Exploring longitudinal relationships between psychological flexibility and medication adherence, mood and general functioning in people with long-term health conditions

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

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Abstract

Introduction: Many people with long-term physical health conditions (LTCs) are non-adherent to prescribed medications and therefore have an increased risk of morbidity and mortality. Several psychological models have attempted to understand why people with LTCs do not adhere, but all have limited explanatory power and interventions stemming from them show modest effects. Few studies have explored the utility of the psychological flexibility model (PF), the transdiagnostic theory underlying Acceptance and Commitment Therapy (ACT), in this context. A small number of preliminary trials for ACT show promising efficacy but have been conducted in specific LTC groups with small samples. Ecological momentary assessment methods (EMA) may build on these studies because they could examine temporal relationships and account for within-individual variability across different contexts and are less prone to recall biases. However, few momentary PF measures have been validated in LTCs samples.

Method: The primary aim of this online longitudinal study (*n*=701) was to examine relationships between validated measures of PF and self-reported intentional and unintentional non-adherence and appointment attendance in people with LTCs at baseline and three months follow-up using binomial regressions. The second aim (not reported in the current thesis) was to preliminarily validate new momentary measures of PF, adherence and mood for future EMA studies to better understand within-individual and group-level variability.

Results: PF variables explained a significant, albeit modest, amount of the variance in intentional and unintentional non-adherence and appointment attendance. However, confirmatory factor, internal consistency and test-re-test analyses indicated MARS-5 items failed to meet established criteria for construct validity and demonstrated poor stability over time. This was supported by the instrument's poor convergence with new appointment attendance scales. PF shared medium to strong relationships with mood and general functioning in expected directions.

Discussion: This project has improved our understanding of the potential applicability of the PF model and ACT in understanding and treating intentional and unintentional non-adherence and appointment non-attendance. However, further clarification of the utility of PF in understanding treatment non-adherence is warranted using prospective or experimental designs in conjunction with more objective valid and reliable adherence measures.

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List of Abbreviations

Abbreviation	Meaning
AAQ-II	Acceptance and Action Questionnaire II
ACT	Acceptance and Commitment Therapy
AFQ-Y8	Avoidance and Fusion Questionnaire for Youth 8 items
BA	Behavioral Awareness subscale of the CompACT
BMQ	Beliefs about Medications Questionnaire
CAMM	Child and Adolescent Mindfulness Measure
CBT	Cognitive Behaviour Therapy
$CD4^+$	Cluster of Differentiation 4 lymphocyte counts
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
COM-B	Capability, opportunity and motivation model of behaviour
CompACT	Comprehensive assessment of Acceptance and Commitment Therapy processes
COPD	Chronic Obstructive Pulmonary Disease
CSM	Common-Sense or 'self-regulatory' Model of illness perceptions
DAI	Drug Attitude Inventory
DBT	Dialectical Behaviour Therapy
DBT-CMI	Dialectical Behaviour Therapy to improve medication adherence in adolescents with Chronic Medical Illness
EFA	Exploratory Factor Analysis
EMA	Ecological Momentary Assessment
eMEMS® caps	electronic Medication Event Monitoring System caps
FACT	Focused Acceptance and Commitment Therapy
FDA	US Food and Drug Administration
GAD-2	Generalised anxiety Disorder Scale 2 items
GAD-7	Generalised anxiety Disorder Scale 7 items
HADS	Hospital Anxiety and Depression Scale
HbA1c	Haemoglobin A1c
HCP	Health Care Professional
HIV	Human immune-deficiency virus
IAPT	Improving Access to Psychological Therapies
ICC	Intra-Class Correlation
ICD-11	WHO International Classification of Diseases, 11th Revision
IPQ-R	Illness Perceptions Questionnaire-Revised
IPQ-R	Illness Perception Questionnaire-Revised
LTC/s	Long-Term physical health Condition/s
MBCT	Mindfulness-based Cognitive Therapy
MBSR	Mindfulness-based Stress Reduction
MI	Motivational interviewing
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
MARS	Medication Adherence Rating Scale

MARS-5	Medication Adherence Rating Scale 5 items
MARS-9	Medication Adherence Rating Scale 9 items
MLR	Maximum Likelihood estimation with Robust standard errors estimator
NRS	Numerical Rating Scale
NS	Non-significant Parameters
OE	Openness to Experience subscale of the CompACT
PF	Psychological Flexibility Model
PHQ-2	Patient Health Questionnaire 2-items
PHQ-8	Patient Health Questionnaire 8-items
PHQ-8-A	Patient Health Questionnaire 8-items adolescent version
PHQ-9	Patient Health Questionnaire
QoL	Quality of Life
RCT	Randomised Controlled Trial
RMSEA	Root Mean Square Error of Approximation estimator
SF-36	Short-Form 36-items quality of life questionnaire
SoMREC	School of Medicine Research Ethics Committee
SRMR	Standardized Root Mean Square Residual
SPSS	Statistical Package for the Social Sciences
TPB	Theory of Planned Behaviour
TRA	Theory of Reasoned Action
TLI	Tucker Lewis Index
VA	Valued Action subscale of the CompACT
VAS	Visual Analogue Scale
WHO	World Health Organisation
WLSMV	Diagonally Weighted Least Squares estimator
WSAS	Work and Social Adjustment Scale
WSAS-A	Work and Social Adjustment Scale modified for Adolescents

Chapter 1: Providing a context: Understanding non-adherence to medication, its psychosocial impact and current evidence for psychological approaches: A review of the literature

This first chapter begins with a narrative literature review (search terms presented in Appendix A), introducing definitions of medication adherence, the extent of non-adherence and its impact in the context of LTCs, and how it is currently operationalised. This section will also include an overview of predominant psychological theories and associated interventions attempting to understand and treat medication non-adherence in people with LTCs. A newer organising framework, the psychological flexibility (PF) model, will also be introduced as a potentially helpful alternative approach. The need to develop novel ultra-brief measures for ecological momentary assessment (EMA) methods to more accurately capture temporal patterns of medication non-adherence in individuals with LTCs will also be discussed. Finally, the chapter will conclude with a context and rationale for the programme of empirical research undertaken in this thesis.

1.1. Adherence in long-term health conditions

Adherence has been defined as "the extent to which the patient's action – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" (World Health Organisation (WHO), 2003, p.3). Conversely, "non-adherence" has either been broadly defined as "an absence in the actions required by the person receiving treatment" (Harrison, Graham, & McCracken, 2017, p.8), or more specifically, "where doses are missed, extra doses are taken, or doses are taken in the wrong quantity or at the wrong time'' (Verbrugghe, Verhaeghe, Lauwaert, Beeckman, & Van Hecke, 2013, p.610). Historically, the terms "adherence" and "compliance" have been used interchangeably within the research literature (Horne et al., 2005).

However, it has been argued that adherence implies individuals are free to choose whether to execute a treatment behaviour, whilst compliance assumes a person passively follows a treatment plan (Osterberg & Blaschke, 2005). The term "concordance" also refers to the process within health consultations where the patient's perceptions/beliefs and preferences are elicited and taken into account by the clinician rather than ignored (Horne et al., 2005), and an "exchange of information, negotiation, and a spirit of cooperation" where setting collaborative treatment goals forms the key focus (Mullen, 1997, p.691). Consistent with concordance and the role of one's motivation and freedom to choose inherent in most psychological approaches (Brawley & Culos-Reed, 2000; Munro, Lewin, Swart, & Volmink, 2007), the term "adherence" will be used throughout the remaining thesis.

Several reviews show rates of non-adherence to prescribed treatments for people with a variety of LTCs range from 25% to 50%, depending on the method of measurement used and type and frequency of treatments recommended (Coleman et al., 2012; DiMatteo, 2004b; DiMatteo, Giordani, Lepper, & Croghan, 2002; Haynes, 2001; Osterberg & Blaschke, 2005). Two of these reviews conducted meta-analyses, which estimate non-adherence rates are around 25% (DiMatteo, 2004b; DiMatteo et al., 2002). Overall, these findings appear consistent with reviews for specific LTCs (e.g., Albert, 2008; Bosworth et al., 2011; Broekmans, Dobbels, Milisen, Morlion, & Vanderschueren, 2009; Harrold & Andrade, 2009; Ho, Bryson, & Rumsfeld, 2009; Restrepo et al., 2008; Wu, Moser, Lennie, & Burkhart, 2008), but evidence indicates rates of non-adherence are generally higher in children and adolescents, ranging from 50% to 88% (McGrady & Hommel, 2013).

A review of several systematic reviews indicates that over seven-hundred potential factors have been studied in conjunction with treatment non-adherence (Kardas, Lewek, & Matyjaszczyk, 2013). Factors broadly range from patient characteristics, type of condition or treatment, psychological and other contextual or socio-economic variables, such as family environment, cost of treatment and low-social economic status, to the type of health system (WHO, 2003). The bewildering array of potentially

important factors highlights the complex and multifaceted nature of non-adherence. This poses the challenge of considering where one might begin in terms of targeting factors for intervention and understanding which may be most amenable to change (Harrison, Graham, & McCracken, 2017).

While some frameworks suggest non-adherence is a 'diagnosable medical condition' (e.g., Marcum, Sevick, & Handler, 2013), pragmatic attempts to distil psychological explanations of non-adherence have resulted in the development of two broader sub-categories. These include "intentional non-adherence", defined as an informed and conscious choice to not take medications as prescribed, and "unintentional non-adherence", arising from unconscious omissions or forgetting (Lehane & McCarthy, 2007). Evidence shows that some patients exhibit non-adherence at the beginning of treatment (Vrijens, Vincze, Kristanto, Urquhart, & Burnier, 2008). Others indicate 25% of people become non-adherent a short time after starting a new treatment (Barber, Parsons, Clifford, Darracott, & Horne, 2004), and of these 45% report their non-adherence was intentional and 55% unintentional. A recent review also suggests unintentional non-adherence in particular tends to worsen with age (Hughes, 2004). However, a more recent correlational study shows that unintentional non-adherence is associated with medication beliefs, alongside socio-demographics and type of illness, suggesting it may be more difficult to disentangle intentional from unintentional non-adherence (Gadkari & McHorney, 2012). For instance, self-reported "forgetting" could either reflect a socially desirable response, or person's reduced ability to engage in informed decision-making because of changes in mood, rather than simply just forgetting.

1.2 The impact of non-adherence in long-term health conditions

Advances in medical treatments have steadily improved the life expectancy of people with several LTCs over the last three to five decades (e.g. cystic fibrosis: McCormick, Green, Mehta, Culross, & Mehta, 2002; human immune-deficiency virus (HIV): Kelly, Otto-Salaj, Sikkema, Pinkerton, & Bloom,

1998; multiple sclerosis: Comi, 2013). However, poor adherence continues to pose an important challenge for clinicians and health care providers, because it affects treatment efficacy (e.g., Cramer, 1998; Stephenson, 1999), attenuates optimum clinical benefit (Dunbar-Jacob & Mortimer-Stephens, 2001), and undermines treatment evaluation (Unni, Shiyanbola, & Farris, 2013). Adherence has therefore been described as a "critical mediator between physician recommendations and patient outcomes" (Kravitz et al., 1993, p.1869), and the WHO have argued that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments." (WHO, 2003, p.21)

The burden of treatment regimens for people with LTCs and their families should not be underestimated. Some treatments need to be performed several times a day, are often complex, time-consuming (e.g., Quittner, Opipari, Regoli, Jacobsen, & Eigen, 1992), have unpleasant side-effects (e.g., Kidder, Wolitski, Campsmith, & Nakamura, 2007; Verbrugghe et al., 2013) and can be associated with a reduction in a person's quality of life (QoL) (e.g., Hodari, Nanton, Carroll, Feldman, & Balkrishnan, 2006; Mills et al., 2006). Furthermore, one meta-analytic review showed that adherence to treatment regimens that involve significant side-effects is also associated with increased mortality (Simpson et al., 2006). However, people with LTCs who regularly miss or change doses of potentially beneficial medications are more likely to experience delayed recovery (e.g., Grijalva et al., 2007), treatment complications (Hughes, Bagust, Haycox, & Walley, 2001), depression (DiMatteo, Lepper, & Croghan, 2000; Gonzalez, Batchelder, Psaros, & Safren, 2011), reduced QoL (Zwikker, van den Bemt, Vriezekolk, van den Ende, & van Dulmen, 2014), and increased risk of morbidity and mortality (DiMatteo et al., 2002; Simpson et al., 2006). A potential weakness of this body of evidence is that the causal direction of these relationships is not always clear and the reverse may also be true.

Non-adherence has been argued to be a significant public health issue (Lam & Fresco, 2015). However, evidence for the socio-economic consequences of non-adherence in LTCs has historically

been described as “poor, disparate, variable and non-existent in many therapeutic areas and patient groups” (Horne et al., 2005, p.89). The negative consequences of non-adherence are likely to be significant, since unused medicines, worsening disease activity or progression, unnecessary escalation of treatment due to ‘ineffectiveness’, and increasing need for general practitioner appointments and hospital admissions (e.g., McDonnell & Jacobs, 2002; Miura et al., 2001), are likely to result in greater health service costs (DiMatteo, 1994; Higgins, Rubin, Kaulback, Schoenfield, & Kane, 2009; Hughes, Bagust, Haycox, & Walley, 2001).

Few large-scale economic analyses of non-adherence across LTCs have been conducted (e.g., Senst et al., 2001), and adherence is not routinely included in pharmacoeconomic analyses (Hughes, Cowell, Koncz, & Cramer, 2007), presumably because combining different adherence and costing data for variable treatments is unfeasible and loses important distinctions between LTCs. However, the economic burden arising from the waste of non-adherence to medication is believed to range from $100 to $300 billion per year (DiMatteo, 2004b; Osterberg & Blaschke, 2005). Some economic studies for specific LTCs and treatments report that non-adherence is associated with higher costs and poorer clinical outcomes (e.g., rheumatoid arthritis: Hughes, 2012, unpublished; oral bisphosphonates for people with osteoporosis: Hiligsmann, Rabenda, Bruyère, & Reginster, 2010), whilst others show non-adherence has negligible consequences in terms of cost-effectiveness (e.g., immunosuppressive therapy after renal transplant: Cleemput, Kesteloot, Vanrenterghem, & De Geest, 2004) or show mixed findings (e.g., diabetes:(Asche, LaFleur, & Conner, 2011). Overall, evidence indicates supporting people with LTCs to achieve optimal adherence is likely to prevent morbidity, delay progression, improve survival and reduce costs. However, an important challenge in this growing economic literature is the variable operational definitions used to measure non-adherence (Cleemput, Kesteloot, & DeGeest, 2002).

1.3 Current challenges with operationalising medication non-adherence

There is currently no 'gold standard' for measuring medication adherence in LTCs. Over the last 50 years, non-adherence has been measured in a variety of ways, but each method has important limitations affecting its precision and accuracy. Examining concentrations of medications or their metabolite, usually in the blood or urine, has traditionally been viewed as a potentially useful biochemical marker of adherence (Osterberg & Blaschke, 2005). However, this method is usually costly and may not be possible for all medications. In addition, such measures can be influenced by diet, absorption and excretion rate, and use of other medications (Vitolins, Rand, Rapp, Ribisl, & Sevick, 2000). Furthermore, taking numerous blood and/or urine samples over time may be too invasive or impractical for the purposes of research or routine clinical practice (e.g. recording daily measures).

Other less invasive measures include pill counts (i.e. number of pills remaining after a given time period compared to the recommended dose), prescription refill records, and medication vial caps (electronic Medication Event Monitoring System or eMEMS® caps), which electronically record time-stamped data of bottle opening (Farmer, 1999). However, these methods can also be expensive and time-consuming, and whilst appearing objective have other important weaknesses. First, they assume all counted pills have been taken and omit key information about correct dosing or timing, making them less compatible with polypharmacy, which is more common in older people with LTCs (Elliott, Ross-Degnan, Adams, Safran, & Soumerai, 2007; Marcum & Gellad, 2012; Payne, Abel, Avery, Mercer, & Roland, 2014). Second, there is no way of knowing whether people have discarded pills, referred to as "dose dumping", or consumed them prior to health visits to appear more 'compliant' because they are aware they are being monitored (Osterberg & Blaschke, 2005). Finally, not all prescribed medications for LTCs comprise oral agents (e.g., insulin injections in diabetes), and therefore capturing non-adherence using different forms of drug administration or polypharmacy becomes increasingly challenging.

