier (83,87,235).

Practical issues such as forgetfulness, financial costs, and scheduling are reported in the literature as adherence determinants (165,182,235). As explained in Chapters 2 and 3, forgetfulness is a well-recognised barrier to adherence (165,182,235). However, the thesis also recognised the difference between difficulty remembering to take the medication and in collecting medication which is reflected in including both concepts in C-MABQ in Chapter 4. The 15-item C-MABQ captures these subtle differences thus identifying some currently underappreciated and unaddressed adherence determinants. Moreover, through our work with patients and their families and friends, this thesis explored the subtle difference in reasons for forgetfulness. Forgetfulness due to scheduling or a hectic lifestyle will require different BCTs than forgetfulness due to lack of prioritisation or motivation.

The systematic review described in Chapter 2 found that historically most studies focus on barriers to adherence. This thesis, however, explored both barriers and facilitators, recognising that facilitators are not always the absence of barriers or the

opposite of barriers. Facilitators such as online prescription ordering and delivery services identified through work with patients and their families and friends are previously unacknowledged and untapped resources that can provide easy access to medication for patients. Using 15-item C-MABQ can help identify patients who may benefit from such services currently provided by most community pharmacies in England.

Social influences as determinant of adherence

Subscale 1 and Q12S of the 15-item C-MABQ represent lack of a supportive healthcare team and unhelpful environment as barriers to adherence. These adherence determinants were mapped to the TDF domain 'Social influences'. Social influences on adherence are often described in the literature in terms of the therapeutic alliance which is a recognised determinant of adherence (39,253,254) (164). Some suggest only a weak association (253) but this determinant was recognised in our systematic review in Chapter 2 and prioritised by patients and their families and friends in Chapter 3. In addition to having a good relationship with the healthcare team, patients' perception of whether they feel listened to and have access to healthcare professionals in a timely manner were important determinants of adherence in this sample. These determinants are also captured in Subscale 1. The influence of media on medication adherence is not widely recognised within the research and clinical environment (21,85). This is evident by the absence of the concept of social influence in many adherence scales. The 15-item C-MABQ systematically investigates this potential determinant of an individual's behaviour and mapping it to the TDF domain allows it to be linked to the appropriate BCTs thus building a foundation to support this previously unaddressed barrier.

Motivational factors influencing adherence

Motivational factors affecting adherence are mapped to the TDF domains 'Emotion', 'Intentions' and 'Social/professional role and identity'.

Determinants mapped to the 'Emotion' domain were prominent in this study and represent over a quarter of 15-item C-MABQ items suggesting their importance. Worry

of side effects, worry of addiction to medication, fear of not being oneself and feeling fed-up taking medication were the determinants reported in this domain that can demotivate patients to adhere. Side effects have been explored extensively and widely recognised as a determinant of adherence although findings were inconsistent (39). In this study, the worry of side effects was more obvious adherence determinant than actual side effects. This distinction is important since the BCTs linked to the 'Emotion' domain will be more appropriate for worry of side effects whereas BCTs associated with the TDF domain 'Environmental context and resources' will be best suited to the latter. Other determinants in 'Emotion' domains are poorly recognised and often uninvestigated. The 15-item C-MABQ provides systematic way to identify these determinants and provides foundation for tailored support.

Most behaviour change theories and frameworks recognise the critical importance of intentions in changing behaviour (49). Accordingly, patients' denial of illness or need for treatment that affect their intentions to adhere is frequently reported in the literature (39,63,165) and in this thesis. However, not wanting to take medication and preference for alternative treatment were less frequently reported but these were predominant adherence determinants in this study. Moreover, as described in Chapter 2, determinants mapped to 'Intentions' domain was broadly underappreciated by healthcare professionals and thus may not be giving adherence support based on patient's need.

Collaborative decision making is a recognised adherence determinant (113) although the amount of involvement a patient needs or wants is an individual choice. What is critical for adherence, however, is whether the patient feels the medication was an imposition, determinant mapped to 'Social/professional role and identity'. Thus, there is a need for healthcare professionals to maintain a delicate balance of involving patients without adding significant burden to patients at the same time ensuring that patients feel they own the treatment decision.

The central theme from the study is 'Working together is paramount for adherence'. Healthcare professional and patients should work together to remove practical barriers, better social influences or to motivate patients to improve adherence. Each patient is unique and so is their needs. The final 15-items C-MABQ can provide an effective tool in identifying individual's unique needs to improve adherence. And since

each statement on the 15 item C-MABQ is mapped to the TDF domain, it provides the foundation for tailored support based on an individual's determinant of adherence.

6.2 STRENGTHS AND LIMITATIONS

The strengths and limitations of four research projects (the systematic review, focus group and interviews, development of C-MABQ and evaluation of C-MABQ) are discussed in the relevant chapters of this thesis (Chapters 2, 3, 4 and 5 respectively). The strengths and limitations associated with the overall programme of work are discussed below.

Historically, adherence determinants are categorised into five dimensions: social/economic factors, therapy-related factors, patient-related factors, condition-related factors and health system-related factors (20,39). In this thesis, we grouped adherence determinants into the TDF domains which provides the foundation for developing tailored adherence support as described in Chapter 1. Underpinning the thesis with the TDF has also allowed comprehensive exploration of the determinants of adherence and thus identified some previously unrecognised determinants. Furthermore, the literature of adherence determinants often does not differentiate between what can be modified within the context of medication adherence and what is non-modifiable. Focussing on modifiable determinants of adherence in this thesis provided healthcare professionals with a list of modifiable determinants that they can work with patients to support adherence.

The thesis followed best practice guidance in questionnaire design thus affording scientific rigour and robustness. Each five empirical studies within the thesis had the benefit of continued support and guidance from patients and their families and friends, healthcare professionals, academic researchers and experts in the field of medication adherence and behaviour change. They provided invaluable support to the research as well as psychological support to me.

As an NIHR funded clinical research project, I was allowed to stay in my clinical role partially and thus continue to have access to NSFT. This has helped significantly in recruitment of participants and collection of patient information such as blood Lithium level.

A very high proportion (45.2%) of survey participants were 65 years old or over compared to around a third of lithium patients in the UK being older (250). In addition, the study was conducted in patients who have been established on lithium and so only determinants related to implementation phase may have been predominant. Thus, the generalisability of C-MABQ15 may be limited to similar population.

The project may have been too ambitious and may have inadvertently led to chasing the project deadlines at the cost of learning.

6.3 Achievements and Challenges

Receiving the NIHR Clinical Doctoral Research Fellowship funding award was my lifetime achievement. I am honoured to have been the first mental health pharmacist in England to receive this reward. This was celebrated in the NSFT, publicised in local newspaper and reported in the Pharmaceutical Journal.

However, transitioning from a clinician to a researcher was a considerable challenge. Learning new topics such as behaviour change theories and computer software like Nvivo and R was exciting but at the same time quite challenging. Being naïve to these subjects invoked anxiety and enthusiasm simultaneously. Learning and applying them in practice for data analysis and interpretation brought a sense of achievement. But I still feel anxious using R despite spending quite a lot of time on it. Learning R and psychometrics were two key challenges as both were totally new to me and I have to admit that I still feel novice at both. I also feel proud of two paper publications (with more scheduled), a video blog published by Psych Congress Network and presenting posters at two conferences.