The most common method of assessing medication adherence includes self-report questionnaires to assess a person's intentions, attitudes or beliefs, behaviours and barriers (Nguyen, Caze, & Cottrell, 2014). Compared to other methods, self-report measures are inexpensive, quick and easy to administer with opportunities for real-time clinician-patient feedback and can be used across LTCs (Lam & Fresco, 2015). Carefully constructed scales can explore how and why a person is non-adherent and disentangle potentially different underlying causes (e.g., Horne & Weinman, 2002), which can inform the development of interventions that specifically target these. Several reviews show moderate levels of concordance between self-report instruments and other more objective measures of adherence, but it is unclear whether the latter are measuring adherence accurately (Choo et al., 1999; Garber, Nau, Erickson, Aikens, & Lawrence, 2004; Nguyen et al., 2014; Shi, Liu, Fonseca, et al., 2010; Shi, Liu, Koleva, et al., 2010). Therefore, using multiple measures to assess non-adherence is regarded as an optimal approach, if deemed useful and feasible (WHO, 2003). Self-report instruments too have important drawbacks. First, many adherence measures have been developed to date, but most have only been validated in a few LTC samples, varying in their focus of questioning and/or phrasing, showing inconsistent estimates of reliability, sensitivity and specificity (Lam & Fresco, 2015; Stirratt et al., 2015). Health provider and patient self-reports typically overestimate adherence because people tend to either engage in socially desirable responding (Horne, 2006), or experience problems with retrospective memory bias when asked to rate their level of adherence over a given timeframe (Nguyen et al., 2014).

In more recent years the LTC literature has seen the emergence of new technologies to measure adherence. For example, studies in cystic fibrosis now utilise nebuliser microchips, which measure dosing, frequency and quality of momentary nebuliser use for inhaled anti-biotics and mucolytics (Latchford, Duff, Quinn, Conway, & Conner, 2009). These methods currently form part of routine clinical practice, providing a potentially more objective and accurate estimate of adherence. Whilst these advances provide an exciting opportunity to measure adherence more objectively in conjunction

with other measures, Latchford et al.'s (2009) study has also demonstrated that calculating adherence using various indices of nebuliser data alone can result in remarkably different findings. In addition, there is no established cut-off for "poor" adherence in this context. Studies like these highlight the perennial issue of how adherence researchers might interpret these more accurate and objective indices of adherence and determine which holds the greatest utility in terms of measuring this complex construct.

Another challenge with measurement is that most adherence studies report an average percentage of adherence or non-adherence within a given sample (see DiMatteo, 2004b; DiMatteo et al., 2002). However, group-level data and subsequent meta-analyses overlook potentially important individual differences, known as aggregation bias (Johnston & Johnston, 2013). For example, though estimates show 25% of *samples of people* with LTCs are "non-adherent" to medication, it is unclear whether *every individual* took 75% of their doses. Established clinical cut-offs or bandings of "non-adherence" and "adherence" (e.g. 80%, see Lam & Fresco, 2015) also have similar difficulties, and rather than being based on empirical evidence, cut-offs typically rely on arbitrary thresholds proposed by expert clinicians (WHO, 2003).

In addition, it has been argued that developing a universal level of "adherence" or "non-adherence" either within or across LTCs is challenging for several reasons (Hughes, 2012, unpublished). First, some LTCs can be progressive and/or fluctuate over time (e.g. multiple sclerosis, rheumatoid arthritis), so treatment need and response may vary considerably between individuals. Second, solely establishing a level of adherence for a given drug via efficacy trials is also problematic, since adherence rates of self-selecting participants may be higher than those recorded in routine clinical practice. Lastly, there is little evidence to indicate whether sporadic episodes of non-adherence, e.g. taking breaks from medications with adverse side-effects, known as "drug holidays" (Hughes, 2004), have a negative impact in the short- or long-term, which will likely vary across LTCs and treatments. For these reasons, establishing

levels of non-adherence for each LTC over the short- and long-term is one proposed strategy (Elliott, 2008). However, one way to circumvent problems with group-level efficacy data and clinical heterogeneity in people with LTCs is to use idiosyncratic methods that include multiple measures of adherence. Such measures would be relatively easy to use and routinely administer in clinical practice (e.g. measuring momentary nebuliser use and ultra-brief self-report scales on an iPhone app) and could explore patterns and potential psychological determinants *within* and *between* individuals over time and across different contexts (see section 1.7 Need for validated momentary assessments). For this reason, self-report questionnaires will be used to measure adherence in the current thesis project.

1.4 Existing psychological models to understand treatment non-adherence

Given the large number of psychosocial factors evaluated to date (Kardas et al., 2013), and the high proportion of these with poor links to any coherent unifying conceptual models or set of guiding principles, the following section reviews the empirical support for existing theories applied to understand and treat non-adherence in people with LTCs.

Since the 1960s "social cognitive" models have attempted to understand the role of planning and rational decision-making processes contributing to behaviour (including treatment non-adherence) resulting in the development of psychological interventions to improve self-management (Brawley & Culos-Reed, 2000; Munro et al., 2007). A unifying assumption of social cognitive models is that a person's adherence to medical advice depends on their expectations surrounding the costs and benefits of executing a given behaviour (Edwards, 1954). Social cognitive models therefore centre on a person's motivation and intentions. Later models also include a person's perceived ability to perform a treatment behaviour or self-efficacy, building on Albert Bandura's (1977) earlier theory. As such, these theories have been better placed to understand intentional rather than unintentional non-adherence. Several other

well-researched models of health behaviour have been applied to adherence more generally, but to date have not been studied as extensively in this area specifically[1].

The following section will first evaluate the evidence for the most prominent social cognitive theories, including the theory of planned behaviour, common-sense model of illness perceptions, and the necessity concerns framework. This will be followed by an outline of a more recent composite health behaviour change model that aims to provide a unifying framework to accommodate all other models, the capability, opportunity and motivation model of behaviour (COM-B) (Michie, van Stralen, & West, 2011), motivational interviewing and third-wave approaches. The efficacy of treatments derived from these theories will also briefly be discussed.

1.4.1 Theory of planned behaviour

The theory of planned behaviour (TPB) (Ajzen, 1988; 2011) (Figure 1) extended Martin Fishbein and Icek Ajzen's earlier work on the theory of reasoned action (TRA) (Fishbein & Ajzen, 1975) by incorporating four cognitive processes that are argued to influence a person's (e.g. adherence) behaviour. The TPB works in a linear fashion, where the most proximal process and strongest predictor of behaviour (Ajzen, 1991) is one's "intention" or motivation to undertake a behaviour. The theory

[1]Other less prominent theories applied to adherence include: behavioural learning perspective (see van Dulmen et al., 2007), health belief model (Rosenstock, 1966) protection motivation theory (R. W. Rogers, 1975), self-efficacy theory (Bandura, 1977), theory of reasoned action (Fishbein & Ajzen, 1975), transtheoretical stages-of-change model (DiClemente & Prochaska, 1983), traditional cognitive-behavioural model (Meichenbaum & Turk, 1987), cognitive analytic approaches (Fosbury, Bosley, Ryle, Sönksen, & Judd, 1997; Walsh, Hagan, & Gamsu, 2000), information-motivation-behavioural skills model (Fisher, Fisher, Amico, & Harman, 2006) and accident causation framework (Garfield, Clifford, Eliasson, Barber, & Willson, 2011).

suggests that if one's intention is stronger, a behaviour is more likely to occur. Two other processes drawn from the TRA are assumed to influence behaviour indirectly via intentions: including (i) a person's "attitudes", beliefs or expectancies surrounding the behaviour, and its value in terms of perceived consequences; and (ii) 'subjective norm', reflecting the perceived social value of performing a given behaviour, including societal pressure, and the extent to which an individual conforms with these views. Finally, drawing on self-efficacy theory, 'perceived behavioural control' is the belief that the person has the necessary skills and resources required to successfully perform the behaviour, based on their previous personal experience or other social influences (e.g., the media). Perceived behavioural control has been shown to influence behaviour more directly compared to attitudes or social norms (Ajzen, 2007). This would suggest that even if a person's intentions are strong, the likelihood of successfully performing an adherence behaviour will also depend on whether they perceive themselves as sufficiently competent to take their medications correctly.

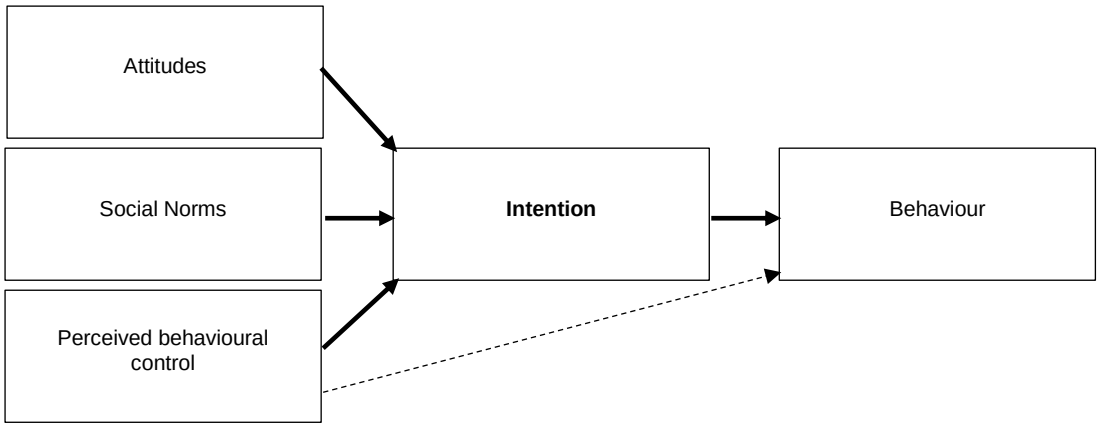

Figure 1: Theory of Planned Behaviour (Ajzen, 1991)

A recent meta-analytic review of twenty-seven studies has examined the magnitude of relationships between TPB constructs and adherence outcomes for a range of treatments (medication, diet and exercise) across a variety of LTCs (e.g. epilepsy, HIV, and chronic obstructive pulmonary disease/COPD) (Rich, Brandes, Mullan, & Hagger, 2015). Consistent with reviews exploring other preventative health behaviours (Abraham, Sheeran, & Johnston, 1998; Albarracin, Johnson, Fishbein,

& Muellerleile, 2001; Armitage & Conner, 2001; DiMatteo, 2004b), findings show collectively attitudes, subjective norm and perceived behavioural control constructs accounted for 33% of the variance in intention, and 9% for adherence behaviour (r=.30). The finding that the TPB is superior in predicting intentions compared to behaviour is also consistent with previous reviews showing that intentions have a modest direct relationship with health behaviours (Sheeran, 2002; Webb & Sheeran, 2006). Overall, these findings suggest the TPB has limited explanatory power to inform the development of interventions to improve adherence and it cannot sufficiently explain why people fail to act in accordance with their intentions, known as the "intention - behaviour gap" (Rich et al., 2015).

Furthermore, the TPB is less likely to be accurate when predicting behaviours requiring certain skills, knowledge or resources that an individual may not have access to (e.g. how to administer certain medications or having appropriate transport to attend clinic appointments for treatment). In addition, it could be argued that several other potentially important factors do not feature in the TPB, including emotional and socio-contextual variables, such as social support (DiMatteo, 2004a) or access to treatment (Mills et al., 2006). This might explain why empirical support for the model is limited, having largely been applied to healthy populations (e.g. dietary patterns) (McDermott et al., 2015).

1.4.2 The common-sense model of illness perceptions

The common-sense or 'self-regulatory' model of illness perceptions (CSM) proposed by Howard Leventhal and colleagues in the 1980s (Leventhal, Meyer, & Nerenz, 1980) suggests people are active problem-solvers, who are motivated to make sense of and manage potential health threats associated with the prevention, adaption and maintenance of behaviours relating to their illness (Leventhal, Nerenz, & Steele, 1984). The CSM posits there are two partly interacting parallel processes, which become activated in response to internal or external cues about symptoms and health threats (see Figure 2).

The first pathway is responsible for the development of a multi-dimensional framework of cognitions, called an 'illness representation' or schema, arising from this evaluative process, which are argued to directly influence coping strategies, including adherence behaviour. An illness representation incorporates five domains, including a person's beliefs related to their overall understanding of their condition ("illness coherence"), symptoms attributed to illness ("identity"), duration ("timeline"), potential "causes", "consequences" on physical, psychological and social functioning, and whether treatment or one's own behaviour can "cure or control" the illness/symptoms. Illness representations are argued to continuously update as the person acquires new illness or health threat information, and the effectiveness of their coping behaviours are appraised for their efficacy. Based on this assessment, the person may persist with a particular coping behaviour or try alternatives.

The second system is an emotional representation pathway, which is triggered by illness representations or external and internal cues (e.g. bodily sensations). Activation of this pathway can also result in the person using potentially successful or unsuccessful coping strategies aiming to attenuate or control negative emotions (e.g. suppression or expression of feelings or avoidance). Combining new and old information and direct experience of a health condition via these two pathways is argued to potentially result in erroneous beliefs about illness and unhelpful strategies for coping with associated emotions, which could lead to non-adherence.

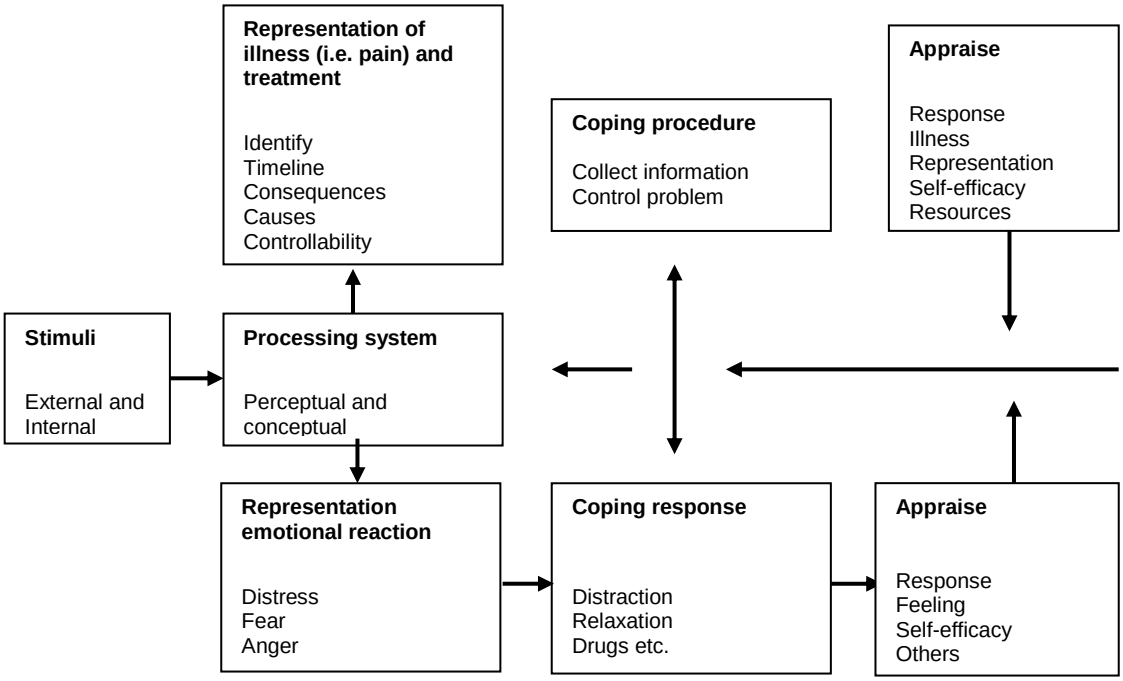

Figure 2: Common Sense Model of Illness Perceptions (Leventhal, Brissette, & Leventhal, 2003)

A relatively recent meta-analysis of twenty-three studies explored predictive relationships between CSM constructs and adherence to medication, diet and exercise recommendations (Brandes & Mullan, 2014). Findings showed that overall illness representations only accounted for a small amount of the variance in adherence outcomes (r=.02 to 0.12), collectively reflecting a relatively weak predictor of adherence compared to constructs from the TPB. It has been argued that the inconsistent findings across studies examining illness perceptions and adherence in LTCs may partly reflect the different aetiology and treatment of conditions (e.g. being born with an illness, rather than developing one in later life) could result in the development of different illness representations (Hughes, 2012). However, others have argued that the narrow focus on a person's disease self-management in the CSM ignores beliefs about medications or treatments themselves, the wider socio-economic context and other potentially important personal motivations, such as a person's broader life values or goals (Graham, Gouick, Krahé, & Gillanders, 2016;. Harrison, Graham, & McCracken, 2017)

1.4.3 Necessity concerns framework

An evolution in thinking about medication adherence in the late 1990s (Horne & Weinman, 1999) resulted in an extension of the health belief model (Rosenstock, 1966) and the notion that proximal beliefs about medications might be more potent predictors of adherence behaviour (Horne, Cooper, Gellaitry, Date, & Fisher, 2007). The necessity-concerns framework is underpinned by the same value-expectancy principle as its predecessor, but instead argues that individuals will weigh-up perceived costs and benefits of treatment, resulting in an intentional decision to adhere or non-adhere to treatment recommendations. Constructs within the model were derived from the development of The Beliefs about Medications Questionnaire (BMQ) (Horne, Weinman, & Hankins, 1999), which explored the role of specific and general beliefs about medications and how they influence adherence behaviour. All scale items were based on the existing literature and interviews with patients. Results identified two categories of medication beliefs, including "general" and "specific", which each comprise two further sub-categories: "general-overuse" (i.e. the patient's perception that doctors over-prescribe medications) and "general-harm" (i.e. that medications are addictive, harmful, or poisonous and should not be continuously taken), but also "specific-necessity" (that medications are necessary and have benefit) and "specific-concern" (i.e. that medications come with actual or potential adverse consequences, including risk of long-term toxicity, dependence and disruption to one's life).

A recent meta-analytic review including ninety-four studies found that necessity (OR=1.74) and concern beliefs (OR=.50) only explain a modest relationship with adherence outcomes, and were similar after stratifying by LTC type, type of adherence measure, country, study design and sample size (Horne et al., 2013). As with other social cognitive models, an important weakness of the necessity concerns framework is the limited scope of the model, since it fails to consider the wider socio-economic context and patient factors, such as emotions and how (along with beliefs) people relate to them. In addition,

social cognitive models in general do not provide explanation of why unintentional non-adherence might occur and/or whether specific beliefs apply to specific medications/regimens.

1.4.4 Interventions stemming from social cognitive models

The wider adherence literature is now replete with trials evaluating interventions for people with LTCs and clinician/providers (see Conn, Ruppar, Enriquez, Cooper, & Chan, 2015) to improve adherence and other patient-centred outcomes, ranging from drug education, behavioural reminders (e.g. calendars/pill boxes) to cognitive-behavioural therapy and motivational interviewing (see reviews (Conn, Ruppar, & Cooper, 2016; Conn, Ruppar, Enriquez, & Cooper, 2016; Dean, Walters, & Hall, 2010; Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; Kripalani, Yao, & Haynes, 2007; McDonald, Garg, & Haynes, 2003; Nieuwlaat et al., 2014; Williams, Manias, & Walker, 2008). However, most of these treatments have either been ineffective or show only modest improvements in adherence. In addition, most are based on an unsatisfactory integration of the previous models or not based on any model at all, and those that were on models that are perhaps too narrow. However, whilst cognitive-behavioural interventions stemming from social cognitive models are more effective than techniques used in current practice, they show small effect sizes overall (Hedges g=0.34) (Easthall, Song, & Bhattacharya, 2013). This finding might reflect the narrow focus and limited explanatory power of social cognitive models in understanding non-adherence. In addition, cognitive-behavioural interventions range from low- to high-intensity, where some are more resource-intensive than others. However, other than treatment setting (i.e. hospital being more effective than community), there is no clear differential pattern of effectiveness according to therapist experience or delivery methods used.

1.4.5 Motivational interviewing interventions

Motivational interviewing (MI), initially developed to treat addictions (Miller, 1983) and now a well-researched intervention for broad range of behavioural problems and diseases (Rubak, Sandbæk, Lauritzen, & Christensen, 2005), is a commonly adopted treatment for non-adherence (Bisonó, Manuel, Forcehimes, OÕDonohue, & Levensky, 2006). Though distinct from social-cognitive models, which also addresses similar volitional processes. MI has four key principles: (i) drawing on earlier Rogerian principles (Rogers, 1957), the therapist is encouraged to actively listen to the person and understand their perspective (expressing empathy); (ii) reflect the person's ambivalence about change, encourage them to provide reasons for change and make explicit the gap between their personal goals and current (i.e. adherence) behaviour (developing discrepancy); (iii) rather than opposing a person's resistance to change the focus is on reflecting this resistance (rolling with resistance); (iv) promoting the person's confidence in the idea that change is possible and conveying that any attempts to change will be meet with support from the therapist (supporting self-efficacy). Currently only a few trials have been reported, which show mixed success in enhancing adherence in only HIV and diabetes (Bisonó et al., 2006), and therefore no robust meta-analysis of RCTs has been conducted to estimate efficacy and magnitude of improvement in adherence behaviours. However, current meta-analytic reviews of MI incorporating trials with adherence outcomes demonstrate modest effects overall, which persist over time (Lundahl & Burke, 2009; Lundahl et al., 2013).

1.4.6 The Capability, Opportunity and Motivation Model of Behaviour (COM-B)

Another recent theoretical development is the Capability, Opportunity and Motivation Model of Behaviour (COM-B) (Michie et al., 2011), which has emerged as a health behaviour change framework aiming to subsume all constructs from earlier models and address important gaps. The COM-B was not

specifically designed to understand and treat non-adherence, but rather takes its root in an extensive consultation process, which initially involved recruiting expert clinicians and researchers to a Delphi study to develop a "behaviour change technique taxonomy" comprising 93 techniques to improve reporting of health behaviour change interventions (Michie et al., 2013). For instance, it has been argued the COM-B may provide an account for both intentional and unintentional non-adherence (Jackson, Eliasson, Barber, & Weinman, 2014). The COM-B attempts to distil a range of factors that might influence an individual's health behaviour, including non-adherence. These include (i) a person's physical and psychological capacity to engage in (i.e. adherence) behaviour ("capacity") – e.g. beliefs about illness, (ii) social or physical contextual factors that might prompt or enable their behaviour ("opportunity") – e.g. treatment cost, and (iii) a person's reflective (e.g. cognitive or evaluative) and automatic (e.g. impulses or affect) volitional processes underlying ("motivation") – e.g. neurocognitive functioning. A key strength of the framework is that it could encourage clinicians to consider a range of potentially amenable factors that might influence adherence behaviour.

The COM-B has several weaknesses. First, the broad range of factors and methods in the framework make it inclusive, but it attempts to combine an exhaustive number of models for health behaviours and associated treatments that have been shown to have modest explanatory power and efficacy. The COM-B also fails to provide a coherent theoretical account of how variables interact to influence non-adherence behaviour that focus on key principles and processes and tries to merge models with potentially distinct ontological and epistemological assumptions. Therefore, formulating why individuals are non-adherent with a framework or method of categorisation that is not underpinned by any particular underlying (and potentially conflictual) theory becomes increasingly challenging.

One appeal of the COM-B is that a range of corresponding behaviour change techniques can be drawn on by clinicians and combined to "build" interventions to improve adherence. However, clinicians may also encounter problems with combining potentially contrary techniques stemming from

different theoretical perspectives. It also becomes difficult to imagine how a "built" intervention in a treatment trial might include a process evaluation without being guided by a coherent explanatory model with a clear set of guiding principles. Currently, there is limited research exploring the efficacy of behaviour change interventions arising from the framework.

1.4.7 Third-wave mindfulness-based approaches

More recently, there has been a growing interest in applying so-called "third-wave" approaches (Hayes, 2004) to improve people's adherence to medical treatment, including Mindfulness-based Stress Reduction (MBSR) and Dialectical Behaviour Therapy (DBT). MBSR and DBT and their operational definitions of mindfulness have drawn mostly on teachings from Mayahana and Theravada Buddhist, as well as yogic, traditions (Kabat-Zinn, 1982).

There are a small but growing number of studies that have examined the applicability of MBSR in addressing treatment non-adherence. Specifically, the 10-week MBSR programme comprising secular mindfulness meditation (seated meditations, body scan practice, mindful yoga/movement and walking meditation) based on Buddhist teachings is regarded as the earliest third-wave development, demonstrating significant reductions in pain severity and interference, negative body image and pain-related drug utilisation and improvements in emotional functioning of patients with chronic pain in the early 1980s (Kabat-Zinn, 1982; Kabat-Zinn, Lipworth, & Burney, 1985). More recently, applications of MBSR for treatment adherence have mostly been confined to HIV. One systemic review, including three studies exploring the utility of MBSR in people with HIV prescribed antiretroviral therapy, shows that adherence-related outcomes (e.g. $CD4^+$ lymphocyte counts and T cell activity) were inconsistent across studies, where some participants experienced improvements whilst others worsened at post-intervention and long-term follow-up (Riley & Kalichman, 2015).

The inconsistent findings of MBSR on improving adherence outcomes suggests the approach may have some limitations. First, MBSR and subsequently Mindfulness-based Cognitive Therapy (MBCT) (Segal, Williams, & Teasdale, 2013) have not been guided initially by a coherent testable theoretical model or key set of guiding principles, but rather have attempted to recognise a range of traditional Eastern meditation methods and only later attempted to understand how they work (Harrison, Scott, Johns, Morris, & McCracken, 2017). Second, aside from engaging a person in mindful practice, MBSR does not incorporate an explicit behavioural activation component (e.g. exposure, setting goals or making commitments), and therefore its limited success may echo previous dismantling studies of traditional cognitive behavioural therapies, which consistently show that behavioural activation exerts the greatest influence on treatment outcomes (Jacobson et al., 1996; Longmore & Worrell, 2007).

A recent conceptual review has also promoted the adapted use of DBT, initially designed for people with Borderline Personality Disorders (Linehan, 1993) to improve medication adherence in adolescents with chronic medical illness (DBT-CMI) (Becky H Lois & Miller, 2018). The authors highlight three overarching goals of the eight individual session intervention, including: (i) increasing a young person's awareness of the consequences of non-adherence, (ii) conceptualising non-adherence as a form of emotional avoidance or crisis-driven behaviour, and teaching mindfulness and emotion regulation strategies to help the person develop more skilful responses to difficult emotions, and (iii) increasing a person's 'radical acceptance' of their illness to enhance distress tolerance, for example when they believe themselves to be "invincible". In addition, three family sessions are aimed at resolving parent-child relational conflicts around their illness and medication use. Primary treatment targets include decreasing non-adherence behaviours that interfere with treatment engagement and QoL, whilst increasing behavioural skills. Secondary targets include alleviating emotional avoidance, social pressures, shifting illness responsibility between parent and teen, and nonacceptance. Evidence for DBT-CMI is in its infancy, but one pilot study shows promising efficacy in terms of improving self-

reported adherence and depression but not QoL in difficult-to-treat youth with end-stage renal disease (Hashim, Vadnais, & Miller, 2013). Another trial targeting non-adherence in adolescents with Type I diabetes is currently underway (Lois et al., 2017, unpublished).

A strength of DBT-CMI is that it brings together a potentially useful combination of mindfulness-based strategies in conjunction with behavioural elements. However, despite providing a more traditional cognitive-behavioural vicious cycle example in their review, Louis and Miller (Lois & Miller, 2018) focus mostly on a range of treatment techniques rather than presenting a coherent testable theory with a set of key processes. Similar to MBSR, the lack of theoretical clarity in DBT more generally is potentially problematic because it undermines attempts to conduct mediational process analyses to evaluate the role of a pre-defined set of independent variables (Harrison et al., 2017). This makes it difficult to disentangle which of the many components that make up DBT-CMI exert most influence on adherence and other key outcomes. Also, given the broader adherence outcomes used in these trials, it remains unclear whether DBT-CMI is better equipped to target intentional and/or unintentional forms of non-adherence.

1.4.8 Summary

Existing psychological theories have for some time argued that people with LTCs are non-adherent to their medications because they do not intend to take them, or because they hold certain unhelpful erroneous beliefs about their illness or treatment. Others suggest a person's confidence in taking a medication determines whether they are adherent or not. Whilst a review of existing reviews published over a decade ago stated that, "interventions to improve patient adherence are unsuccessful and sound theoretical foundations are lacking" (van Dulmen et al., 2007, p.1), current empirical studies have shown these constructs do help to understand adherence and patient centred outcomes, accounting for some of the variance in medication taking behaviour (Conn, Enriquez, Ruppar, & Chan, 2016).

However, they are not strong predictors of adherence and are less theoretically equipped to explain unintentional non-adherence. In addition, psychological treatments aiming to directly enhance self-efficacy and change potentially unhelpful beliefs about illness and medication have mostly shown mixed findings in terms of improving adherence, and effect sizes overall are modest. Furthermore, few have directly targeted potentially difficult emotions arising from being asked to adhere to long-term treatments, but those that have indicate some preliminary efficacy. There are also a vast number of attempts to tackle non-adherence by using information and advice-giving interventions, which show limited efficacy overall (Conn, Ruppar, Enriquez, et al., 2016; Nieuwlaat et al., 2014). Taken together, this suggests there may be other more potent predictors of adherence that could potentially be targeted in the context of psychological intervention.

1.5 Utility of the psychological flexibility model to understand adherence to medical treatment

Another third-wave approach, the Psychological Flexibility model (PF), which underlies Acceptance and Commitment Therapy (ACT) (Hayes, Strosahl, & Wilson, 1999), offers an alternative framework for understanding and treating intentional and unintentional non-adherence to medication in the context of LTCs. It is beyond the scope of this summary to describe PF and ACT's underlying philosophical assumptions (functional-contextualism and its pragmatic truth criterion to scientific enquiry) (Vilardaga, Hayes, & Schelin, 2007) and basic level theory[2] in great detail here (see Hayes et al., 2001).

[2]Relational frame theory (RFT) is a post-Skinnerian account of human language and cognition rooted in operant principles (Hayes, Barnes-Holmes, & Roche, 2001), which focuses on generalised response classes, experiential avoidance and "relational responding" (for a more detailed summary see Torneke, 2010).

PF has been defined as, "the capacity for an individual to persist with, or change, behaviour in a manner that includes conscious and open contact with thoughts and feelings, appreciates what situations afford, and serves one's goals and values" (Scott & McCracken, 2015, p.91). Conceived as a transdiagnostic theory of "normal" human behaviour (McCracken & Morley, 2014), PF incorporates six integrated processes: acceptance, cognitive defusion, self-as-context, present moment focus or awareness, values and committed action (Figure 3). The first four have been broadly categorised as 'acceptance and mindfulness' processes, whilst the remaining two reflect more 'commitment and behaviour change' processes (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). Acceptance or willingness is the ability to openly engage in activities in the presence of unwanted experiences, without struggling with them, when doing so is guided by one's goals (Scott & McCracken, 2015). Cognitive defusion is the ability to experience a distinction between thoughts and the things they describe and to contact experiences directly, without being dominated by the literal meaning and influences carried in thought content (Fletcher & Hayes, 2005). Self-as-context refers to perspective skills or one's ability to experience a point of view distinct from thought content and arising feelings, where they are neither defined by nor harmed by them (Hayes et al., 1999). Present-focussed awareness, similar to other mindfulness definitions, is ongoing, non-judgmental awareness of one's experience and the capacity to attend and flexibly, fluidly, and voluntarily switch focus between the immediate internal and external environment (Zhang et al., 2017). Values are freely chosen, verbally constructed qualities of purposive action that we define as important, which are never fully achieved and guide our goals (Hayes et al., 2006). Committed action is flexibility persisting with goals or actions informed by values in a manner that incorporates discomfort and failure and still continue, or are abandoned if unworkable (McCracken, 2013).

In the context of adherence, PF suggests a person may not adhere due to three potentially unhelpful patterns of behaviour: i. *Closed:* Avoiding situations and related private emotional experiences, such as thoughts, mood states, or bodily sensations; ii. *Unaware:* Being overly influenced by, or entangled with, potentially unhelpful thoughts, including a pre-occupation with the past or future, or unable to take a

point of view separate from these thoughts and feelings; and iii. *Disengaged*: Failing to identify and pursue valued life directions and related goals and persisting inflexibly or impulsively in potentially "unworkable" behaviour.

For example, a person with a LTC might believe that medication is helpful or necessary, but may still not adhere because they try to control or eliminate uncomfortable physiological sensations, thoughts and emotions related to their condition, treatment and/or wider life circumstances (e.g. shame, fear, anxiety taking antiretroviral therapy) (*closed);* and often dwell on the past or worry about the future to the extent they are not present in the here and now (e.g. worry, anxiety and fear after a breast cancer diagnosis and taking Tamoxifen) (*unaware*). Therefore, taking medication becomes an aversive experience, and though the person might believe treatment is effective (e.g. ACE inhibitors for hypertension), they cannot see if or how taking medication serves their long-term values or goals (e.g. being independent, healthy and continuing with work and/or being a good parent) (*disengaged*). The emphasis of experiential avoidance in PF could potentially either equate to (i) a person actively choosing not to follow their treatment regimen, or (ii) becoming so pre-occupied with their private aversive experiences (wittingly or unwittingly) and efforts to reduce or eliminate them, it reduces their present moment awareness and they forget to take their medications. Therefore, PF does obviously not distinguish between intentional and unintentional forms of non-adherence.

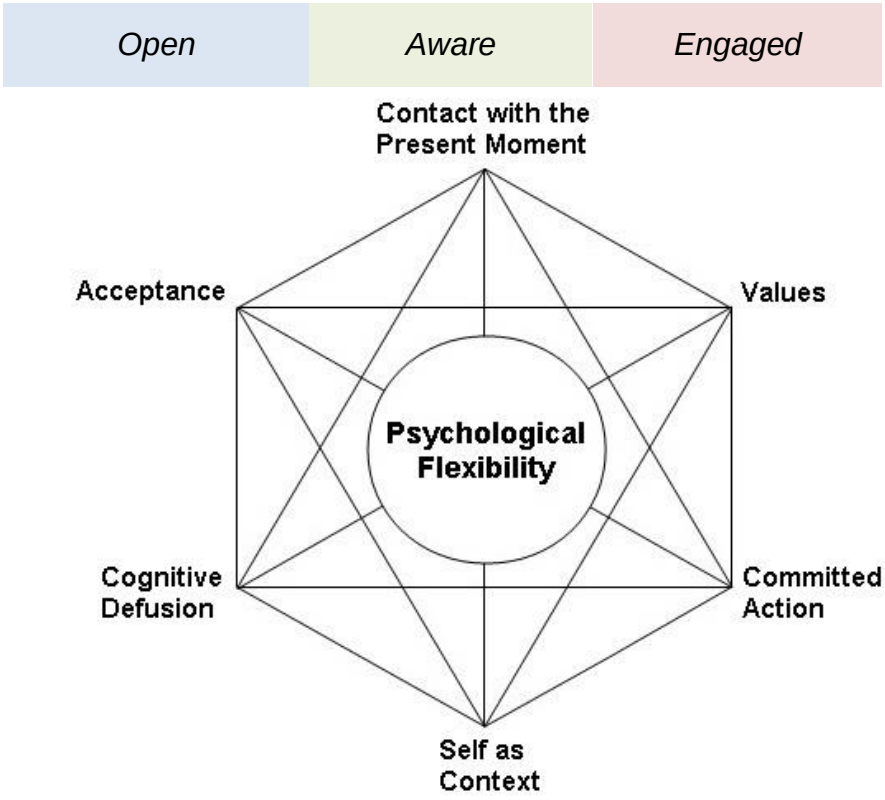

Figure 3: ACT's six- and three-processes psychological flexibility model (reproduced from Harrison et al., 2016).