As I was preparing to conduct focus group discussions with patients and their families and friends for Chapter 3, COVID-19 lockdown struck. This added work burden as all had to be rescheduled and participants had to be informed. Additionally, I had to get used to working within the constraint of lockdown including home-schooling which significantly impacted my productivity. But on the positive side, due to lockdown I saved a lot of time which otherwise would have been spent socialising and outdoor events.

There were also some life emergency events, passing away of my father-in-law and terminal illness of mother-in-law, during my PhD which was practically and psychologically challenging.

6.4 Implications for clinical practice, policy and research

6.4.1 Clinical practice and policy

The NICE clinical guideline highlights the need to prioritise medication adherence to get the best out of medication (21). It states*: "Addressing non-adherence is not about getting patients to take more medicines per se. Rather, it starts with an exploration of patients' perspectives of medicines and the reasons why they may not want or are unable to use them. Healthcare professionals have a duty to help patients make informed decisions about treatment and use appropriately prescribed medicines to best effect."* The UK General Medical Council, the Royal Pharmaceutical Society and the Royal College of Nursing also recommend healthcare professionals to explore non-adherence and its determinants. There is, however, a lack of a clinical tool to guide healthcare professionals in exploring barriers and facilitators of medication adherence in mental health in general and bipolar disorder in particular (87). The 15-item C-MABQ fulfils that need.

Raise awareness of adherence determinants among healthcare professionals

As described in Chapter 2, it is apparent that healthcare professionals do not necessarily fully take the patient's perspective into account during the process of prescribing medication. Medication is only effective if taken correctly. This includes the prophylactic use of medication in bipolar disorder whilst feeling well. Healthcare professionals may be significantly underestimating the adherence determinant affecting patients particularly the determinants mapped to 'Emotion' and 'Intentions'. The patient obviously has the final say (except under certain Mental Health Act) in the decision to take medication, but this process should allow a detailed exploration from both sides as to the potential barriers and facilitators. From there the patient and their families can make a genuinely informed decisions about their treatment. Raising awareness of broad range of adherence determinants relevant to bipolar disorder is thus important first step.

Furthermore, as noted earlier, online prescription ordering and delivery services were reported as facilitators and thus healthcare professionals should be aware of local services and resources and direct patients appropriately.

Current practice may not be providing tailored adherence support

The study provides theory and evidence-based modifiable determinants that influence a patient's adherence to their prescribed medication. All these determinants should, therefore, be considered and discussed with patients at every review. The current practice focuses on practical barriers to adherence such as providing information and education, managing side effects, offering medication choices (21,85,235). This is not aligned with the broad range of determinants reported in this thesis. It is noteworthy that whilst many areas of concern overlap, albeit not to the same extent, the healthcare professionals and patients may be further apart as a starting point than most healthcare professionals assume. The use of the 15-item C-MABQ and subsequent targeted discussions or interventions should help ensure a smoother and more therapeutic process with significantly improved outcomes.

Determinants that need focussing

Practical barriers are important and are captured by the 15-item C-MABQ. Determinants mapped to the TDF domains 'Emotion', 'Intentions' and 'Social influences' are underappreciated by healthcare professionals and rarely addressed. This thesis demonstrate that determinants mapped to these domains are predominant determinants of adherence in addition to practical barriers mapped to 'Memory, attention and decision processes' and 'Goals'. Addressing patient's concerns about side effects, addiction, their preference of non-medicinal treatment or empathetic timely support may be critical for adherence in many patients.

Using 15-item C-MABQ in clinical practice should facilitate a comprehensive discussion between healthcare professional and patient to identify potential barriers to adherence and interventions tailored, where possible, at overcoming these barriers. Thus, use of 15-item C-MABQ fulfils NICE recommendation. Any patient scoring 4 or 5 (i.e., presence of a barrier) on any of the 15-item C-MABQ items requires support to address that determinant regardless of the patient's current adherence status since it

is causing the patient difficulty. Addressing such difficulty support a key principle of NHS England's medicine optimisation agenda which is to understand and improve patient's experience with medication (255). 15-item C-MABQ provides a framework for patients and healthcare professionals to work together to reach a mutually agreeable decision. This supports the national policy of making 'No decision about me without me' a norm in the UK National Health Service (256).

6.4.2 Research

- The systematic review in Chapter 2 reported that less than 10% of the studies used blood levels of medication for adherence measurement. The use of different objective measures in general such as medication event monitoring system may provide more accurate measure of adherence for future research. Such objective measures should always be complemented with a validated subjective measure of adherence. Empirical study comparing currently available validated subjective measures of adherence in bipolar disorder may help select best subjective measure for future studies. However, it is noteworthy that currently available subjective measures focus on assessing adherence and not on adherence determinants.
- The 15-item C-MABQ demonstrated criterion validity against MARS-5 but failed to establish criterion validity against blood Lithium levels. Owing to the complexities, difficulties and limitation of blood Lithium level as an objective measure of adherence, future work on the 15 item C-MABQ with different objective measure is required for definitive trial.
- Each of the 15-item C-MABQ statements is mapped to its respective TDF domains. However, this thesis did not link these statements with the most appropriate BCTs to support adherence. Future research should involve an empirical work with experts in behaviour change experienced in linking BCTs to the TDF domains is required for clinical utility and broader implementation of this adherence tool.
- A feasibility study of 15-item C-MABQ in clinical practice to identify implementation problem and to select best clinical outcome measure for the intervention using appropriate BCTs will help its wider acceptance and use.
- 15-item C-MABQ may be appropriate for patients prescribed different medication for bipolar disorder, patients at different stages of treatment (e.g., initiation or

maintenance) and other mental health conditions but it should be investigated since adherence determinants may differ. As explained in Chapter 5, the population in this study may have different adherence determinants as the study did not include patients at the treatment initiation stage, patients who discontinued treatment or patients not diagnosed with bipolar disorder. Thus, research in different population using 50-item C-MABQ (Appendix 4.9) and then using item reduction analysis with item response theory and classical test theory is prudent.

6.5 CONCLUSION

Healthcare professionals may not be fully aware of a broad range of determinants that may be affecting patients' adherence and thus many not providing tailored support to patients. Particularly adherence determinants mapped to the TDF domains 'Emotion' and 'Intentions' may currently be overlooked by healthcare professionals. Current practice of focus on addressing practical barriers to adherence assumes unintentional non-adherence thus undermines intentional non-adherence and fail to acknowledge determinants affecting motivation to take medication.

The 15-item C-MABQ provides healthcare professionals with theory and evidence-based adherence tool to identify determinant of non-adherence. It explores the most prominent determinants spanned across six TDF domains and captures both practical and perceptual determinants of adherence. Thus, the 15-item C-MABQ provides a healthcare professionals potential foundation to develop tailored adherence support based on the individual's prominent adherence determinant.

Blood Lithium level as a measure of adherence poses many complexities and limitations and may not reliably ascertain non-adherence. Thus, a feasibility study is required to establish an appropriate outcome measure for a definitive trial. Such study should also include empirical work linking most appropriate behaviour change techniques to each statement representing unique adherence determinants. This will enhance its clinical utility and its consequent use in NHS clinical practice.