ACT is a newer form of cognitive-behaviour therapy (CBT), which aims to modify the three psychological *inflexibility* processes described above. ACT focuses on *how* private events, such as thoughts, feelings and behaviours are experienced (i.e. *contextual* change), rather than *what* is experienced. The focus differs slightly to "second-wave" traditional cognitive behavioural approaches (Beck, 1979), which assume a more rational, refuting stance to align beliefs or thought *content* with essential 'truths'. As such, ACT encourages the person to learn mindfulness and acceptance-based strategies to change their relationship with their private experience and clarify their values in the service of pursuing valued actions or goals. It has recently been argued that ACT and other mindfulness-based interventions may be more helpful when a person's beliefs appear highly plausible in the context of LTCs and may be useful to improve adherence (Graham et al., 2016).

The six PF processes have been further condensed into three broader sub-processes, including: (i.) *Open:* Being open and willing to have potentially unpleasant thoughts, feelings and bodily sensations without trying to change them; (ii.) *Aware:* Being in the present moment, able to recognise and disentangle oneself from the influence of potentially unhelpful thoughts and feelings, with the aim of being (iii.) *Engaged***:** Persisting in or initiating behaviours that allow the person to work towards freely chosen valued life directions, and flexibly disengage from actions if they prove to be unhelpful to enable more effective patterns of behaviour (Hayes, Villatte, Levin, & Hildebrandt, 2011; Scott, McCracken, & Norton, 2016).

ACT could improve medication non-adherence. For example, a person who demonstrates PF may still experience negative emotions and worry about their LTC. However, they may also develop the ability to open-up to these difficult private experiences, enabling them to choose to follow (or not follow) their treatment regimen, and engage in meaningful actions or goals in a more effect way. ACT assumes that adherence behaviour can occur in the presence of contrary or disturbing thoughts or feelings, or a lack of confidence. It also brings into focus the pragmatic question of how effective or "workable" a person's behaviour is by setting it against their values. This patient-centred focus on values and "workability" provides a useful framework to enhance the clarity of a person's informed consent to treatment, which along with available medical advice, may help the individual and their families to more fully consider whether they adhere or non-adhere to their medications as prescribed.

1.6 Evidence for the psychological flexibility model in treating non-adherence

Review evidence for PF (Levin, Hildebrandt, Lillis, & Hayes, 2012; Ruiz, 2010) and the efficacy of ACT for a range of clinical problems is mounting but there are still few interventions and those that exist seem very limited in scope and quality (e.g., Graham et al., 2016; Hann & McCracken, 2014;

Swain, Hancock, Hainsworth, & Bowman, 2013). However, there is growing support for the idea that PF processes mediate improvements in treatment outcomes (Stockton et al., 2018).

At least two correlational studies have shown that greater PF is significantly associated with better self-reported and more objective measures of adherence (i.e. HbA1c) in people with Type I diabetes mellitus (Kamody et al., 2017), and higher rates of influenza vaccination uptake in people with chronic respiratory diseases (Cheung & Mak, 2016). However, a more recent study found only small bivariate relationships between PF overall and three sub-processes (cognitive fusion, self-as-context and committed action) and self-reported most recent $CD4^+$ counts and intentional and unintentional non-adherence to antiretroviral treatment in people with HIV (Harrison, Scott, Graham, & Harrison, 2019, unpublished). However, associations for intentional and unintentional non-adherence were no longer significant after controlling for relevant demographic and disease variables. Cross-sectional studies have three important weaknesses. First, they are correlational in nature, so it cannot be assumed that the relationship between PF, mood and adherence is causal and there might be potential for reverse causality, or that PF reflects a marker for a different variable, such as distress (Wolgast, 2014). Second, group-based designs lose important within-individual change in context. Therefore, a more robust approach would be to conduct a sufficiently powered longitudinal study to estimate the temporal relationships between PF, mood and adherence over time. Third, given the limitations of group-level designs in understanding adherence, the longitudinal study could also preliminarily validate new momentary measures against established measures for use in future diary-based studies.

Two conceptual reviews have highlighted the applicability of PF and ACT as a potentially useful intervention to support health behaviour change more generally (Kashdan & Rottenberg, 2010; Zhang et al., 2017). In addition, three conceptual and one systematic review have also suggested that PF and ACT may have some utility in terms of improving adherence to treatment recommendations in the context of chronic pain (Harrison, Graham, & McCracken, 2017), adolescents with Type I diabetes

(Hadlandsmyth, Nesin & Greco, 2013), LTCs more generally (Graham et al., 2016) and psychosis (Moitra & Gaudiano, 2016; Spidel, Lecomte, Kealy, & Daigneault, 2018). All four reviews indicate few trials have specifically investigated the efficacy of ACT in improving adherence to prescribed medications in LTCs, and even fewer in child or adolescent populations. Two preliminary evaluations show ACT may improve adherence in LTCs, including reducing viral load and increasing $CD4^+$ lymphocyte counts to highly active antiretroviral therapy in adults with HIV (Moitra, Herbert, & Forman, 2011) and increasing men's attendance to intracavernosal injection therapy as part of an erectile dysfunction programme after radical prostatectomy compared to enhanced monitoring (Nelson, Kenowitz, & Mulhall, 2014). However, neither study measured PF at pre- and post-treatment, nor examined its role as a potential mediator of treatment effect.

1.7 Need for validated momentary assessments of PF, mood and adherence

As mentioned previously, a key problem with most adherence research is that studies rely on group-based designs, which lose important individual differences, and self-report scales can often result in retrospective memory biases (Moskowitz & Young, 2006). Ecological Momentary Assessment (EMA) is an established real-time idiographic diary-based method that attempts to capture an individual's representation of experience as it occurs within the context of everyday life (Hektner, Schmidt, & Csikszentmihalyi, 2007; Stone & Shiffman, 1994).

In recent years, the psychology literature has seen a resurgence of interest in EMA methods due largely to increased availability of advanced smartphone technologies (Heron & Smyth, 2010; Leventhal, Phillips, & Burns, 2016; Runyan & Steinke, 2015). In the health context, a few studies have used EMA methods to examine relationships between constructs from social cognitive models and adherence outcomes in LTCs, demonstrating mixed results (Basen-Engquist et al., 2013; Bond et al.,

2013). However, currently no studies have used EMA methods to explore relationships between PF, mood and adherence in people with LTCs specifically, despite reflecting a potentially more reliable way to examine their dynamic interactions over time (Moitra & Gaudiano, 2016).

A principle advantage of EMA is the potential to examine relationships between variables in conjunction with relevant situations or events, or sudden changes in routine, such as going on holiday (Hektner et al., 2007), which for example may result in higher rates of unintentional non-adherence (de Klerk et al., 2003). Specifically, EMA can explore temporal relationships between PF and adherence time-series data in conjunction with the presence or absence of a given contextual variable/s (e.g. being on holiday or not), or the different levels of a given contextual variable (e.g. a weekend break, fortnight trip or longer). Therefore, using EMA could for the first time allow for a more valid and reliable examination of an individual's daily or momentary patterns of adherence behaviour in relation to mood and PF across different contexts.

An important challenge is that established group-based measures of adherence, mood and PF are not validated for use in EMA and other idiographic methods generally, and due to the high number of items may be too burdensome (Boorsbom, Mellenbergh, & Van Heerden, 2002). Therefore, ultra-brief momentary measures need to be developed with experts by experience and statistically validated to ensure they measure constructs accurately. Currently, there is little established guidance on validating momentary measures, but existing cross-sectional and EMA studies with large samples in chronic pain, social anxiety and healthy university students have preliminarily investigated the reliability, concurrent and predictive validity of new momentary measures of experiential avoidance (e.g., Kashdan et al., 2014; Machell, Goodman, & Kashdan, 2015; Scott, unpublished, 2017) and cognitive fusion (Bolderston, Gillanders, Turner, Taylor, & Coleman, 2018). EMA multilevel analyses are powered on repeated measures within individuals, which means the number of participants required may be relatively small (Nezlek, 2001; 2003; 2007; 2008; 2012). However, a large number of participants and

repeated measurement is needed to reliably validate momentary measures in conjunction with established group-level measures that relies on large samples, which may not always be possible for rare LTCs or hard-to-reach groups. One way to circumvent this problem is to conduct a large longitudinal study to preliminarily validate new momentary measures of adherence, mood and the transdiagnostic PF processes against existing group-level measures in people with a range of LTCs.

1.8 Aims

Given the challenges outlined, the overarching project aims to conduct a large three month online longitudinal study to assess the utility of PF model processes to improve prediction and inform novel intervention development for medication non-adherence in LTCs. A secondary aim is to develop and evaluate ultra-brief momentary measures of adherence and appointment attendance, mood and PF for the purpose of future EMA designs to further examine the applicability of PF in this area.

The project has two objectives:

1. Examine the extent to which PF processes measured using validated trait/group-level scales predict self-reported adherence to medication and appointment attendance in people with LTCs after accounting for demographic, illness and other contextual variables (e.g. age, gender, type of LTC, country of residence).

2. Design and statistically validate new ultra-brief momentary self-report scales of PF, mood and medication adherence in conjunction with established trait/group-level measures and general functioning in people with LTCs.

Findings for the secondary aim and objective will not be reported in the current thesis due to shortage of space but will written up for peer-reviewed publication after thesis submission. The methods section

will include information related to the secondary aim to contextualise decisions made regarding the primary aim.

The current study is therefore the first to examine cross-sectional and longitudinal relationships between established and new momentary measures of PF and self-reported intentional and unintentional non-adherence and percentage of routine appointments for illness attended outcomes in people with LTCs. Overall, the current project contributes to a growing body of research evaluating the potential utility of PF and ACT to better understand and treat non-adherence in people with LTCs.

1.8.1 Study Hypotheses

Based on the primary aim and objective above, the current study has two specific hypotheses:

Cross-sectional data:

1. Greater psychological inflexibility will be associated with poorer adherence and appointment attendance, independent of demographic and illness characteristics. Specifically, higher levels of psychological inflexibility will predict higher rates of intentional and unintentional non-adherence and fewer routine appointments attended in the last three and twelve months. Greater psychological inflexibility will also be correlated with poorer general functioning.

Longitudinal data:

2. Greater psychological inflexibility will predict poorer adherence and appointment attendance in previously expected directions in hypothesis one, independent of demographic and illness characteristics. Greater psychological inflexibility will also be related to poorer general functioning over time.

Chapter 2: Method

The first chapter highlighted the modest predictive power of existing psychological models as applied to treatment non-adherence in people with LTCs. It also indicated the potentially novel applicability of the Psychological Flexibility (PF) model in this context. The current chapter will summarise the proposed methods used in the project, which aims to (i) explore cross-sectional and longitudinal relationships between PF processes, self-reported adherence, mood and general functioning, and (ii) preliminarily validate novel momentary measures of PF, mood and medication adherence in conjunction with established group-level measures.

2.1 Design

The current study was an online longitudinal survey. A full pre-registration summary of the project can be found at the Centre for Open Science: https://osf.io/aste7/?view_only=df6a676512344b71a7dd373ae144f8c2

2.3 Ethical clearance

The study was approved by the Faculty of Medicine and Health Research Office School of Medicine Research Ethics Committee (SoMREC) in June 2018 (MREC17-068) (Appendix B). Informed consent was obtained online.

2.4 Participants and procedure

All participants were asked to complete a battery of baseline self-report questionnaires, including established trait/group-based measures of PF, mood and adherence, along with corresponding new ultra-brief momentary scales. Participants were also asked to complete questions about demographic and illness characteristics and general functioning. At three months, all participants were invited via email to repeat the same questionnaire battery (minus the demographic questions) to explore temporal relationships. The decision to follow-up participants at three months reflected a compromise between the primary and secondary aims, providing an opportunity to preliminarily assess psychometric properties of new momentary and established group-based scales over time. Specifically, it was assumed this timeframe provided the minimum amount of time required to capture any significant changes in established group-based scales, whilst allowing for detection of any subtle fluctuations in momentary/state scales.

2.4.1 Eligibility criteria and recruitment

All participants were recruited via international online advertisements on 441 LTC organisation websites, registries or patient groups and forums, Twitter feeds and Facebook pages after approaching relevant gatekeepers. Efforts were made to contact a range of organisations to recruit people with different LTCs according to an alphabetical list. The eligibility criteria for the online survey were (i) people with any type of LTC who are (ii) 13 years of age or over, and (iii) prescribed medication to manage their LTC. All participants were required to read the corresponding participant information sheets (Appendix C.1 to C.3) and sign the consent form electronically, including parents of adolescents.

2.4.2 Sample size

No published studies have reported on direct predictors or correlates between established group-level measures of PF and self-reported adherence and general functioning in LTCs. However, other psychological constructs from social cognitive models range from small to medium effect sizes in the context of adherence (Brandes & Mullan, 2014; Horne et al., 2013; Rich et al., 2015). Consistent with established rules of thumb (Green, 1991) and according to G*Power version 3.1.9.2. (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007), at least *n*=92 participants were required to detect a moderate effect size of 0.15 (and *n*=647 for a small effect size of 0.02) to achieve 80% power at a two-tailed alpha level of 0.05 using a multiple linear regression fixed model with R^2 increase, including seven demographic and disease variables, and five PF predictors. The latter was also sufficient for exploratory factor analyses (EFA) for the new 9- and reduced 3-item momentary PF scale baseline data based on a three or single-factor solution (Tabachnick & Fidell, 1996). It was also recommended that confirmatory factor analysis (CFA) for the 9- and reduced 3-item momentary PF scales follow-up data were run with at least *n*=200 participants (Brown, 2015).

Based on attrition rates in similar prospective studies, we expected a conservative estimate of 40% attrition over 3-months (e.g., Banning, 2012; Carrieri et al., 2006; Golin et al., 2002). Therefore, assuming a medium effect size, 80% power and a 0.05 level of significance, a baseline sample size of at least *n*=154 participants (or *n*=1078 to detect a small effect) was needed to achieve sufficient power for the longitudinal analysis.

2.5 Established measures

Two versions of the online longitudinal survey were launched, one for adults (Appendix D) and for adolescents (Appendix E). Therefore, different versions of validated scales for mood and PF in these populations were included (see Table 1). All authors were asked for their permission to use or adapt a modified version of their measure unless it was freely available. The online survey asked participants to complete the battery of questionnaires twice: once at baseline (0 months) and following one reminder email at 3 months follow-up.

Table 1: List of established and new non-validated self-report measures used in both the adolescent and adult versions of the online survey

Measure	Construct	Reference
Adolescent version		
Modified Work and social adjustment (WSAS) Modified version	General functioning	(Mundt et al., 2002)
Medication Adherence Rating Scale 5 items (MARS-5)	Medication adherence	(Horne et al., 2001)
New single-item momentary numerical rating scales (NRS) for daily and hourly self-reported adherence	Momentary measure of medication adherence	NA
New single-item numerical rating scales (NRS) for percentage of attendance to appointments for LTC in last 2-3 and 12 months	Health care utilisation / attendance	NA
Avoidance and Fusion Questionnaire for Youth 8 items (AFQ-Y8)	PF	(Greco et al., 2008)
Child and Adolescent Mindfulness Measure (CAMM)	Mindfulness	(Greco et al., 2011)
New 9-item momentary measure of PF: Open, Aware, Engaged	Momentary measure of PF	NA
New single-item numerical rating scales (NRS) for percentage of attendance to appointments for LTC in last 2-3 and 12 months	Health care utilisation / attendance	NA
Generalised anxiety Disorder Scale 7 items (GAD-7)	Anxiety	(Mossman et al., 2017)

Patient Health Questionnaire 8-items adolescent version (PHQ-8-A)	Depression	(Johnson et al., 2002)
Modified Generalised anxiety Disorder Scale 2 items (GAD-2)	Momentary self-report measure of anxiety	(Skapinakis, 2007)
Modified Patient Health Questionnaire 2-items (PHQ-2)	Momentary self-report measure of depression	(Kroenke et al., 2003)
Adult version		
Work and social adjustment (WSAS)	General functioning	(Mundt et al., 2002)
Medication Adherence Rating Scale 5 items (MARS-5)	Medication adherence	(Horne et al., 2001)
New single-item momentary numerical rating scales (NRS) for daily and hourly self-reported adherence	Momentary self-report measure of medication adherence	NA
Acceptance and Action Questionnaire II (AAQ-II)	PF	(Bond et al., 2011)
Comprehensive assessment of Acceptance and Commitment Therapy processes (CompACT)	Self-report measure of three facets of PF	(Francis, Dawson, & Golijani-Moghaddam, 2016)
New 9-item momentary measure of PF: Open, Aware, Engaged	Momentary measure of PF	NA
Patient Health Questionnaire 8-items (PHQ-8)	Group-based self-report measure of mood / emotional functioning	(Kroenke et al., 2009)
Generalised anxiety Disorder Scale 7 items (GAD-7)	Group-based self-report measure of mood / emotional functioning	(Spitzer et al., 2006)
Modified Generalised anxiety Disorder Scale 2 items (GAD-2)	Momentary self-report measure of anxiety	(Skapinakis, 2007)

Modified Patient Health Questionnaire 2-items (PHQ-2)	Momentary measure of depression	(Kroenke et al., 2003)

2.5.1 Demographic and disease variables

All participants were asked to report their age, ethnicity, gender, education level, and employment and relationship status, and time since diagnosis, which were entered as covariates if related to adherence outcomes at the bivariate level.

2.5.2 Established psychological flexibility scales

Two validated PF scales for adults were included:

1. The Acceptance and Action Questionnaire (AAQ-II) (Bond et al., 2011) is a broad measure of PF based on the Acceptance and Action Questionnaire (AAQ) (Hayes et al., 2004). Items include statements such as, "*My painful experiences and memories make it difficult for me to live a life that I would value*" or "*Emotions cause problems in my life*", using a scale from 1 ("never true") to 7 ("always true"). The AAQ-II is scored as a total sum score of all 7-items. Bond et al. report the AAQ-II has improved validity and reliability=.84; test–retest reliability α=.81 and .79) compared to its predecessor and is the most widely used measure of PF. However, recent evidence suggests that the AAQ-II may be tapping a measure of generalised distress (Wolgast, 2014) and may not adequately assesses all six PF processes.

Given these challenges, an additional PF scale was included to assess the previously defined "open, aware, and engaged" facets summarised in Chapter 1 (Hayes et al., 2011):

2. The Comprehensive assessment of Acceptance and Commitment Therapy processes (CompACT) Scale (Francis et al., 2016) is a relatively recent 23-item measure of PF, comprising Openness to Experience (OE), Behavioral Awareness (BA) and Valued Action (VA) subscales that map directly onto the new 9-item momentary PF scale of "Open, Aware, Engaged". After reversing 12 items, scores are derived by summing responses for the Openness to Experience, Behavioral Awareness and Valued Action subscales, where higher scores represent greater PF. The three subscales can also be added together to derive the total CompACT score. Based on an email communication with the last author (Appendix F) both the summed and mean scores (accounting for 20% of missing items) were calculated. The scale demonstrated good internal consistency (α=.87 to .90), and convergent and divergent validity. However, currently there is no longitudinal data supporting the test-re-test reliability of the CompACT.

Two validated PF scales for adolescents were included:

1. The Avoidance and Fusion Questionnaire for Youth 8-items (AFQ-Y-8) (Greco, Lambert, & Baer, 2008) is a broad measure of PF based on the Acceptance and Action Questionnaire (AAQ) (Hayes et al., 2004). Items include statements such as, "*My life won't be good until I feel happy*" or "*I stop doing things that are important to me whenever I feel bad*" using a 0 ("not true at all") to 4 ("very true") point scale. The AFQ-Y-8 is scored as a total sum score of all 17-items, where higher scores represent greater avoidance and cognitive fusion. Greco et al. (2008) show the AFQ-Y-8 has adequate validity and reliability (α=.89) when evaluated in a random sample of youths who on average were 12.6 years old.

2. The Child and Adolescent Mindfulness Measure (CAMM) (Greco, Baer, & Smith, 2011) was used to measure present-moment awareness and nonjudgmental, nonavoidant responses to thoughts and feelings, which reflects acceptance, present moment awareness, self-as-context and defusion processes within the PF model. The CAMM was designed for children of ages 9 upwards, with items including "*I get upset with myself for having feelings that don't make sense*" or "*It's hard for me to pay attention to only one thing at a time*" on 0 ("never true") to 4 ("always true") point scale. After reversing all scores, the CAMM is scored as a total sum score of all 17-items, where higher scores correspond to greater levels of mindful awareness. The CAMM has adequate validity and reliability (α=.77).

2.5.6 Established adherence scale

A recent review shows several self-report instruments for adherence have been developed (Nguyen et al., 2014), but most assess beliefs or barriers rather than aspects of medication-taking behaviour *per se*, and even fewer provide information on their psychometric properties. The most well-validated adherence measure is the Morisky-8 (Morisky, Green, & Levine, 1986). However, unfortunately the developers of the Morisky-8 charge a fee to use this questionnaire, and the project had insufficient funds to purchase the rights to use the scale for the current online study. In addition, similar to most other self-report instruments, the Morisky-8 does not distinguish between intentional and unintentional non-adherence.

The Medication Adherence Report Scale 5-item scale (MARS-5) was therefore selected to assess self-reported intentional and unintentional non-adherence to medication (Horne, Hankins, & Jenkins, 2001). The MARS-5 includes wording that attempts to reduce social pressure to avoid inflated reports of adherence with five statements that does not specify a timeframe, e.g. "*I forget to take my medication*" or "*I adjust the dosage of my medication*", using a 5-point scale: 5 ("never"), 4 ("rarely"),

3 (“sometimes”), 2 (“often”), 1 (“very often”). Four items measure intentional and one unintentional non-adherence. Following a pragmatic approach used in previous studies with other LTCs (de Vries et al., 2014; Moon, Moss-Morris, Hunter, & Hughes, 2017), the total score and intentional and unintentional subscale scores were dichotomised because the distribution was significantly negatively skewed. Specifically, adherence was conservatively defined as a total score of 25 (i.e. 100%). Based on previous studies (Daleboudt, Broadbent, McQueen, & Kaptein, 2011; de Vries et al., 2014; Moon et al., 2017; Timmers et al., 2014), participants were categorised as unintentionally non-adherent if they scored <5 on the single-item subscale, and intentionally non-adherent if they scored <20 on the four-item subscale.

The MARS-5 is based on the original MARS and MARS-9 (Horne & Weinman, 2002), which were derived from the Drug Attitude Inventory (DAI) (Thompson, Kulkarni, & Sergejew, 2000), and have both been used with mixed success to assess adherence in a range of LTCs (Salt, Peden, & Horne, 2012). The clinician administered version of the MARS-5 shows unacceptable levels of sensitivity with pharmacy records in people taking blood-pressure-lowering drugs in a primary care (Van De Steeg, Sielk, Pentzek, Bakx, & Altiner, 2009). However, the patient self-report version of the MARS-5 shows good internal reliability and test-retest reliability (α=0.83) (Horne et al., 2001). It has been used in a variety of LTCs, including patients with breast cancer (Boonstra et al., 2013; Grunfeld, Dhesy-Thind, Levine, Care, & Cancer, 2005), COPD (George, Kong, Thoman, & Stewart, 2005) and inflammatory bowel disease (Ediger et al., 2007).

Few studies have evaluated the validity of the MARS-5, but those that have found moderate to strong convergent validity with other scales and adequate internal consistency (α=.77) (e.g., rheumatoid arthritis: Salt, Hall, Peden, & Home, 2012). Salt et al.’s (Salt, et al., 2012) review indicates there are mixed findings for correlations between the MARS-5 and more objective adherence measures. Specifically, the MARS-5 is significantly associated with continuous electronic adherence (r=.42, p=.001) in asthma patients. However, it has also been shown to have a small association with medication

refill adherence, with low sensitivity (13%) and specificity (94%), and positive predictive values (57%) in people with COPD (Tommelein, Mehuys, Van Tongelen, Brusselle, & Boussery, 2014). Beyond the LTC literature, the MARS-5 has demonstrated strong correlations with health care professional scores (r=.50) and serum concentration of prescribed medication (r=.52) in people diagnosed with schizophrenia or bipolar disorder (Jónsdóttir et al., 2010). When set against serum concentration the MARS-5's sensitivity (98%) and negative predictive value (89%) were good, but specificity was poor (33%). Although the MARS-5 has not yet been validated in many LTC samples, established self-report adherence scales do not distinguish between intentional and unintentional non-adherence.

2.5.8 Established mood scales

The Patient Health Questionnaire 8-items (PHQ-8) (Kroenke, Strine, et al., 2009) and adolescent version (PHQ-8-A), taken from the previous 9-item PHQ-A (Johnson, Harris, Spitzer, & Williams, 2002), assessed self-reported symptoms of depression. The PHQ-8 was used instead of the PHQ-9 to avoid causing distress from the PHQ-9's item asking about thoughts about suicide. This was felt to be important in the context of an online survey, where it will not always be possible to fully address risk related to this disclosure, particularly if the person does not share identifiable information or is based outside of the UK. The PHQ-8 is scored as a total sum score of all 8-items, where higher scores correspond to higher levels of depression. The established cut-point of ≥10 on the PHQ-8 was applied, with sensitivity and specificity for major depressive disorder 100% and 95% respectively, whilst any depressive disorder was 70% and 98% respectively (Kroenke, Strine, et al., 2009). The PHQ-A sensitivity and specificity for major depression was 73% and 94% respectively, whilst for any mood disorder was 61% and 94% (Johnson et al., 2002).

The Generalised Anxiety Disorder Scale 7-items (GAD-7) was used to estimate self-reported anxiety (Mossman et al., 2017; Spitzer, Kroenke, Williams, & Löwe, 2006). Both the PHQ-8 and GAD-7 use

the same scale: 0 (“Not at all”), (1) “Several days”), 2 (“More than half the days”) and 3 (“Nearly every day”). The GAD-7 is scored as a total sum score of all 7-items, where higher scores correspond to higher levels of anxiety. The established cut-point of ≥10 on the GAD-7 was applied, showing good sensitivity (89%) and specificity (82%) (Spitzer et al., 2006). Similarly, the PHQ-8 and PHQ-8-A are also most optimal with a cut-point of ≥10, demonstrating satisfactory psychometric properties with sensitivity ranging from 70% and specificity 98%.

2.5.10 Established and modified general functioning scales

The Work and Social Adjustment Scale (WSAS) examined the extent to which a person’s LTC interferes with everyday life (Mundt, Marks, Shear, & Greist, 2002). Other scales of general functioning for adolescents were explored (e.g., Adams, Streisand, Zawacki, & Joseph, 2002; Varni, Burwinkle, Seid, & Skarr, 2003; Wardenaar et al., 2013), but were either too burdensome, costly or had subscales that did not obviously reflect items in the WSAS. The WSAS has not been validated in adolescent samples with LTCs, and therefore the language of items was modified to take this into account to reflect the WSAS for adolescents (WSAS-A), e.g. “*Because of my illness my social leisure activities (with other people e.g*. [*parties, outings, visits, dating, having people over*]) *are* [*badly affected*]” or “*Because of my illness, my private leisure activities (done alone, such as [reading, playing, walking alone*]) *are* [*badly affected*]” (Appendix E). This aimed to provide an estimate of whether PF predictor variables were significantly associated with self-reported adherence but also illness-related functioning. The WSAS is scored as a total sum score of all 4-items, where higher scores correspond to greater impairment of functioning

2.6 Development of new momentary measures

New momentary measures of PF, adherence and mood were developed and included as part of the battery of questionnaires completed at baseline and three months.

2.6.1 Experts by experience involvement

The development of the novel PF measures in this study incorporated feedback from experts with lived experience of LTCs. To our knowledge, few existing PF measures have been developed incorporating feedback from expert service-users by experience and/or representatives. Therefore, consistent with the available guidance for the development and use of patient-reported outcome measures (FDA, 2006; Snyder et al., 2012; Wild et al., 2005), three adults and two adolescents with different LTCs (inflammatory bowel disease, multiple sclerosis, chronic constipation, an endocrine disorder and a traumatic brain injury) provided feedback on the participant information sheet and battery of questionnaires overall. Gaining expert by experience feedback on the new hourly and daily momentary measures of PF initial item pool comprising 22 statements enabled the author to establish whether items on the questionnaire were interpreted as intended or had face validity. In addition, experts were asked to rank the 22-items to indicate which were the most important and understandable to them (Appendices G and H) and were paid £25 in gift vouchers to thank them for their time.

Based on this feedback, the 22-item momentary measure of PF was reduced to an initial 9-item scale. The scale was further reduced to 3-items based on established exploratory and confirmatory factor analyses. All experts by experience felt that the wider survey and 22-item PF momentary scale had little potential for causing distress and participant burden of the overall questionnaire was minimal.

2.6.2 New momentary scales of psychological flexibility

All participants completed the new hourly and daily momentary 9-item PF scales described above at baseline and 3-months follow-up, which aimed to capture psychological inflexibility and the inverse of the three 'Open, Aware, Engaged' sub-processes, namely 'Closed, Unaware, Disengaged". Some of the items were drawn from existing PF group-level and momentary scales with author's permission (Greco et al., 2011; Kashdan et al., 2013; Kashdan et al., 2014; Machell et al., 2015). The scale was further reduced to 3-items based on the baseline EFA results, informing items selected for the CFA within the follow-up data analysis. The initial 9-item scale included items such as "*Today / Within the last hour or so… I struggled to control my thoughts or feelings"* (Closed), *"I found it difficult to stay focused on what was happening in the present"* (Unaware) or *"I stopped doing things that were important to me when I felt bad."* (Disengaged) using a 0 ("not at all") to 10 ("very much") scale (see Appendices D and E).

2.6.3 New momentary adherence scale

A review of adherence measures suggests using multiple methods to assess adherence to medication due to limitations of self-report scales (Bond, 2016). In addition, treatment recommendations can extend beyond simply prescribing medication, and although more established scales are relatively short, few have been developed for use in EMA studies. Although several reviews summarise guidance or criteria on how to develop new adherence measures (Garfield et al., 2011; Lam & Fresco, 2015; Stirratt et al., 2015), few provide guidance on developing ultra-brief momentary scales specifically.

Two novel single-item momentary numerical rating scales (NRS) for self-reported hourly and daily adherence to medication were developed: "*In the past hour / Today, how good have you been at taking your medications for your illness on time and as prescribed*?" ranging from 0 ("not good at all") to 10 ("extremely good"). The new scales do not separate intentional or unintentional non-adherence, since it is assumed PF has the potential to influence both.

In addition, two new single-item NRS asking about the participant's percentage of attendance to routine clinical appointments in the last 2 to 3 and 12 months were also included as a key outcome: "*In the last two to three months / In the last year, what percentage of routine appointments for your illness have you attended?"* on a 0 to 100% scale.

2.6.4 New momentary mood scales

In addition to PF and adherence, two new momentary NRS for self-reported mood and anxiety were also included (Appendices D and E). With permission of the authors, a modified version of the GAD-2 (Skapinakis, 2007) and PHQ-2 (Kroenke, Spitzer, & Williams, 2003) for momentary assessment were preliminarily evaluated. Changes pertaining to timeframe include, "*Today / over the last hour or so how often have you been bothered by the following problems?"* ranging from 0 ("Not at all") to 3 ("Very much"), both with a cut-point of ≥3. The GAD-2 demonstrates acceptable levels of sensitivity (92%) and specificity (76%) in the context of primary care, whilst the PHQ-2 performs less well at 62% and 95%, respectively.

2.7 Analysis

Four adolescents completed the online survey but only one provided consent, therefore only the adult sample were included in the following analyses to address the primary aim/objective. Analyses pertaining to the secondary aim, including exploratory and confirmatory factor analyses, internal consistency and test-re-test reliability statistics for the new 9- and 3-item PF scales are not reported here.

Continuous variables from the baseline and follow-up data were checked for kurtosis and skewness parameters to identify violations of normality according to established guidance (George & Mallery, 2010) and internal consistencies were assessed. Confirmatory Factor Analyses (CFA) were conducted using Mplus version 7 (Muthén & Muthén, 2006) to test previously identified or hypothesised factor structures of established PF, mood and adherence scales at baseline. Given the large sample size and ordinal nature of the data, the Diagonally Weighted Least Squares (WLSMV) estimator was used for normally distributed measures, whilst Maximum Likelihood estimation with Robust standard errors (MLR) was used for the non-normal MARS-5 (Li, 2016). There are various methods of assessing model or absolute fit. However, the Root Mean Square Error of Approximation (RMSEA), Tucker Lewis Index (TLI), Comparative Fit Index (CFI) and Standardized Root Mean Square Residual (SRMR) are recommended (Brown, 2015; Jackson, Gillaspy, & Purc-Stephenson, 2009). According to Hu and Bentler (Hu & Bentler, 1999), RMSEA values <0.06, TLI/CFI values of >0.95 and SRMR values of <.08 indicate acceptable model fit. For categorical data, the less commonly reported Weighted Root Mean Square Residual (WRMR) with a value of >1 indicate acceptable model fit (DiStefano, Liu, Jiang, & Shi, 2018).