References

1. Global Burden of Disease 2017. Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018 Nov;392(10159):1789-1858.
2. Vazquez GH, Holtzman JN, Lolich M, Ketter TA, Baldessarini RJ. Recurrence rates in bipolar disorder: Systematic comparison of long-term prospective, naturalistic studies versus randomized controlled trials. Eur Neuropsychopharmacol 2015 Oct;25(10):1501-1512.
3. Bobo WV, Epstein RA, Lynch A, Patton TD, Bossaller NA, Shelton RC. A randomized open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization, and urgent care referral in community-treated patients with rapid cycling bipolar disorder. Clin Neuropharmacol 2011 Nov-Dec;34(6):224-233.
4. Costa LdS, Alencar AP, Neto PJN, Santos, Maria do Socorro Vieira dos, da Silva CGL, Pinheiro SdFL, et al. Risk factors for suicide in bipolar disorder: A systematic review. J Affect Disord 2015 Jan; 170:237-254.
5. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.) (DSM-5). Arlington, VA.
6. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 11th ed.; 2019.
7. National Institute of Health and Care Excellence (NICE). Bipolar disorder: assessment and management (Clinical Guideline, CG 185). 2014.
8. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol 2018 Apr;8(9):251-269.
9. Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. Int Rev Psychiatry 2010 Nov;22(5):437-452.
10. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016 Jun;30(6):495-553.
11. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018 Mar;20(2):97-170.
12. Cavanagh K. Geographic Inequity in the Availability of Cognitive Behavioural Therapy in England and Wales: A 10-Year Update. Behav Cogn Psychother 2014 Jul;42(4):497-501.

13. Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005 Jul;162(7):1281-1290.

14. Buckley P, Foster A, Patel N, Wermert A. Adherence to Mental Health Treatment. Oxford: Oxford University Press; 2009.

15. Vargas-Huicochea I, Huicochea L, Berlanga C, Fresan A. Taking or not taking medications: psychiatric treatment perceptions in patients diagnosed with bipolar disorder. J Clin Pharm Ther 2014 Dec;39(6):673-679.

16. Chakrabarti S. Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors. World J Meta-Anal 2017 Aug;5(4):103-123.

17. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand 2002 Mar;105(3):164-172.

18. Prajapati AR, Dima A, Mosa G, Scott S, Song F, Wilson J, et al. Mapping modifiable determinants of medication adherence in bipolar disorder (BD) to the theoretical domains framework (TDF): a systematic review. Psychol Med 2021 May;51(7):1082-1098.

19. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008 Apr;28(4):437-443.

20. De Geest S, Sabate E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nurs 2003 Dec;2(4):323.

21. National Institute of Health and Care Excellence (NICE). Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (Clinical Guideline, CG 76). 2009.

22. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000 Jul;133(1):21-30.

23. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatric services 2004 Aug;55(8):886-891.

24. Fleck DE, Corey KB, Strakowski SM, Keck Jr PE. Factors associated with medication adherence in African American and white patients with bipolar disorder. J Clin Psychiatry 2005 May;66(5):646-652.

25. Vieta E, Montgomery S, Sulaiman AH, Cordoba R, Huberlant B, Martinez L, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Neuropsychopharmacol 2012 Apr;22(11):825-835.

26. Morselli PL, Elgie R. GAMIAN-Europe*/BEAM survey I - Global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. Bipolar Disord 2003 Aug;5(4):265-278.

27. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. Hum Psychopharmacol 2008 Mar;23(2):95-105.

28. Johnson FR, Ozdemir S, Manjunath R, Hauber AB, Burch SP, Thompson TR. Factors that affect adherence to bipolar disorder treatments: a stated-preference approach. Med Care 2007 Jun;45(6):545-552.

29. Kutzelnigg A, Kasper S, Kopeinig M, Chen CK, Fabian A, Pujol-Luna MG, et al. Compliance as a stable function in the treatment course of bipolar disorder in patients stabilized on olanzapine: results from a 24-month observational study. Clin Transl Imaging 2014 Oct;2(1):1-14.

30. Jawad I, Watson S, Haddad PM, Talbot PS, McAllister-Williams RH. Medication nonadherence in bipolar disorder: a narrative review. Ther Adv Psychopharmacol 2018 Oct;8(12):349-363.

31. Sperber CM, Samarasinghe SR, Lomax GP. An upper and lower bound of the Medication Possession Ratio. Patient Prefer Adherence 2017 Aug; 11:1469-1478.

32. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. Br J Clin Pharmacol 2000 Aug;50(2):166-171.

33. Chauhan N, Chakrabarti S, Grover S. Identifying Poor Adherence in Outpatients with Bipolar Disorder: A Comparison of Different Measures. J Neurosci Rural Pract 2021 Sep;13(1):12-22.

34. Gutierrez-Rojas L, Jurado D, Martinez-Ortega JM, Gurpegui M. Poor adherence to treatment associated with a high recurrence in a bipolar disorder outpatient sample. J Affect Disord 2010 Dec;127(1):77-83.

35. Samalin L, Nourry A, Charpeaud T, Llorca PM. What is the evidence for the use of second-generation antipsychotic long-acting injectables as maintenance treatment in bipolar disorder? Nord J Psychiatry 2014 May;68(4):227-235.

36. Keck PE,Jr, McElroy SL, Strakowski SM, West SA, Sax KW, Hawkins JM, et al. 12-Month Outcome of Patients with Bipolar Disorder Following Hospitalization for a Manic Or Mixed Episode. Am J Psychiatry 1998 May;155(5):646-652.

37. Gonzalez-Pinto A, Mosquera F, Alonso M, Lopez P, Ramirez F, Vieta E, et al. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord 2006 Oct;8(5):618-624.

38. Scott J, Tacchi MJ. A pilot study of concordance threapy for individuals with bipolar disorders who are non-adherent with lithium prophylaxis. Bipolar Disord 2002 Dec;4(6):386-392.

39. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry 2009 Mar;70 Suppl 4:1-46; quiz 47-8.

40. Hong J, Reed C, Novick D, Haro JM, Aguado J. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: Results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) Study. Psychiatry Res 2011 May;190(1):110-114.

41. Bagalman E, Durden E, Yu-Isenberg KS, Crivera C, Dirani R, Bunn WB. Indirect costs associated with nonadherence to treatment for bipolar disorder. J Occup Environ Med 2010 May;52(5):478-485.

42. Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 2007 Oct;23(10):2305-2312.

43. Young AH, Rigney U, Shaw S, Emmas C, Thompson JM. Annual cost of managing bipolar disorder to the UK healthcare system. J Affect Disord 2011 Oct;133(3):450-456.

44. Conner M, Norman P. Health behaviour: Current issues and challenges. Psychol Health 2017 Aug;32(8):895-906.

45. Short SE, Mollborn S. Social Determinants and Health Behaviors: Conceptual Frames and Empirical Advances. Curr Opin Psychol 2015 Oct; 5:78-84.

46. Easthall C, Taylor N, Bhattacharya D. Barriers to medication adherence in patients prescribed medicines for the prevention of cardiovascular disease: a conceptual framework. Int J Pharm Pract 2019 Jun;27(3):223-231.

47. Brown T, Twigg M, Taylor N, Easthall C, Hartt J, Budd T, et al. Final Report for the IMAB-Q Study: Validation and Feasibility Testing of a Novel Questionnaire to Identify Barriers to Medication Adherence. 2017.

48. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. Framework for the development and evaluation of complex interventions: gap analysis, workshop and consultation-informed update. Health Technol Assess 2021 Sep;25(57):1-132.

49. Michie S, West R, Campbell R, Brown J, Gainforth H. ABC of Behaviour Change Theories. 1st ed. UK: Sliverback; 2014.

50. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev 2015 Aug;9(3):323-344.