Pearson's *r* correlations, t-tests and Chi^2 tests (or non-parametric equivalents, including Pearson's biserial correlations p^b for continuous variables) were used to examine: (i) differences between validated continuous and dichotomous outcome variables in relation to participant demographics (e.g. age, gender, ethnicity) and illness characteristics (e.g. time since diagnosis); and (ii) PF measures in relation to adherence, routine appointment attendance, anxiety and depression and general functioning at baseline to assess criterion validity. Convergence between adherence and attendance measures at baseline was also assessed. Separate multiple binomial logistic regression analyses were conducted to assess baseline relationships between PF predictors and intentional and unintentional non-adherence and routine appointment attendance outcome variables. Baseline demographic and disease variables showing a significant bivariate relationship with non-adherence at baseline were entered in the first step of the regressions. Validated PF measures formed the predictors in the second step. Standard $p<.05$ criteria were applied to all statistical analyses.

Predictive validity was assessed by examining Pearson's *r* or p^b between validated PF, emotional and general functioning scales at baseline in relation to adherence outcomes at three months follow-up. Test-retest validity of all measures were calculated using Intra-class correlations (ICC) to determine if participants' responses were consistent over time, assessing the reliability of the scales. ICC values vary between of 0 and 1, where the latter indicates perfect reliability. According to established guidance for 95% confidence intervals values less than 0.5=poor, between 0.5 and 0.75=moderate, 0.75 and 0.9=good, and greater than 0.90=excellent (Koo & Li, 2016).

Finally, separate multiple binomial logistic regression analyses were conducted to assess baseline and longitudinal relationships between PF predictors and intentional and unintentional non-adherence and routine appointment attendance outcome variables. Baseline demographic and disease variables showing a significant bivariate relationship ($p<.05$) with non-adherence were entered in the first step. PF processes were entered in the following step to assess their association with adherence after

demographic and disease variables were accounted for. The proportion of explained variance in these models were assessed using Nagelkerke R^2 (pseudo R^2). The -2 Log Likelihood statistic (-2LL) assessed model fit. Specifically, lower -2LL values indicate superior model fit, such that if adding variables in each step reduces the -2LL value, they have improved the model fit as represented by a non-significant (p>.05) Hosmer and Lemeshow Chi^2 Test value. Diagnostic checks, including checking residuals (Cook's distance and Leverage hat values), outliers (standardised residuals and DFBeta), linearity of the logit (check predictor by In*(predictor interaction) and multicollinearity (linear regression collinearity VIF and tolerance values), were conducted to confirm the validity of all regression models following established guidelines (Field, 2013). All analyses were conducted using SPSS Version 24 (IBM Corp., New York).

Chapter 3: Results

Between June and December 2018 *N*=709 people with LTCs, including *n*=4 adolescents and *n*=705 adults, currently prescribed medications for their illness completed the online baseline survey hosted by Online Surveys. Seven cases were excluded for the following reasons: not prescribed medication/s for their LTCs (*n*=2), LTC was mental health problem (*n*=2), adolescents who did not get parental consent (*n*=3). Therefore, given that only one adolescent had usable data, only the adult data (*n*=701) were analysed and reported in the following sections.

3.1 Baseline analyses

3.1.1 Demographic and disease characteristics of overall sample

Participants (*N*=701) were predominantly white-Caucasian (97.0%) and female (73.0%), on average in their mid-fifties (*M*= 54.93, *SD*= 15.81), with most responders from the UK (92.7%). Thirty-eight percent were retired, 10.8% medically retired, 19.4% in full- and 12.6% part-time employment, 5.0% self-employed, 3.3% full/part-time students, 3.4% homemakers and 2.9% unemployed, whilst 4.5% selected "other" status. Fifty-nine percent were married or in a civil partnership, 10.4% cohabiting, 3.1% widowed, 8.3% separated/divorced, 18.4% single, whilst 0.6% indicated "other" status. Forty-one percent of participants were diagnosed with Parkinson's disease and 57.3% reported having more than one LTC. Participants on average reported they were diagnosed with their primary LTC for *M*=8.65 (*SD*=10.08) years, experienced mild levels of anxiety and depression, and fell within the 'normal subclinical populations' range in terms of general functioning (Table 2).

3.1.2 Descriptive statistics of measures

As shown in Table 2, The MARS-5 total sum score, MARS-5 total mean item score adjusted (with less than 20% missing items) and intentional non-adherence subscale were all significantly negatively skewed, but the unintentional sub-scale score distribution was normal. Therefore, established binary cut-offs for the MARS-5 total and subscale scores were used in all analyses. All measures showed Means/SDs that were largely consistent with the measure validation studies (Bond et al., 2011; Francis et al., 2016; Jónsdóttir et al., 2010; Kroenke, Spitzer, Williams, & Löwe, 2009; Mundt et al., 2002; Spitzer et al., 2006).

Self-reports of attendance to routine clinical appointments in the last *2-3 months* and *12 months* using the single-item NRS were also significantly negatively skewed. Therefore, 'near perfect' binary cut-offs modelled on the MARS-5 were applied in all analyses (see adherence and attendance convergence rates in section 3.1.5). The number of participants completing the 2-3- and 12-month appointment attendance NRS were lower than the MARS-5 because many people indicated these timescales were not applicable. To preserve statistical power, all cases (including any with missing items) were used to calculate summed scores and variances for each of the psychological scales. As shown in Table 2, the variances were checked against those calculated with 20.0 to 25.0% of missing data, depending on the number of scale items to explore if there were any clear differences. Missing data was remarkably low, and few obvious differences were identified, therefore summed scores were used in all analyses.

Table 2: Baseline descriptive data for all measures in the adult sample

Measure	*n*	Mean (SD)	Skewness (SE)	Kurtosis (SE)	Reliability Cronbach α
Adherence and attendance					
MARS-5 total sum score	697	21.01 (4.02)	-1.93 (.09)*	4.89 (.18)	.77
MARS-5 total mean item score adjusted (<20% of missing items)	683	4.27 (.66)	-1.33 (.09)*	1.77 (.18)	
MARS-5 Intent sum score	693	17.29 (3.29)	-1.70 (.09)*	3.39 (.18)	
MARS-5 Unintent sum score	692	3.85 (.89)	-.44 (.09)	-.28 (.18)	
Single item appointment attendance in last *2-3 months* NRS (%)	592	91.80 (24.70)	-3.13 (.10)*	8.37 (.20)	NA
Single item appointment attendance in last *12 months* NRS (%)	680	94.82 (16.72)	-4.21 (.09)*	18.44 (.18)	NA
Functioning					
WSAS total sum score	701	16.97 (10.99)	.26 (.09)	-.95 (.18)	.93
Mood					
PHQ-8 total sum score	699	8.94 (6.26)	.58 (.09)	-.58 (.18)	.89
PHQ-8 total mean item score adjusted (<25% of missing items)	699	1.12 (.78)	.57 (.09)	-.60 (.185)	
GAD-7 total sum score	699	6.56 (5.86)	.88 (.09)	-.23 (.18)	.92
GAD-7 total mean item score adjusted (<25% of missing items)	699	.93 (.83)	.87 (.09)	-.23 (.18)	
Psychological flexibility processes					
AAQ-II total sum score	700	20.61 (10.62)	.54 (.09)	-.56 (.18)	.94
AAQ-II total mean item score adjusted (<25% of missing items)	700	2.94 (1.15)	.54 (.09)	-.56 (.18)	
CompACT total sum score	700	81.02 (21.38)	-.18 (.09)	-.61 (.18)	.88

CompACT total mean item score adjusted (<25% of missing items)	699	3.75 (1.01)	-.11 (.09)	-.59 (.18)	
OE subscale sum score	700	34.03 (11.90)	.07 (.09)	-.64 (.18)	.82
OE mean item score adjusted (<25% of missing items)	693	3.44 (1.18)	.06 (.09)	-.66 (.18)	
BA subscale sum score	700	16.37 (6.15)	-.37 (.09)	-.39 (.18)	.79
BA mean item score adjusted (<25% of missing items)	697	3.50 (1.43)	-.15 (.09)	-.66 (.18)	
VA subscale sum score	700	30.61 (7.63)	-.72 (.09)	.20 (.18)	.85
VA mean item score adjusted (<25% of missing items)	698	4.38 (1.09)	-.75 (.09)	.27 (.18)	

*****Non-normal distribution

Adherence measures: MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent'); MARS-5 Intent (Medication Adherence Rating Scale five items intentional non-adherence subscale score: 20='adherent' <20='non-adherent'); MARS-5 Unintent (Medication Adherence Rating Scale five items unintentional non-adherence subscale score: 5='adherent', <5='non-adherent').

Attendance measures: <100% appointment attendance in last 2-3/12 months NRS (%) (Single item appointment attendance in last 2-3/12 months Numerical Rating Scale percentage, binary cut-offs: 100%=adherent; <100%=non-adherent).

Mood and functioning: PHQ-8 (Patient Health Questionnaire 8-items: 0-4 'No significant depressive symptoms', 5-9 'mild depressive symptoms', 10-14 'moderate depressive symptoms', 15-19 'moderately severe depressive symptoms', 20-24 'severe depressive symptoms'; GAD-7 (Generalised Anxiety Disorder 7-items: 0-4 'Minimal', 5- 9'Mild', 10-14 'Moderate', 15-22 'Severe'; WSAS (Work and Social Adjustment Scale: 0-9 'Normal subclinical populations', 10-19 'Normal subclinical populations', 20-40 'moderately severe or worse psychopathology').

Psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (Comprehensive assessment of Acceptance and Commitment Therapy processes total sum score); CompACT total BA (CompACT Behavioral Awareness subscale) CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).

All confirmatory factor analyses of established measures are presented in Appendix I). In summary, most scales met at least two of the four absolute goodness of fit indices, indicating acceptable construct validity. However, the MARS-5 only met one of these indices, indicating the underlying single factor structure tested was not a good fit with the data overall. Additionally, the CompACT was tested for both three and single factor solutions, but also only met the WRMR goodness of fit criteria. Both measures showed a small proportion of items factor loadings ranged from .7 to .9, therefore underlying

constructs identified in previous validation studies did not extend to the current sample and therefore interpretations should be tempered with caution.

3.1.3 Demographic and disease characteristics for adherent and non-adherent subgroups

According to the MARS-5 cut-offs 88.6% of the sample were non-adherent. Of those, 74.8% were intentionally non-adherent, whilst 84.3% were unintentionally non-adherent (Table 3). As shown in Table 3, there was a significantly larger proportion of non-adherers from the UK compared to other countries. Non-adherers reported significantly more years living with their primary LTC and worse general functioning and depression compared to adherers. However, there were no differences in levels of anxiety and any other demographic and disease variables.

Table 3: Participant characteristics according to MARS-5 cut-offs (*n*=699)

	Adherent (according to MARS-5 cut-off) (*n*=80, 11.4%)	Non-adherent (according to MARS-5 cut-off) (*n*=619, 88.6%)	*p* value
Mean age (SD)	57.08 (12.92)	54.57 (16.10)	.18[1]
Gender (%)			.17[2]
Female	53 (67.1)	456 (74.1)	
Male	26 (32.9)	158 (25.7)	
Other ("Non-binary")	0	1 (0.9)	
Country (%)			.01[3]
UK	69 (86.3)	579 (93.7)	
Non-UK	11 (13.8)	39 (6.3)	
White ethnicity (%)	77 (96.3)	598 (97.1)	.69[4]
Mean education years (SD)	16.24 (3.28)	16.59 (3.59)	.45[5]
Employment status (%)			.40[6]
Full time	14 (17.5)	121 (19.7)	
Part time	11 (13.8)	77 (12.5)	
Self-employed	7 (8.8)	29 (4.7)	
Homemaker	1 (1.3)	23 (3.7)	
Retired	28 (35.0)	234 (38.1)	
Medically retired	8 (10.0)	67 (10.9)	
Unemployed	2 (2.5)	18 (2.9)	
Full/part-time student	3 (3.8)	20 (3.3)	
Other	6 (7.5)	25 (4.1)	
Relationship status (%)			.39[7]
Single	9 (11.3)	119 (19.3)	
Married or civil partnership	58 (72.5)	355 (57.4)	
Separated or divorced	9 (11.3)	49 (7.9)	
Cohabiting	1 (1.3)	72 (11.7)	
Widowed	2 (2.5)	20 (3.2)	
Other	1 (0.1)	3 (0.4)	
Mean years since diagnosis (SD)	6.60 (8.67)	8.84 (10.02)	.05[8]
More than one LTC (%)	39 (48.8)	359 (58.5)	.09[9]

Mean Depression PHQ-8 (SD)	7.10 (6.26)	9.18 (6.25)	<.01[10]
Mean Anxiety GAD-7 (SD)	5.87 (6.10)	6.65 (5.82)	.26[11]
Functioning WSAS	12.38 (11.04)	17.57 (10.83)	<.01[12]
Intentionally non-adherent MARS-5 (%)	NA	460 (74.8)	NA
Unintentionally non-adherent MARS-5 (%)	NA	516 (84.3)	NA
<100% appointment attendance in last *2-3 months* NRS (%)	6 (9.1)	84 (16.0)	NA
<100% item appointment attendance in last *12 months* NRS (%)	7 (9.1)	105 (17.5)	NA

Adherence measures: MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent'); MARS-5 Intent (Medication Adherence Rating Scale five items intentional non-adherence subscale score: 20='adherent' <20='non-adherent'); MARS-5 Unintent (Medication Adherence Rating Scale five items unintentional non-adherence subscale score: 5='adherent', <5='non-adherent').
Attendance measures: <100% appointment attendance in last 2-3/12 months NRS (%) (Single item appointment attendance in last 2-3/12 months Numerical Rating Scale percentage, binary cut-offs: 100%=adherent; <100%=non-adherent).
Mood and functioning: PHQ-8 (Patient Health Questionnaire 8-items: 0-4 'No significant depressive symptoms', 5-9 'mild depressive symptoms', 10-14 'moderate depressive symptoms', 15-19 'moderately severe depressive symptoms', 20-24 'severe depressive symptoms'; GAD-7 (Generalised Anxiety Disorder 7-items: 0-4 'Minimal', 5- 9'Mild', 10-14 'Moderate', 15-22 'Severe'; WSAS (Work and Social Adjustment Scale: 0-9 'Normal subclinical populations', 10-19 'Normal subclinical populations', 20-40 'moderately severe or worse psychopathology').
Psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (Comprehensive assessment of Acceptance and Commitment Therapy processes total sum score); CompACT total BA (CompACT Behavioral Awareness subscale) CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).
Statistical analyses: [1]t(697)=1.33, *p*=.18, 95% CI=-1.17,6.18 two-tailed; [2]Male versus female as too few expected counts for "other": $\chi^2(1, 693)=1.85$, *p*=.17; [3]$\chi^2(1, 698)=5.89$, p<.01; [4]White versus everything else (as too few expected counts for other groupings): Likelihood ratio(1, 696)=.15, *p*=.69); [5]t(514)=-.74, *p*=.45, 95% CI=-1.29,.58 two-tailed; [6]'Working/in education' versus 'everything else' (as too few expected counts for other): $\chi^2(1, 640)=.70$, *p*=.40; [7]'In a relationship' versus 'not in a relationship' (as too few expected counts for 'other'): $\chi^2(1, 698)=.72$, *p*=.39; [8]t(689)=-1.91, *p*=.05, 95% CI=-4.55,.06 two-tailed; [9]χ^2 (1, 694)=2.73, p<.09; [10]t(695)=-2.78, *p*=<.01, 95% CI=-3.55,-.61 two-tailed; [11]t(695)=-1.11, *p*=.26, 95% CI=-2.15,.59 two-tailed; [12] t(697)=4.02, *p*=<.01, 95% CI= -7.72,-2.65 two-tailed.

Table 4 provides a summary of primary LTCs reported by participants in the online sample (for a more detailed summary of LTCs see Appendix J). There was no significant association between the

proportion of people with Parkinson's disease who were adherent and non-adherent compared with all other LTCs.

Table 4: Primary LTC types of the sample across MARS-5 cut-offs (*n*=695)

	Adherent (according to MARS-5 cut-off) (*n*=80, 11.5%)	Non-adherent (according to MARS-5 cut-off) (*n*=617, 88.5%)	*p* value
Parkinson's Disease *vs.*	36 (45.0)	250 (40.6)	.45[1]
All other LTCs (%)	44 (55.0)	366 (59.4)	
Type of LTC by ICD-11 disease category			
Allergies	1 (1.3)	3 (0.5)	
Autoimmune	20 (25.0)	157 (25.4)	
Birth defect	0	2 (0.3)	
Cancers (all types)	3 (3.8)	9 (1.5)	
Cardiovascular/Circulatory	7 (8.8)	39 (6.3)	
Endocrine	0	18 (2.9)	
Genitourinary	0	2 (.03)	
Hereditary	0	29 (4.7)	
Immunodeficiency	6 (7.5)	11 (1.8)	
Infectious	0	2 (.03)	
Inflammatory	1(1.3)	18 (2.9)	
Neurodegenerative	41 (51.3)	263 (42.6)	
Neurology other	0	1 (0.2)	
Trauma/injury	0	6 (0.9)	
Other conditions	1 (1.3)	55 (8.9)	
LTC not reported	0	2 (.3)	

Adherence measures: ICD-11 (WHO International Classification of Diseases, 11th Revision (ICD-11) MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent').
Statistical analyses: [1]χ^2 (1, 696)=.57, *p*=.45

3.1.4 Attendance at routine clinical appointments

Available data for the single-item percentage of appointments attended in *last 2-3 months* NRS (*n*=592) indicated that *n*=501 (84.6%) people reported they attended 100% of appointments related to their LTC, whilst *n*=91 (15.4%) reported attending <100%. Similarly, for the percentage of appointments attended in last *12 months* NRS (*n*=701), five-hundred and sixty-seven (83.4%) attended 100% of appointments, whilst one-hundred and thirteen (16.6%) attended <100%.

3.1.5 Convergence between MARS-5 and attendance to routine clinical appointments

As indicated in Table 5, *n*=590 people with LTCs completing the single-item percentage of appointments attended in *last 2-3 months* NRS (dichotomised as 100%= 'adherent', <100%=non-adherent) and MARS-5, *n*=60 (10.2%) were identified as 'adherent' and *n*=84 (14.2%) 'non-adherent' on both measures, indicating 24.4% convergence and no significant association between cut-offs (χ^2 (1,590)=2.18, *p*=.13). Of the *n*=678 people completing both the single-item percentage of appointments attended in *last 12 months* NRS (dichotomised in the same way) and MARS-5, *n*=70 (10.3%) were identified as 'adherent' and *n*=105 (15.5%) 'non-adherent' on both measures, indicating 25.8% convergence and no significant association between cut-offs (χ^2(1, 678)=3.47 *p*=<.06).

Table 5: Cross-tabulations of convergence between the MARS-5 and routine appointment attendance measures

		MARS-5		
		Adherent	Non-adherent	Total
Percentage of appts. attended in last 2-3 months NRS	Adherent	60	440	500
	Non-adherent	6	84	90
Total		66	524	590

		Adherent	Non-adherent	Total
Percentage of appts. attended in last 12 months NRS	Adherent	70	496	565
	Non-adherent	7	105	112
Total		77	601	678

3.1.6 Adherence and general functioning

General functioning showed a small significant relationship with the dichotomised MARS-5 total and intentional and unintentional non-adherent subscale dichotomised scores (Table 6). Medium to large relationships between self-reported general functioning, PF processes and anxiety and depression were also identified, falling in expected directions. General functioning showed a small significant relationship with both appointment attendance measures, and medium relationships with mood and PF measures.

3.1.7 Bivariate analyses adherence, psychological flexibility, mood and general functioning

Several demographic and clinical variables were associated with increased cases of *intentional* non-adherence, including being female (69.0% vs. male 59.0%: $\chi^2(1, 689)=5.96$, $p=.01$), younger ('adherers' $M=57.35$, SD=14.86); 'non-adherers' $M=53.47$, SD=16.10: $t(693)=3.08$, $p<.01$, 95% CI=1.41, 6.35, two-tailed) in a relationship (71.9% vs. 63.8% not in a relationship: $\chi^2(1, 694)=4.25$, $p=.03$), having more years of education ('adherers' $M=16.11$, SD=3.41; 'non-adherers' $M=16.79$, SD=3.61: $t(511)=-2.04$, $p=.04$, 95%CI=-1.33,-.02, two-tailed), an LTC that is not Parkinson's Disease (72.4% vs. 56.9%: $\chi^2(1, 692)=17.87$, $p<.01$), more than one LTC ($\chi^2(1, 690)=7.59$, $p<.01$), more years since diagnosis ('adherers' $M=6.95$, SD=8.15; 'non-adherers' $M=9.45$, SD=10.61: $t(685)=-3.14$, $p<.01$, 95% CI=-4.06,-.93, two-tailed) and higher levels of self-reported depression and anxiety (Table 6).

Variables associated with *unintentional* non-adherence included not working (77.4% vs. 69.6%: $\chi^2(1)=4.78$, $p=.02$), having Parkinson's Disease as opposed to any other LTC ($\chi^2(1)=4.57$, $p=.03$), more years since diagnosis ('adherers' $M=7.26$; 'non-adherers' $M=9.06$, $t(682)=-2.07$, $p=.03$, 95% CI=-3.49,-.09, two-tailed), more than one LTC ($\chi^2(1)=5.81$, $p=.01$) higher levels of depression (Table 6) and residing in the UK (75.7% vs. 61.2%:$\chi^2(1)=5.04$, $p=.02$). Therefore, these variables were entered in the first step of the regression models as covariates.

Demographic and clinical variables associated with single-item percentage of appointments attended in *last 2-3 months* NRS binary cut-off include having more than one LTC ($\chi^2(1,587)=8.77$, $p<.01$) and worse mood (Table 6). Variables associated with the single-item percentage of appointments attended in *last 12 months* NRS binary cut-off included being female (84.7% vs. male 54.3%: $\chi^2(1,586)=8.55$, $p<.01$), being younger ('adherers' $M=55.76$; 'non-adherers' $M=50.15$, $t(678)=3.48$, $p<.01$, 95% CI=2.44, 8.77, two-tailed), having more than one LTC ($\chi^2(1)=29.85$, $p<.01$), LTCs other than Parkinson's disease ($\chi^2(1,677)=17.00$, $p<.01$), having more years since diagnosis ('adherers' $M=8.20$;

'non-adherers' *M*=10.19, t(671)=-1.90, *p*=.05, 95% CI=-4.03, .05, two-tailed) and worse mood (Table 6). Therefore, these variables were entered in the first step of corresponding regression models as covariates.

Table 6: Bivariate correlations (Bca 95% CIs) between adherence and appointment attendance, psychological flexibility, and mood and general functioning measures at baseline (sample sizes range from *n*=577 to *n*=700)

	MARS-5 Intent	MARS-5 Unintent	<100% App. 2-3 mo.	<100% App. 12 mo.	WSAS	PHQ-8	GAD-7	AAQ-II	CompACT total	CompACT total OE	CompACT total BA	CompACT total VA
MARS-total dich	*.50** (.45,.56)*	*.61** (.56,.69)*	*.05 (-.01,.12)*	*.06 (-<.01,.12)*	*.15** (.07,.22)*	*.11** (.03,.18)*	*.04 (-.03,.12)*	*.09* (.02,.16)*	*-.07* (-.14,<-.01)*	*-.02 (-.09,.04)*	*-.08* (-.16,-<.01)*	*-.09** (-.16,-.02)*
MARS-5 Intent		*.14** (.06, .21)*	*.07 (<.01,.15)*	*.12** (.04,.19)*	*.22** (.14,.29)*	*.15** (.07,.21)*	*.10* (.03,.16)*	*.16** (.08,.22)*	*-.08* (-.15,<-.01)*	*-.05 (-.11,.02)*	*-.07 (-.14,<.01)*	*-.10** (-.17,-.03)*
MARS-5 Unintent			*.10** (.02,.16)*	*.09** (.02,.16)*	*.11** (.04,.18)*	*.12** (.04,.20)*	*.05 (.02,.13)*	*.07 (-<.01,.14)*	*-.08* (-.16, <.01)*	*-.06 (-.13,.01)*	*-.10** (-.17,-.02)*	*.06 (-.13,.01)*
<100% App. 2-3 mo.				*.61** (.51,.69)*	*.18** (.10,.27)*	*.22** (.1,3.30)*	*.17** (.07,.25)*	*.16** (.07,.25)*	*-.16** (-.24,-.07)*	*-.10** (-.18,-.01)*	*-.12** (-.21,-.04)*	*-.18** (-.26,-.09)*
<100% App. 12 mo.					*.23** (.14,.30)*	*.25** (.17,.33)*	*.24** (.16,.31)*	*.19** (.11,.27)*	*-.19** (-.27,-.12)*	*-.15** (-.22,-.08)*	*-.15** (-.24,-.09)*	*-.18** (-.26,-.11)*
WSAS						.59** (.54,.64)	.44** (.37,.49)	.53** (.47,.59)	-.36** (-.43,-.30)	-.30** (-.37,-.23)	-.29** (-.36,-.23)	-.31** (-.37,-.23)
PHQ-8							79** (.76,.82)	.72** (.69,.76)	-.66** (-.70,-.61)	-.68** (-.64,-.54)	-.53** (-.59,-.48)	-.49** (-.54,-.42)
GAD-7								.75** (.72,.78)	-.68** (-.72,-.65)	-.66* (-.70,-.63)	-.51** (-.56,-.45)	-.46** (-.53,-.40)
AAQ-II									-.73** (-.77,-.70)	-.71** (-.74,-.67)	-.56** (-.60,-.50)	-.50** (-.58,-.43)
CompACT total										.92** (.91,.93)	.74** (.70,.77)	.76** (.73,.79)
CompACT total OE											.59** (.54,.63)	.55* (.49,.60)
CompACT total BA												.34** (.27,.41)

Italics=point biserial Pearson's correlations; **Correlation is significant <.01 (2-tailed); *Correlation is significant <.05 (2-tailed); Bca 95% bootstrapped CI (bias corrected and accelerated *r* value 95% confidence intervals with 1000 samples).

Psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (Comprehensive assessment of Acceptance and Commitment Therapy processes total sum score); CompACT total BA (CompACT Behavioral Awareness subscale); CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).

Adherence and appointment attendance measures: All measures were coded 0='adherent', 1='non-adherent'. %App. 2-3 mo. (Single item percentage of appointment attendance in last 2-3 months numerical rating scale, 100%=adherent, <100%=non-adherent"); %App. 12 mo. (Single item percentage of appointment attendance in last 12 months numerical rating scale, 100%=adherent, <100%=non-adherent"). MARS-5 (Medication Adherence Rating Scale five items total score), MARS-total dich (MARS-5 total score dichotomised), MARS-5 Intent (Medication Adherence Rating Scale five items intentional non-adherence subscale score: 20 coded as 0='adherent', <20 1= 'non-adherent'); MARS-5 Unintent (Medication Adherence Rating Scale five items unintentional non-adherence subscale score: 5 coded as 0='adherent', <5 coded as 1='non-adherent),

Mood and functioning: PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items); WSAS (Work and Social Adjustment Scale).

All biserial relationships between PF processes and the dichotomised adherence outcomes were in expected directions (Table 6). However, intentional non-adherence showed only small significant associations with PF and 'valued action', whilst 'openness to experience' and 'behavioural awareness' subscales were unrelated. Bootstrapped 95% confidence intervals indicated the AAQ-II total score showed a stronger relationship with intentional non-adherence compared to the CompACT. Similarly, unintentional non-adherence showed small associations with PF as measured the CompACT but not the AAQ-II, and 'openness to experience' and 'valued action' subscales were unrelated.

3.1.8 Binomial regressions intentional and unintentional non-adherence

The first logistic regression satisfied all diagnostic assumptions (see file subfolder 'Regression diagnostics' in CD enclosed) and tested the components of the PF model in predicting intentional non-adherence, controlling for relevant demographic and disease variables (Table 7). Demographic and disease variables accounted for 9.7% (Nagelkerke R^2=.097) of the variance in *intentional* non-adherence, significantly improving the model fit ($\chi^2(6)=35.06$, $p<.01$). Specifically, more years of education (OR=1.07, 95% CI=[1.01, 1.13]) and years since diagnosis (OR=1.03, 95% CI=[1.00, 1.05]) was associated with increased odds of intentional non-adherence. Adding PF processes did not significantly improve the model fit ($\Delta\chi^2(2)=.86$ (p=.64), only explaining a further 0.3% (Nagelkerke ΔR^2=.003) of the variance.

Table 7 Multiple binomial logistic regression to predict intentional non-adherence (MARS-5)

Step 1: Demographic and disease variables	*n*=494			R^2=.097
$\chi^2(9)=35.68$, p<.01				
-2LL=586.51 ($\chi^2(8)10.08.$, *p*=.25)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Gender[1]	-.41	-.89, .11	.66	.41, 1.06
Age	<-.01	-.02, .01	.99	.97, 1.01
Relationship status[2]	-.33	-.82, .10	.71	.45, 1.13
Years of education	.06*	.01, .13*	1.07	1.01, 1.13
LTC type[3]	<-.01	-.58, .62	.99	.56, 1.73
More than one LTC	.24	-.21, .68	1.27	.83, 1.93
Years since diagnosis	.03*	<.01, .05*	1.03	1.00, 1.05
Depression (PHQ-8)	.03	-.01, .09	1.03	.98, 1.09
Anxiety (GAD-7)	.00	-.05, .06	1.00	.95, 1.06
Step 2: Psychological flexibility processes				R^2=.10
$\Delta\chi^2$ (2)=.86 (*p*= .64)				
-2LL=585.65 ($\chi^2(8)$ 9.11, *p*=.33)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	-<.01	-.03, .03	1.00	.96, 1.03
Valued Action (CompACT total VA)	-.01	-.04, .01	.98	.95, 1.01

Adherent=0, Non-adherent=1; [1]Female=0 with "other" case excluded; [2]In a relationship=0; [3]Parkinson's disease =0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples); *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total VA (Comprehensive assessment of Acceptance and Commitment Therapy processes Valued Action subscale); PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items)

The second logistic regression satisfied all diagnostic assumptions and tested the components of the PF model in predicting *unintentional* non-adherence, controlling for relevant demographic and disease variables (Table 8). Demographic and disease variables were entered in the first step and PF scores in the second step. Demographic and disease variables accounted for 8.3%

(Nagelkerke R^2=.083) of the variance in unintentional non-adherence, significantly improving the model fit $\chi^2(5)=36.01$ ($p<.001$). Having LTCs other than Parkinson's disease (OR=.43, 95% CI=[.27,.69]) was associated with decreased odds of unintentional non-adherence. Conversely, more years since diagnosis (OR=1.02, 95% CI=[1.00,.1.05]), having more than one LTC (OR=1.74, 95% CI=[1.16,2.59]), and higher levels of depression (OR=1.05, 95% CI=[1.02, 1.09]) was associated with increased odds of unintentional non-adherence. Adding behavioural awareness (i.e. 'Aware' processes, incorporating present moment awareness and self-as-context) did not significantly improve the model fit ($\Delta\chi^2(1)=2.28$, p=.13), 2LL=664.38, Nagelkerke ΔR^2=.005).

Table 8: Multiple binomial logistic regression to predict unintentional non-adherence (MARS-5)

Step 1: Demographic and disease variables	*n*=617			R^2=.083
χ^2 (5)=36.01 (*p*<.001)				
-2LL=670.25 (χ^2(8)8.23, *p*=.41)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Occupational status[1]	.11	-.35, .57	1.12	.74, 1.69
LTC type[2]*	-.82*	-1.3, -.34*	.43	.27, .69
Years since diagnosis	.02*	<.07, .05*	1.02	1.0, 1.05
More than one LTC	.55*	.13, .99*	1.74	1.16, 2.59
Depression (PHQ-8)	.05*	.02, .09*	1.05	1.02, 1.09
Step 2: Psychological flexibility processes $\Delta\chi^2$ (1)=2.28, *p*=.13)				R^2=.088
-2LL=667.97 (χ^2(8)5.33, *p*=.72)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Behavioural awareness (CompACT total BA)	-.02	-.07, .01	.97	.93, 1.0

Adherent=0, Non-adherent=1; [1]Working=0; [2]Parkinson's disease=0; [3]UK=0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples); *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total BA (Comprehensive assessment of Acceptance and Commitment Therapy processes Behavioural Awareness subscale); PHQ-8 total (Patient Health Questionnaire 8-items).

3.1.9 Binomial regressions routine appointment attendance

The third logistic regression did not satisfy the linearity of the logit assumption for the AAQ-II (*p*=.02) and standardized residuals were slightly exceeded (6% >1.96 SD), so should be interpreted with caution in testing components of the PF model in predicting nonattendance to related health care appointments in the last 2-3 months (i.e. anything less than 100%) controlling

for relevant demographic and disease variables (Table 9). Demographic and disease variables accounted for 9.3% (Nagelkerke R^2=.093) of the variance in nonattendance, significantly improving the model fit ($\chi^2(3)=32.29$, $p<.01$). Being more depressed (OR=1.10, 95% CI=[1.04, 1.17]) was associated with increased odds of nonattendance. Adding PF processes did not significantly improve the model fit ($\Delta\chi^2(4)=7.39$, p=.11, 2LL=466.68), explaining a further 2% (Nagelkerke ΔR^2=.02) of the variance. However, engaging in valued action (OR=.95, 95% CI=[.92,.98]) was associated with decreased odds of non-attendance.