51. The World Bank. Theories of Behavior Change. Available at: https://assets.publishing.service.gov.uk/media/57a08b4bed915d622c000bfd/BehaviorChangeweb.pdf. Accessed 02/16, 2022.

52. National Institute of Health and Care Excellence (NICE). Behaviour change: general approaches (Public health guideline, PH6). 2007.

53. Easthall C. The Development and Evaluation of Pharmacy-led Medication Adherence Services. UK: University of East Anglia; 2014.

54. Bandura A. Social foundations of thought and action: A social cognitive theory. Englewood Cliffs, NJ, US: Prentice-Hall, Inc; 1986.

55. Boston University School of Public Health. The Social Cognitive Theory. 2019; Available at: https://sphweb.bumc.bu.edu/otlt/mph-modules/sb/behavioralchangetheories/behavioralchangetheories5.html. Accessed 02/20, 2022.

56. Rosenstock IM. Historical Origins of the Health Belief Model. Health Educ Monogr 1974 Dec;2(4):328-335.

57. Montano D, Kasprzyk D. Theory of reasoned action, theory of planned behavior, and the integrated behavior model. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behaviour and Health Education Theory, Research, and Practice. 5th ed. CA: Jossey-Bass; 2015. p. 69-70.

58. Lee TS, Kilbreath SL, Sullivan G, Refshauge KM, Beith JM. The development of an arm activity survey for breast cancer survivors using the Protection Motivation Theory. BMC Cancer 2007 May; 7:75-2407-7-75.

59. Prestwich A, Sniehotta FF, Whittington C, Dombrowski SU, Rogers L, Michie S. Does theory influence the effectiveness of health behavior interventions? Meta-analysis. Health Psychol 2014 May;33(5):465-474.

60. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol 1983 Jun;51(3):390-395.

61. Schwarzer R. (2014, Oct 13). Health Action Process Approach. hapa2014 [Video]. YouTube. https://www.youtube.com/watch?v=aTJ-yUl2TdE

62. Schwarzer R. The Health Action Process Approach (HAPA). 2014; Available at: http://www.hapa-model.de/. Accessed 02/02, 2022.

63. Garcia S, Martinez-Cengotitabengoa M, Lopez-Zurbano S, Zorrilla I, Lopez P, Vieta E, et al. Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review. J Clin Psychopharmacol 2016 Aug;36(4):355-371.

64. Holmes EA, Hughes DA, Morrison VL. Predicting adherence to medications using health psychology theories: a systematic review of 20 years of empirical research. Value Health 2014 Dec;17(8):863-876.

65. Patton DE, Hughes CM, Cadogan CA, Ryan CA. Theory-Based Interventions to Improve Medication Adherence in Older Adults Prescribed Polypharmacy: A Systematic Review. Drugs Aging 2017 Feb;34(2):97-113.

66. Greer AE, Milner K, Marcello R, Mazin K. Health Action Process Approach: Application to Medication Adherence in Cardiac Rehabilitation (CR) Patients. Edu Gerontol 2015 Oct;41(10):685-694.

67. Asgari S, Abbasi M, Hamilton K, Chen Y, Griffiths MD, Lin C, et al. A theory-based intervention to promote medication adherence in patients with rheumatoid arthritis: A randomized controlled trial. Clin Rheumatol 2021 Jan;40(1):101-111.

68. Skinner EA. A guide to constructs of control. J Pers Soc Psychol 1996 Sep;71(3):549-570.

69. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care 2005 Feb;14(1):26-33.

70. Noar SM, Zimmerman RS. Health Behavior Theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? Health Educ Res 2005 Jun;20(3):275-290.

71. Fishbein M. The role of theory in HIV prevention. AIDS Care 2000 Jun;12(3):273-278.

72. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci 2012 Apr; 7:37-5908-7-37.

73. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci 2017 Jun;12(1):77-017-0605-9.

74. Rahman M, Judah G, Murphy D, Garfield SF. Which domains of the theoretical domains framework should be targeted in interventions to increase adherence to antihypertensives? A systematic review. J Hypertens 2022 May 1;40(5):853-859

75. Tesfaye WH, Erku D, Mekonnen A, Tefera YG, Castelino R, Sud K, et al. Medication non-adherence in chronic kidney disease: a mixed-methods review and synthesis using the theoretical domains framework and the behavioural change wheel. J Nephrol 2021 Aug;34(4):1091-1125.

76. Allemann SS, Nieuwlaat R, van den Bemt BJ, Hersberger KE, Arnet I. Matching Adherence Interventions to Patient Determinants Using the Theoretical Domains Framework. Front Pharmacol 2016 Nov; 7:429.

77. Michie S, Johnston M, Francis J, Hardeman W. From Theory to Intervention: Mapping Theoretically Derived Behavioural Determinants to Behaviour Change Techniques. Appl Psychol 2008 Jul; 57: 660-680.

78. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95.

79. Michie S, Wood CE, Johnston M, Abraham C, Francis JJ, Hardeman W. Behaviour change techniques: the development and evaluation of a taxonomic method for reporting and describing behaviour change interventions (a suite of five studies involving consensus methods, randomised controlled trials and analysis of qualitative data). Health Technol Assess 2015 Nov;19(99):1-188.

80. The UCL Centre for Behaviour Change. The Behaviour Change Taxonomy v1. 2019; Available at: https://www.bct-taxonomy.com/interventions. Accessed 11/11, 2019.

81. Cane J, Richardson M, Johnston M, Ladha R, Michie S. From lists of behaviour change techniques (BCTs) to structured hierarchies: comparison of two methods of developing a hierarchy of BCTs. Br J Health Psychol 2015 Feb;20(1):130-150.

82. Kahwati L, Viswanathan M, Golin CE, Kane H, Lewis M, Jacobs S. Identifying configurations of behavior change techniques in effective medication adherence interventions: a qualitative comparative analysis. Syst Rev 2016 May; 5:83-016-0255-z.

83. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014 Nov;(11):CD000011.

84. Hartung D, Low A, Jindai K, Mansoor D, Judge M, Mendelson A, et al. Interventions to Improve Pharmacological Adherence Among Adults With Psychotic Spectrum Disorders and Bipolar Disorder: A Systematic Review. Psychosomatics 2017 Mar - Apr;58(2):101-112.

85. Care Quality Commission (CQC). NHS Patient Survey Programme: 2018 community mental health survey. 2018:30.

86. Atreja A, Bellam N, Levy SR. Strategies to enhance patient adherence: making it simple. MedGenMed 2005 Mar;7(1):4.

87. Nguyen TM, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. Br J Clin Pharmacol 2014 Mar;77(3):427-445.

88. Hawkshead J, Krousel-Wood M. Techniques for Measuring Medication Adherence in Hypertensive Patients in Outpatient Settings. Dis Manage Health Outcomes 2007 Aug;15(2):109-118.

89. Gagne C, Godin G. Improving self-report measures of non-adherence to HIV medications. Psychol Health 2005 Dec;20(6):803-816.

90. LaFleur J, Oderda GM. Methods to measure patient compliance with medication regimens. J Pain Palliat Care Pharmacother 2004 Feb;18(3):81-87.

91. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999 Jun;21(6):1074-90.

92. Johnson SB. Methodological issues in diabetes research. Measuring adherence. Diabetes Care 1992 Nov;15(11):1658-1667.

93. George J, Kong DC, Stewart K. Adherence to disease management programs in patients with COPD. Int J Chron Obstruct Pulmon Dis 2007;2(3):253-262.

94. Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? Ann Allergy Asthma Immunol 1997 Sep;79(3):177-85; quiz 185-6.

95. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace 2015 Apr;17(4):514-523.

96. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. Health Psychol 2004 Mar;23(2):207-218.

97. Boateng GO, Neilands TB, Frongillo EA, Melgar-Quinonez HR, Young SL. Best Practices for Developing and Validating Scales for Health, Social, and Behavioral Research: A Primer. Front Public Health 2018 Jun; 6:149.

98. *Oxford English Dictionary Online*: Oxford University Press, 2017.

99. Devine F, Edwards T, Feldman SR. Barriers to treatment: describing them from a different perspective. Patient Prefer Adherence 2018 Jan; 12:129-133.

100. Kane JM, Petrides G, Perlis RH, DiCarlo LA, Au-Yeung K, Duong J. First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder. J Clin Psychiatry 2013 Jun;74(6).

101. Veritas Health Innovation Ltd. Covidence Systematic Review Software. Melbourne, Australia. 2018.

102. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol 2012 Nov; 12:181-2288-12-181.

103. QSR International Pty Ltd. Nvivo 12 for Windows. NVivo qualitative data analysis Software. 2018.

104. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan;350:g7647.

105. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

106. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep; 13:117-2288-13-117.

107. Katrak P, Bialocerkowski AE, Massy-Westropp N, Kumar S, Grimmer KA. A systematic review of the content of critical appraisal tools. BMC Med Res Methodol 2004 Sep; 4:22-2288-4-22.

108. Critical Appraisal Skills Programme (CASP). 10 Questions To Help You Make Sense of Qualitative Research. CASP Qual Checklist. 2018.

109. Center for Evidence Based Management 2014. Adapted from Crombie, The Pocket Guide to Critical Appraisal; the critical appraisal approach used by the Oxford Centre for Evidence Medicine, checklists of the Dutch Cochrane Centre, BMJ editor's checklists and the checklists of the EPPI Centre.

110. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct;343: d5928.

111. Frambach JM, van der Vleuten CP, Durning SJ. Quality criteria in qualitative and quantitative research. Acad Med 2013 Apr;88(4):552.

112. Vieta E, Azorin JM, Bauer M, Frangou S, Perugi G, Martinez G, et al. Psychiatrists' perceptions of potential reasons for non- and partial adherence to medication: results of a survey in bipolar disorder from eight European countries. J Affect Disord 2012 Dec;143(1-3):125-130.

113. Younas M, Bradley E, Holmes N, Sud D, Maidment ID. Mental health pharmacists views on shared decision-making for antipsychotics in serious mental illness. Int J Clin Pharm 2016 Oct;38(5):1191-1199.

114. Pope M, Scott J. Do clinicians understand why individuals stop taking lithium? J Affect Disord 2003 May;74(3):287-291.

115. Maczka G, Siwek M, Skalski M, Grabski B, Dudek D. Patients' and doctors' attitudes towards bipolar disorder - Do we share our beliefs? Arch Psychiatry Psychother 2010 May;12(2):43-50.

116. Greene M, Yan T, Chang E, Broder MS, Hartry A, Touya M. Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. J Med Econ 2018 Feb;21(2):127-134.

117. Gianfrancesco FD, Sajatovic M, Tafesse E, Wang RH. Association between antipsychotic combination therapy and treatment adherence among individuals with bipolar disorder. Ann Clin Psychiatry 2009 Jan;21(1):3-16.

118. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. Am J Psychiatry 2002 Nov;159(11):1927-1929.

119. Jonsdottir H, Opjordsmoen S, Birkenaes AB, Simonsen C, Engh JA, Ringen PA, et al. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr Scand 2013 Jan;127(1):23-33.

120. Ralat SI, Depp CA, Bernal G. Reasons for Nonadherence to Psychiatric Medication and Cardiovascular Risk Factors Treatment Among Latino Bipolar Disorder Patients Living in Puerto Rico: A Qualitative Study. Community Ment Health J 2018 Aug;54(6):707-716.

121. Manwani SG, Szilagyi KA, Griffin ML, Weiss RD, Hennen J, Zablotsky B Adherence to pharmacotherapy in bipolar disorder patients with and without co-occurring substance use disorders. J Clin Psychiatry 2007 Aug;68(8):1172-1176.

122. Bauer M, Glenn T, Alda M, Sagduyu K, Marsh W, Grof P, et al. Regularity in daily mood stabilizer dosage taken by patients with bipolar disorder. Pharmacopsychiatry 2013 Jul;46(5):163-168.

123. Nagesh HN, Kishore MS, Raveesh BN. Assessment of adherence to psychotropic medications in a psychiatric unit of district hospital. Natl J Physiol Pharm Pharmacol 2016 Jul;6(6):581-585.

124. Roe D, Goldblatt H, Baloush-Klienman V, Swarbrick M, Davidson L. Why and how people decide to stop taking prescribed psychiatric medication: exploring the subjective process of choice. Psychiatr Rehabil J 2009 Jul;33(1):38-46.

125. Stentzel U, van den BN, Schwaneberg T, Radicke F, Hoffmann W, Schulze LN, et al. Predictors of medication adherence among patients with severe psychiatric disorders: Findings from the baseline assessment of a randomized controlled trial (Tecla). BMC Psychiatry 2018 May;18(1).

126. Jose TT, Bhaduri A, Mathew B. A study of the factors associated with compliance or non-compliance to lithium therapy among the patients with bipolar affective disorder. Nurs J India 2003 Jan;94(1):9-11.

127. Hajda M, Kamaradova D, Latalova K, Prasko J, Ociskova M, Mainerova B, et al. Self-stigma, treatment adherence, and medication discontinuation in patients with bipolar disorders in remission - a cross sectional study. Activitas Nervosa Superior Rediviva 2015 Apr;57(1):6-11.

128. Arvilommi P, Suominen K, Mantere O, Valtonen H, Isometsa E, Leppamaki S. Predictors of adherence to psychopharmacological and psychosocial

treatment in bipolar i or II disorders - An 18-month prospective study. J Affect Disord 2014 Feb;155(1):110-117.

129. Grover S, Ghosh A, Sarkar S, Chakrabarti S, Avasthi A. Sexual dysfunction in clinically stable patients with bipolar disorder receiving lithium. J Clin Psychopharmacol 2014 Aug;34(4):475-482.

130. Agyapong VIO, Nwankwo V, Bangaru R, Kirrane R. Sources of patients' knowledge of the adverse effects of psychotropic medication and the perceived influence of adverse effects on compliance among service users attending community mental health services. J Clin Psychopharmacol 2009 Dec;29(6):565-570.

131. Averous P, Charbonnier E, Lagouanelle-Simeoni MC, Dany L, Prosperi A. Illness perceptions and adherence in bipolar disorder: An exploratory study. Compr Psychiatry 2018 Jan; 80:109-115.

132. Bates JA, Whitehead R, Bolge SC, Kim E. Correlates of medication adherence among patients with bipolar disorder: results of the bipolar evaluation of satisfaction and tolerability (BEST) study: a nationwide cross-sectional study. Prim Care Companion J Clin Psychiatry 2010 Oct;12(5).

133. Belzeaux R, Correard N, Azorin JM, Etain B, Loftus J, Bellivier F, et al. Depressive residual symptoms are associated with lower adherence to medication in bipolar patients without substance use disorder: Results from the FACE-BD cohort. J Affect Disord 2013 Dec;151(3):1009-1015.

134. Bener A, Dafeeah EE, Salem MO. A study of reasons of non-compliance of psychiatric treatment and patients' attitudes towards illness and treatment in Qatar. Issues Ment Health Nurs 2013 Apr;34(4):273-80.

135. Clatworthy J, Parham R, Horne R, Bowskill R, Rank T. Adherence to medication in bipolar disorder: A qualitative study exploring the role of patients' beliefs about the condition and its treatment. Bipolar Disord 2007 Sept;9(6):656-664.

136. Clatworthy J, Bowskill R, Parham R, Rank T, Scott J, Horne R, et al. Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. J Affect Disord 2009 Jul;116(1):51-55.

137. Col SE, Caykoylu A, Karakas UG, Ugurlu M. Factors affecting treatment compliance in patients with bipolar I disorder during prophylaxis: A study from Turkey. Gen Hosp Psychiatry 2014 Mar;36(2):208-213.

138. Copeland LA, Zeber JE, Salloum IM, Pincus HA, Fine MJ, Kilbourne AM. Treatment adherence and illness insight in veterans with bipolar disorder. J Nerv Ment Dis 2008 Jan;196(1):16-21.

139. Correard N, Consoloni JL, Azorin JM, Belzeaux R, Raust A, Etain B, et al. Neuropsychological functioning, age, and medication adherence in bipolar disorder. PLoS ONE 2017 Sep;12(9).

140. Darling CA, Olmstead SB, Lund VE, Fairclough JF. Bipolar disorder: medication adherence and life contentment. Arch Psychiatr Nurs 2008 Jun;22(3):113-126.

141. De Las CC, Penate W, Sanz EJ. Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. Eur J Clin Pharmacol 2014 Jan;70(1):89-98.

142. De Las CC, Penate W, Cabrera C. Perceived health control: A promising step forward in our understanding of treatment adherence in psychiatric care. J Clin Psychiatry 2016 Oct;77(10).

143. Deegan PE. The importance of personal medicine: A qualitative study of resilience in people with psychiatric disabilities. Scand J Public Health 2005 Oct; 33:29-35.

144. Greenhouse WJ, Meyer B, Johnson SL. Coping and medication adherence in bipolar disorder. J Affect Disord 2000 Sep;59(3):237-241.

145. Hibdye G, Bekan L, Dessalegne Y, Debero N, Sintayehu M. Prevalence of drug non adherence and associated factors among patients with bipolar disorder at outpatient unit of Amanuel Hospital, Addis Ababa, Ethiopia, 2013. Afr J Psychiatry (South Africa) 2015 Jan; 18:1-7.

146. Hou R, Cleak V, Peveler R. Do treatment and illness beliefs influence adherence to medication in patients with bipolar affective disorder? A preliminary cross-sectional study. Eur Psychiatry 2010 May;25(4):216-219.

147. Inder M, Lacey C, Crowe M. Participation in decision-making about medication: A qualitative analysis of medication adherence. Int J Ment Health Nurs 2019 Feb;28(1):181-189.

148. Kamaradova D, Latalova K, Prasko J, Kubinek R, Vrbova K, Mainerova B, et al. Connection between self-stigma, adherence to treatment, and discontinuation of medication. Patient Prefer Adherence 2016 Jul; 10:1289-1298.

149. Keck PE, McElroy SL, Strakowski SM, Balistreri TM, Kizer DI, West SA. Factors associated with maintenance antipsychotic treatment of patients with bipolar disorder. J Clin Psychiatry 1996 Apr;57(4):147-151.

150. Keck PE, McElroy SL, Strakowski SM, Bourne ML, West SA. Compliance with maintenance treatment in bipolar disorder. Psychopharmacol Bull 1997;33(1):87-91.

151. Kraemer S, Minarzyk A, Eppendorfer S, Henneges C, Hundemer HP, Wilhelm S, et al. Comparably high retention and low relapse rates in different subpopulations of bipolar patients in a German non-interventional study. BMC Psychiatry 2013 Jul;13:193.

152. Novick D, Montgomery W, Aguado J, Haro J, El-Shafei A, Katagari H, et al. Comparative clinical outcomes of orodispersable versus standard oral

olanzapine tablets in non-adherent patients with schizophrenia or bipolar disorder. Eur Neuropsychopharmacol 2015 Sept;25:S514-S515.

153. Perron BE, Zeber JE, Kilbourne AM, Bauer MS. A brief measure of perceived clinician support by patients with bipolar spectrum disorders. J Nerv Ment Dis 2009 Aug;197(8):574-579.

154. Rosa AR, Marco M, Fachel JM, Kapczinski F, Stein AT, Barros HM. Correlation between drug treatment adherence and lithium treatment attitudes and knowledge by bipolar patients. Prog Neuropsychopharmacol Biol Psychiatry 2007 Jan;31(1):217-224.

155. Rosenblat JD, Simon GE, Sachs GS, Deetz I, Doederlein A, DePeralta D, et al. Factors That Impact Treatment Decisions: Results From an Online Survey of Individuals With Bipolar and Unipolar Depression. Prim Care Companion CNS Disord 2018 Nov;20(6):10.4088/PCC.18m02340.

156. Sajatovic M, Bauer MS, Kilbourne AM, Vertrees JE, Williford W. Self-reported medication treatment adherence among veterans with bipolar disorder. Psychiatric services 2006 Jan;57(1):56-62.

157. Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, et al. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Compr Psychiatry 2009 Mar;50(2):100-107.

158. Sajatovic M, Levin J, Fuentes-Casiano E, Cassidy KA, Tatsuoka C, Jenkins JH. Illness experience and reasons for nonadherence among individuals with bipolar disorder who are poorly adherent with medication. Compr Psychiatry 2011 May;52(3):280-287.

159. Sharma S, Kumar N, Chakraborti S, Sinha S, Kumari S, Gajendragad JM. Prevalence and factors associated with medication compliance in Indian patients suffering from mental disorders. Trop Doct 2012 Jan;42(1):28-31.

160. Teter CJ, Falone AE, Weiss RD, Bakaian AM, Tu C, Ongur D. Medication adherence and attitudes in patients with bipolar disorder and current versus past substance use disorder. Psychiatry Res 2011 Dec;190(2):253-258.

161. Weiss RD, Greenfield SF, Najavits LM, Soto JA, Wyner D, Tohen M, et al. Medication compliance among patients with bipolar disorder and substance use disorder. J Clin Psychiatry 1998 May;59(4):172-4.

162. Zeber JE, Copeland LA, Good CB, Fine MJ, Bauer MS, Kilbourne AM. Therapeutic alliance perceptions and medication adherence in patients with bipolar disorder. J Affect Disord 2008 Apr;107(1-3):53-62.

163. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33(1):159-174.

164. Johnston M, Carey RN, Connell Bohlen L, Johnston DW, Rothman A, de Bruin M, et al. Linking behavior change techniques and mechanisms of action:

Triangulation of findings from literature synthesis and expert consensus. Ann Behav Med 2018 October.

165. MacDonald LA. Medication adherence in bipolar diosrder: Understanding patients' perspectives to inform intervention development. London: University College London; 2017.

166. Torres-Robles A, Wiecek E, Tonin FS, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. Comparison of Interventions to Improve Long-Term Medication Adherence Across Different Clinical Conditions: A Systematic Review With Network Meta-Analysis. Front Pharmacol 2018 Dec; 9:1454.

167. Salzmann-Erikson M, Sjodin M. A narrative meta-synthesis of how people with schizophrenia experience facilitators and barriers in using antipsychotic medication: Implications for healthcare professionals. Int J Nurs Stud 2018 Sep; 85:7-18.

168. Kikkert MJ, Schene AH, Koeter MW, Robson D, Born A, Helm H, et al. Medication adherence in schizophrenia: exploring patients', carers' and professionals' views. Schizophr Bull 2006 Oct;32(4):786-794.

169. Crayton E, Fahey M, Ashworth M, Besser SJ, Weinman J, Wright AJ. Psychological Determinants of Medication Adherence in Stroke Survivors: a Systematic Review of Observational Studies. Ann Behav Med 2017 Dec;51(6):833-845.

170. Priebe S, Bremner SA, Lauber C, Henderson C, Burns T. Financial incentives to improve adherence to antipsychotic maintenance medication in non-adherent patients: A cluster randomised controlled trial. Health Technol Assess 2016 Sept;20(70):121-121.

171. Herzberg PY, Glaesmer H, Hoyer J. Separating optimism and pessimism: a robust psychometric analysis of the revised Life Orientation Test (LOT-R). Psychol Assess 2006 Dec;18(4):433-438.

172. Millstein RA, Celano CM, Beale EE, Beach SR, Suarez L, Belcher AM, et al. The effects of optimism and gratitude on adherence, functioning and mental health following an acute coronary syndrome. Gen Hosp Psychiatry 2016 Nov - Dec; 43:17-22.

173. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res 2000 May;42(3):241-247.

174. Kitzinger J. Qualitative research. Introducing focus groups. BMJ 1995 Jul ;311(7000):299-302.

175. Deane FP, McAlpine E, Byrne MK, Davis EL, Mortimer C. Are carer attitudes toward medications related to self-reported medication adherence amongst people with mental illness? Psychiatry Res 2018 Feb; 260:158-163.

176. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One 2013 Dec;8(12): e80633.

177. Ritchie J, Lewis J. Qualitative Research Practice: A Guide for Social Science Students and Researchers. UK: Sage Publication; 2003.

178. Smith J. Qualitative Psychology: A Practical Guide to Research Methods. 3rd ed.: SAGE Publications; 2015.

179. Sofaer S. Qualitative research methods. Int J Qual Health Care 2002 Aug;14(4):329-336.

180. Guest G, Namey E, Taylor J, Eley N, McKenna K. Comparing focus groups and individual interviews: findings from a randomized study. Int J Soc Res Methodol 2017 Feb;20(6):693-708.

181. McEachan RR, Lawton RJ, Jackson C, Conner M, Meads DM, West RM. Testing a workplace physical activity intervention: a cluster randomized controlled trial. Int J Behav Nutr Phys Act 2011 Apr; 8:29-5868-8-29.

182. Lacey J, Cate H, Broadway DC. Barriers to adherence with glaucoma medications: a qualitative research study. Eye 2009 Apr;23(4):924-932.

183. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Health 2015 Sep;42(5):533-544.

184. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008 Jun;31(3):213-224.

185. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA 2002 Dec;288(22):2880-2883.

186. Morris NS, MacLean CD, Chew LD, Littenberg B. The Single Item Literacy Screener: evaluation of a brief instrument to identify limited reading ability. BMC Fam Pract 2006 Mar; 7:21-2296-7-21.

187. Carroll C, Booth A, Leaviss J, Rick J. "Best fit" framework synthesis: refining the method. BMC Med Res Methodol 2013 Mar; 13:37-2288-13-37.

188. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ 2000 Jan;320(7227):114-116.

189. Furber C. Framework analysis: a method for analysing qualitative data. Afr J Midwifery Womens Health 2013 Sept;4(2): 97-100.

190. Taibanguay N, Chaiamnuay S, Asavatanabodee P, Narongroeknawin P. Effect of patient education on medication adherence of patients with

rheumatoid arthritis: a randomized controlled trial. Patient Prefer Adherence 2019 Jan; 13:119-129.

191. Kessels RP. Patients' memory for medical information. J R Soc Med 2003 May;96(5):219-222.

192. Sarafis P, Tsounis A, Malliarou M, Lahana E. Disclosing the truth: a dilemma between instilling hope and respecting patient autonomy in everyday clinical practice. Glob J Health Sci 2013 Dec;6(2):128-137.

193. Choudhry NK, Krumme AA, Tong AY, Khan NF, Franklin JM, Ercole PM, et al. Effect of reminder devices on medication adherence: The REMIND randomized clinical trial. JAMA Intern Med 2017 May;177(5):624-631.

194. Santo K, Singleton A, Rogers K, Thiagalingam A, Chalmers J, Chow CK, et al. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial. Heart 2019 Feb;105(4):323.

195. Williams M, Jordan A, Scott J, Jones MD. Operating a patient medicines helpline: a survey study exploring current practice in England using the RE-AIM evaluation framework. BMC Health Serv Res 2018 Nov;18(1):868-018-3690-9.

196. Norfolk County Council. Population Norfolk : Census Population Estimates. 2022; Available at: https://www.norfolkinsight.org.uk/population/#/view-report/63aeddf1d7fc44b8b4dffcd868e84eac/___iaFirstFeature/G3. Accessed 07/22, 2022.

197. Peterson R. Constructing Effective Questionnaires: SAGE Publications; 2013.

198. GOV.UK. Sentence length: why 25 words is our limit. 2014; Available at: https://insidegovuk.blog.gov.uk/2014/08/04/sentence-length-why-25-words-is-our-limit/. Accessed 1/03, 2022.

199. SurveyMonkey. 3 ways to improve the visual design of your survey. Available at: https://www.surveymonkey.com/curiosity/3-ways-to-improve-visual-design-of-surveys/#:~:text=Typically%2C%20sans-serif%20fonts%20like,appealing%20and%20easy%20to%20read. Accessed 02/02, 2022.

200. Alchemer. Beginner's Guide to Fonts and Colors for Survey Design. 2021; Available at: https://www.alchemer.com/resources/blog/guide-fonts-colors-survey-design/. Accessed 03/03, 2022.

201. Blair J, Czaja R, Blair E. Designing Surveys - A guide to decisions and procedures. 2nd ed. USA: Sage; 2014.

202. Salkind N. Encyclopedia of Research Design. 1st ed.: SAGE Publications; 2010.

203. Willis G. Cognitive Interviewing: A “How To” Guide. Short course presented at the 1999 Meeting of the American Statistical Association. 1999.

204. Rattray J, Jones MC. Essential elements of questionnaire design and development. J Clin Nurs 2007 Feb;16(2):234-243.

205. Swain L. Basic Principles of Questionnaire Design. Survey Methodology 1985 Dec;11(2):161-170.

206. Wang L, Miller MJ, Schmitt MR, Wen FK. Assessing readability formula differences with written health information materials: Application, results, and recommendations. Res Social Adm Pharm 2013 September;9(5):503-516.

207. Paz SH, Liu H, Fongwa MN, Morales LS, Hays RD. Readability estimates for commonly used health-related quality of life surveys. Qual Life Res 2009 Sep;18(7):889-900.

208. Walsh TM, Volsko TA. Readability assessment of internet-based consumer health information. Respir Care 2008 Oct;53(10):1310-1315.

209. Cutts M. Oxford Guide to Plain English. Oxford: Oxford University Press; 2020.

210. Oliffe M, Thompson E, Johnston J, Freeman D, Bagga H, Wong PKK. Assessing the readability and patient comprehension of rheumatology medicine information sheets: a cross-sectional Health Literacy Study. BMJ Open 2019 Feb ;9(2): e024582-2018-024582.

211. Dima AL. Scale validation in applied health research: tutorial for a 6-step R-based psychometrics protocol. Health Psychol Behav Med 2018 May;6(1):136-161.

212. APA Dictionary of Psychology. Washington, DC: American Psychological Association. VandenBos, Gary R, APA Dictionary of Psychology. Washington, DC: American Psychological Association, 2015. 2022; Available at: https://dictionary.apa.org/ability-parameter. Accessed 01/03, 2022.

213. Price P, Jhangiani R, Chiang I. Chapter 5: Psychological Measurement. Research Methods in Psychology. 2nd ed. Canada: Pressbooks; 2013.

214. Cappelleri JC, Jason Lundy J, Hays RD. Overview of classical test theory and item response theory for the quantitative assessment of items in developing patient-reported outcomes measures. Clin Ther 2014 May;36(5):648-662.

215. Stochl J, Jones PB, Croudace TJ. Mokken scale analysis of mental health and well-being questionnaire item responses: a non-parametric IRT method in empirical research for applied health researchers. BMC Med Res Methodol 2012 Jun; 12:74-2288-12-74.

216. Baghaei P. Mokken Scale Analysis in Language Assessment. New York: Waxmann; 2021.

217. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ 2011 Jun; 2:53-55.

218. Crutzen R, Peters GY. Targeting Next Generations to Change the Common Practice of Underpowered Research. Frontiers in Psychology 2017 Jul;8:1184.

219. Revelle W, Zinbarg RE. Coefficients Alpha, Beta, Omega, and the glb: Comments on Sijtsma. Psychometrika 2008 Dec;74(1):145.

220. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. 2021; Available at: http://www.medicinescomplete.com. Accessed 09/09, 2021.

221. Tehseen S, Ramayah T, Sajilan S. Testing and Controlling for Common Method Variance: A Review of Available Methods. J Manag Sci 2017 Mar; 4:142-168.

222. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. Qual Life Res 2012 May;21(4):651-657.

223. Comrey AL, Lee HB. A First Course in Factor Analysis. Second ed. Oxford/ New York: Psychology Press; 2016.

224. Park MS, Kang KJ, Jang SJ, Lee JY, Chang SJ. Evaluating test-retest reliability in patient-reported outcome measures for older people: A systematic review. Int J Nurs Stud 2018 Mar;79:58-69.

225. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007 Jan;60(1):34-42.

226. Edwards PJ, Roberts I, Clarke MJ, Diguiseppi C, Wentz R, Kwan I, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev 2009 Jul;2009(3):MR000008.

227. Harrison S, Henderson J, Alderdice F, Quigley MA. Methods to increase response rates to a population-based maternity survey: a comparison of two pilot studies. BMC Medical Res Methodol 2019 Mar;19(1):65.

228. R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

229. Meijer RR, Sijtsma K, Smid NG. Theoretical and Empirical Comparison of the Mokken and the Rasch Approach to IRT. Appl Psychol Meas 1990 Sept;14(3):283-298.

230. Van der Ark, L. Andries. Mokken Scale Analysis in R. J Stat Soft 2007 Feb; 20(11):1.

231. Van Abswoude AAH, van der Ark LA, Sijtsma K. A comparative study of test data dimensionality assessment procedures under nonparametric IRT models. Appl Psychol Meas 2004 Jan;28(1):3-24.

232. Dirlik E. Investigating Invariant Item Ordering Using Mokken Scale Analysis for Dichotomously Scored Items. Int J Progress Educ 2020 Jun;16(3):84-96.

233. Sijtsma K. On the Use, the Misuse, and the Very Limited Usefulness of Cronbach's Alpha. Psychometrika 2008 Dec;74(1):107.

234. Horne R. The nature, determinants and effects of medication beliefs in chronic illness. London: University of London; 1997.

235. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol 2020 Jul;86(7):1281-1288.

236. Jonsdottir H, Opjordsmoen S, Engh JA, Friis S, Andreassen OA, Birkenaes AB, et al. Medication adherence in outpatients with severe mental disorders relation between self-reports and serum level. J Clin Psychopharmacol 2010 Apr;30(2):169-175.

237. Dharmendra MS, Eagles JM. Factors associated with patients' knowledge of and attitudes towards treatment with lithium. J Affect Disord 2003 June;75(1):29-33.

238. Hopkins HS, Gelenberg AJ. Serum lithium levels and the outcome of maintenance therapy of bipolar disorder. Bipolar Disord 2000 Sep;2(3 Pt 1):174-179.

239. Sproule B. Lithium in bipolar disorder: Can drug concentrations predict therapeutic effect? Clin Pharmacokinet 2002 Feb;41(9):639-660.

240. Broadbent E, Petrie KJ, Maina J, Weinman J. The Brief Illness Perception Questionnaire. J Psychosom Res 2006 Jun; 60:631 – 637.

241. Dima A, Lewith GT, Little P, Moss-Morris R, Foster NE, Hankins M, et al. Patients' treatment beliefs in low back pain: development and validation of a questionnaire in primary care. Pain 2015 Aug;156(8):1489-1500.

242. Cohen J. A power primer. Psychol Bull 1992 Jul;112(1):155-159.

243. Ratner B. The correlation coefficient: Its values range between +1/−1, or do they? J Target Meas Anal Mark 2009 Jun;17(2):139-142.

244. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016 Jun;15(2):155-163.

245. Matheson GJ. We need to talk about reliability: making better use of test-retest studies for study design and interpretation. PeerJ 2019 May;7:e6918.

246. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012 May;73(5):691-705.

247. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol 2013 Jul; 4:91.

248. Essential Pharma Ltd. Priadel 200 mg prolonged-release tablets SmPC. 2022 [Cited 02/02/2022]. Available from: https://www.medicines.org.uk/emc/product/13162/smpc#gref.

249. Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, et al. Comparison of Standard and Low Serum Levels of Lithium for Maintenance Treatment of Bipolar Disorder. N Engl J Med 1989 Nov;321(22):1489-1493.

250. Prescribing Observatory for Mental Health. 2019. Topic 7f. Monitoring of patients prescribed lithium. Prescribing Observatory for Mental Health, CCQI 306.

251. The King's Fund. Has the government put mental health on an equal footing with physical health? 2015; Available at: https://www.kingsfund.org.uk/projects/verdict/has-government-put-mental-health-equal-footing-physical-health. Accessed 02/02, 2022.

252. Department of Health, UK. Achieving parity of esteem between mental and physical health. 2013.

253. Chang JG, Roh D, Kim CH. Association between Therapeutic Alliance and Adherence in Outpatient Schizophrenia Patients. Clin Psychopharmacol Neurosci 2019 May;17(2):273-278.

254. Misdrahi D, Petit M, Blanc O, Bayle F, Llorca PM. The influence of therapeutic alliance and insight on medication adherence in schizophrenia. Nord J Psychiatry 2012 Feb;66(1):49-54.

255. NHS England. Medicines Optimisation. 2020; Available at: https://www.england.nhs.uk/medicines-2/medicines-optimisation/. Accessed 03/02, 2022.

256. Department of Health (UK). Liberating the NHS: No decision about me, without me. 2012.