Table 9: Multiple binomial logistic regression to predict appointment nonattendance in the last 2-3 months

Step 1: Demographic and disease variables	*n*=587			R^2=.093
χ^2 (3) = 32.29 (*p*<.01)				
-2LL = 474.08 (χ^2(8)6.01, *p*=.64)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
More than one LTC	.46	-.06,.97	1.59	.94, 2.67
Depression (PHQ-8)	.09*	.04,.15*	1.10	1.04, 1.17
Anxiety (GAD-7)	-.01	-.07,.04	.98	.92,1.04
Step 2: Psychological flexibility processes				R^2=.113
$\Delta\chi^2$ (4) = 7.39 (*p*=.11)				
-2LL = 466.68 (χ^2(8)10.36, *p*=.24)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	<.01	-.03,.045	1.00	.96,1.04
Openness to Experience subscale (CompACT total OE)	.02	<-.00,.06	1.02	.99,1.06
Behavioural awareness (CompACT total BA)	-.01	-.065,.02	.98	.93,1.02
Valued Action (CompACT total VA)	-.04*	-.08,-.01*	.95	.92,.98

Adherent=0, Non-adherent=1; [1]Female=0 with "other" case excluded; [2]White=0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples); *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total BA (Comprehensive assessment of Acceptance and Commitment Therapy processes Behavioral Awareness subscale); CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale; PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items)

The final logistic regression satisfied all diagnostic assumptions and tested the components of the PF model in predicting nonattendance to related health care appointments in the last *12 months* (i.e. anything less than 100%) controlling for relevant demographic and disease variables (Table 10). Demographic and disease variables accounted for 16.1% (Nagelkerke R^2=.161) of the variance in nonattendance, significantly improving the model fit (χ^2(7)=65.53 (p<.01). Having more than one LTC (OR=1.10, 95% CI=[.55,2.20]) and higher levels of depression (OR=1.05, 95% CI=[1.00,1.11]) was associated with increased odds of nonattendance. Adding PF processes

did not significantly improve the model fit ($\Delta\chi^2$=3.42, p=.48, 2LL= 515.31), explaining a further 0.8% (Nagelkerke ΔR^2=.008) of the variance and none of the processes were related.

Table 10: Multiple binomial logistic regression to predict appointment nonattendance in the last 12 months

Step 1: Demographic and disease variables	n=658			$\boldsymbol{R^2}$=. 161
χ^2 (7) = 65.53 (p<.01)				
-2LL = 518.74 (χ^2(8)4.65, p=.79)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Age	<-.01	-.02,.012	.99	.97,1.01
Gender[1]	-.34	-1.12,.27	.70	.37,1.34
More than one LTC	.95*	.44,1.62*	2.60	1.50,4.51
LTC type[2]	.10	-.57,.85	1.10	.55,2.20
Years since diagnosis	.01	<-.01,.03	1.01	.99,1.03
Depression (PHQ-8)	.05*	<-.01,.11*	1.05	1.00,1.11
Anxiety (GAD-7)	.03	-.02,.09	1.03	.97,1.09
Step 2: Psychological flexibility processes				$\boldsymbol{R^2}$=.169
$\Delta\chi^2$ (4) = 3.42 (p=.48)				
-2LL = 515.31 (χ^2(8)6.68, p=.57)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	-.01	-.05,.02	.98	.94,1.02
Openness to Experience subscale (CompACT total OE)	<.01	-.02,.04	1.00	.97,1.04
Behavioural awareness (CompACT total BA)	-.01	-.06,.02	.98	.93,1.02
Valued Action (CompACT total VA)	-.02	-.07,<.01	.97	.93,1.00

Adherent=0, Non-adherent=1; [1]Female=0 with "other" case excluded; [2]Parkinson's Disease=0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples);; *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total BA (CompACT Behavioral Awareness subscale); CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale; PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items)

3.2 Longitudinal analyses

3.2.1 Demographic and disease characteristics of the follow-up sample

Of the *n*=701 adults who completed the baseline questionnaires *n*=341 completed the 3-month follow-up questionnaire. However, five were excluded, either not having provided an identifying email/name to link-up the data (3) or was a duplicate (2). On average, the *n*=336 participants (48.07%) completed the follow-up questionnaire *M*=94.63 (SD=5.66) days after baseline.

Consistent with the baseline only sample (*n*=365), follow-up participants (*n*=336) were mostly white-Caucasian (97.33: $\chi^2(1,698)=.229$, $p=.63$) and female (72.5%: $\chi^2(1,695)=.282$, $p=.59$). However, the follow-up sample were on average significantly older (*M*=56.72, SD=15.20: t(699)=-2.893, $p=<.01$, 95% CI= -5.77, -1.10, two-tailed). Most resided in the UK (92.9%) compared to other countries (6.9%: $\chi^2(1,700)=.020$, $p=.88$). Forty-two percent of participants were retired, 12.9% medically retired, 35.7% were in full- or part-time employment or education, 3.3% were homemakers and 1.8% were unemployed. There were significantly fewer participants working/in education in the follow-up sample ($\chi^2(1,642)=7.19$, $p=<.01$). Sixty-one percent of participants were married or in a civil partnership, 8.3% cohabiting, 17.9% single, 9.2% separated or divorced, 2.4% widowed and 0.6% described their relationship status as "other", showing similar proportions of participants in relationships compared to the baseline sample ($\chi^2(1,700)=0.42$, $p=.83$).

A larger proportion of participants in the follow-up sample were diagnosed with Parkinson's disease (46.9% versus 36.1%: $\chi^2(1,698)=8.35$, $p<.01$). Similar to the baseline only sample, 55.8%

reported more than one LTC (χ^2(1,696)=.59, p<.43). Follow-up participants on average reported similar years of disease duration with their primary LTC (M=8.23, SD=9.82: t(691)=1.05, p=.29, 95%CI=-.69,-2.31, two-tailed) and as shown in Table 11 mild levels of anxiety (t(697)=1.81, p=.06, 95%CI=-.06,1.67), but also reported significantly lower levels of depression (t(697)=1.98, p=.04, 95%CI=<.01,1.86). Compared to the baseline only sample, the follow-up sample had a lower proportion of non-adherers according to the MARS-5 (85.0% versus 90.0%, χ^2(1,698)=4.95, p=.02), but similar rates of intentional (64.8% versus 67.0%, χ^2(1, 693)=.39, p=.63) and unintentional non-adherence (73.5% versus 75.6% χ^2(1,692)=.38, p=.53).

3.2.2 Descriptive statistics

All measures showed Means/*SD*s that were largely consistent with measure validation samples and the baseline sample and missing data was minimal, therefore summed scores were used in all analyses (Table 11).

Table 11: Follow-up descriptive data for measures in the adult sample

Measure	*n*	Mean (SD)	Skewness (SE)	Kurtosis (SE)	Reliability Cronbach α
Adherence and attendance					
MARS-5 total sum score	336	21.38 (13.40)	-1.79 (.13)*	4.60 (.26)	.77
MARS-5 total mean item score adjusted (<20% of missing items)	333	4.32 (.65)	-1.34 (.13)*	1.97 (.26)	
MARS-5 Intent sum score	333	17.60 (2.81)	-1.35 (.13)	1.88 (.26)	
MARS-5 Unintent sum score	336	3.94 (.87)	-.48 (.13)	-.34 (.26)	
Single item appointment attendance in last *2-3 months* NRS (%)	288	91.07 (25.49)	-3.00 (.14)*	7.56 (.28)	NA
Single item appointment attendance in last *12 months* NRS (%)	332	94.71 (17.31)	-4.28 (.13)*	18.70 (.26)	NA
Functioning					
WSAS total sum score	332	16.05 (10.76)	.40 (.13)	-.80 (.26)	.93
Mood					
PHQ-8 total sum score	336	8.27 (6.21)	.74 (.13)	-.32 (.26)	.89
PHQ-8 total mean item score adjusted (<25% of missing items)	336	1.03 (.77)	.73 (.13)	-.33 (.26)	
GAD-7 total sum score	336	6.03 (5.84)	1.01 (.13)*	.06 (.26)	.93
GAD-7 total mean item score adjusted (<25% of missing items)	336	.86 (.83)	.99 (.13)	<.01 (.26)	
Psychological flexibility processes					
AAQ-II total sum score	335	19.69 (10.25)	.69 (.13)	-.29 (.26)	.94

AAQ-II total mean item score adjusted (<25% of missing items)	335	2.81 (1.46)	.68 (.13)	-.30 (.26)	
CompACT total score	336	89.66 (23.94)	-.25 (.13)	-.30 (.26)	.91
CompACT total mean item score adjusted (<25% of missing items)	336	3.92 (1.04)	-.25 (.13)	-.25 (.26)	
OE subscale sum score	336	35.22 (12.24)	-.06 (.13)	-.57 (.26)	.85
OE mean item score adjusted (<25% of missing items)	333	3.55 (1.22)	-.08 (.13)	-.55 (.26)	
BA subscale sum score	336	17.91 (7.42)	-.09 (.13)	-.88 (.26)	.85
BA mean item score adjusted (<25% of missing items)	336	3.59 (1.48)	-.10 (.13)	-.86 (.26)	
VA subscale sum score	336	36.46 (8.21)	-.69 (.13)	.33 (.26)	.85
VA mean item score adjusted (<25% of missing items)	336	4.57 (1.02)	-.68 (.13)	.21 (.26)	

*****Non-normal distributions

Adherence measures: MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent'); MARS-5 Intent (Medication Adherence Rating Scale five items intentional non-adherence subscale score: 20='adherent' <20='non-adherent'); MARS-5 Unintent (Medication Adherence Rating Scale five items unintentional non-adherence subscale score: 5='adherent', <5='non-adherent').

Attendance measures: <100% appointment attendance in last 2-3/12 months NRS (%) (Single item appointment attendance in last 2-3/12 months Numerical Rating Scale percentage, binary cut-offs: 100%=adherent; <100%=non-adherent).

Mood and functioning: PHQ-8 (Patient Health Questionnaire 8-items: 0-4 'No significant depressive symptoms', 5-9 'mild depressive symptoms', 10-14 'moderate depressive symptoms', 15-19 'moderately severe depressive symptoms', 20-24 'severe depressive symptoms'; GAD-7 (Generalised Anxiety Disorder 7-items: 0-4 'Minimal', 5- 9'Mild', 10-14 'Moderate', 15-22 'Severe'; WSAS (Work and Social Adjustment Scale: 0-9 'Normal subclinical populations', 10-19 'Normal subclinical populations', 20-40 'moderately severe or worse psychopathology').

Psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (CompACT total sum score); CompACT total BA (CompACT Behavioral Awareness subscale) CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).

3.2.3 Test-retest reliability of all scales

Intraclass Correlation Coefficients (ICC) for baseline and three-month follow-up established scales data are shown in Table 12, which according to established cut-offs for 95% confidence intervals indicate most measures demonstrated acceptable levels of reliability (moderate to excellent) indicating they are stable over time (Koo & Li, 2016). However, the MARS-5 total and intentional dichotomised ratings at follow-up were poor to moderate.

Table 12: Test-retest statistics for all scales at baseline and three months

Measure	*n*	Baseline Mean (SD)	Follow-up Mean (SD)	ICC (*p*-value)	95% CI
Adherence and attendance					
MARS-5 total dichotomised	335	.86 (.33)	.85 (.35)	.31 (<.01)	.19, .47
MARS-5 Intent dichotomised	331	.65 (.47)	.62 (.48)	.24 (<.01)	.064, .39
MARS-5 Unintent dichotomised	332	.73 (.44)	.71 (.45)	.75 (<.01)	.69, .79
Single item appointment attendance in last 2-3 months NRS (%)	249	.17 (.38)	.16 (.37)	.66 (<.01)	.56, .73
Single item appointment attendance in last 12 months NRS (%)	329	.15 (.36)	.16 (.37)	.63 (<.01)	.54, .70
Functioning					
WSAS total score	336	15.98 (11.01)	16.08 (10.76)	.92 (<.01)	.91, .94
Mood					
PHQ-8 total score	335	8.45 (6.24)	8.28 (6.22)	.88 (<.01)	.85, .90
GAD-7 total score	335	6.1 (5.83)	6.04 (5.84)	.87 (<.01)	.84, .90
Psychological Flexibility processes					
AAQ-II	335	19.78 (10.53)	19.69 (10.25)	.91 (<.01)	.89, .93

CompACT total score	336	83.07 (21.41)	89.59 (23.95)	.87 (<.01)	.78, .91
OE subscale	336	34.77 (12.04)	35.22 (12.24)	.87 (<.01)	.84, .90
BA subscale	336	16.73 (6.07)	17.91 (7.42)	.75 (<.01)	.69, .80
VA subscale	336	31.56 (7.49)	36.46 (8.21)	.72 (<.01)	.32, .85

ICC (Intraclass Correlation Coefficient using an absolute agreement definition); 95% CI (95% Confidence Interval).

Adherence measures: MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent'); MARS-5 Intent (Medication Adherence Rating Scale five items intentional non-adherence subscale score: 20='adherent' <20='non-adherent'); MARS-5 Unintent (Medication Adherence Rating Scale five items unintentional non-adherence subscale score: 5='adherent', <5='non-adherent').

Attendance measures: <100% appointment attendance in last 2-3/12 months NRS (%) (Single item appointment attendance in last 2-3/12 months Numerical Rating Scale percentage, binary cut-offs: 100%=adherent; <100%=non-adherent).

Mood and functioning: PHQ-8 (Patient Health Questionnaire 8-items: 0-4 'No significant depressive symptoms', 5-9 'mild depressive symptoms', 10-14 'moderate depressive symptoms', 15-19 'moderately severe depressive symptoms', 20-24 'severe depressive symptoms'; GAD-7 (Generalised Anxiety Disorder 7-items: 0-4 'Minimal', 5- 9'Mild', 10-14 'Moderate', 15-22 'Severe'; WSAS (Work and Social Adjustment Scale: 0-9 'Normal subclinical populations', 10-19 'Normal subclinical populations', 20-40 'moderately severe or worse psychopathology').

Psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (CompACT total sum score); CompACT total BA (CompACT Behavioral Awareness subscale) CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).

3.2.4 Demographic and disease characteristics for adherent and non-adherent subgroups

Consistent with the baseline total sample, 85.4% of the follow-up sample were non-adherent, of which 62.8% were intentionally non-adherent and 83.2% unintentionally non-adherent (Table 13). There was still a significantly larger proportion of non-adherers from the UK compared to adherers. Non-adherers reported significantly worse general functioning and anxiety and

depression compared to adherers. However, there were no differences for any other demographic and disease variables.

Table 13: Participant characteristics at follow-up according to MARS-5 cut-offs (*n*=336)

	Adherent (according to MARS-5 cut-off) (*n*=49, 14.6%)	Non-adherent (according to MARS-5 cut-off) (*n*=287, 85.4%)	*p* value
Mean age (SD)	56.65 (13.73)	56.73 (15.46)	.97[1]
Gender (%)			.38[2]
Female	33 (67.3)	209 (73.1)	
Male	16 (32.7)	76 (26.6)	
Other ("Non-binary")	0	1 (0.4)	
Country (%)			.16[3]
UK	43 (87.8)	269 (93.7)	
Non-UK	7 (14.0)	17 (5.9)	
White ethnicity (%)	47 (95.9)	279 (97.6)	.53[4]
Mean education years (SD)	16.71 (2.96)	16.46 (3.63)	.68[5]
Employment status (%)			.02[6]
Full time	13 (26.5)	42 (14.7)	
Part time	6 (12.2)	28 (9.8)	
Self-employed	3 (6.1)	16 (5.6)	
Homemaker	0	11 (3.9)	
Retired	17 (34.7)	124 (43.5)	
Medically retired	4 (8.2)	39 (13.7)	
Unemployed	1 (2.0)	5 (1.8)	
Full/part-time student	3 (6.0)	8 (2.8)	
Other	2 (4.0)	12 (4.2)	
Relationship status (%)			.56[7]
Single	5 (10.0)	55 (19.2)	
Married or civil partnership	34 (68.0)	173 (60.5)	
Separated or divorced	8 (16.3)	23 (8.0)	
Cohabiting	2 (4.1)	26 (9.1)	
Widowed	0	8 (2.8)	

Other	0	2 (0.7)	
Mean years since diagnosis (SD)	6.0 (6.71)	8.62 (10.22)	.08[8]
More than one LTC (%)	23(46.9)	164 (57.3)	.37[9]
Mean Depression PHQ-8 (SD)	6.31 (5.86)	8.81 (6.24)	.01[10]
Mean Anxiety GAD-7 (SD)	4.52 (5.72)	6.42 (5.82)	.03[11]
Functioning WSAS	12.71 (10.19)	16.6 (10.77)	.01[12]
Intentionally non-adherent MARS-5 (%)	NA	209 (73.6)	NA
Unintentionally non-adherent MARS-5 (%)	NA	238 (83.2)	NA
Single item appointment attendance in last *2-3 months* NRS (%)	6 (14.3)	45 (18.3)	NA
Single item appointment attendance in last *12 months* NRS (%)	2 (4.1)	54 (19.1)	NA

Adherence measures: MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent'); MARS-5 Intent (Medication Adherence Rating Scale five items intentional non-adherence subscale score: 20='adherent' <20='non-adherent'); MARS-5 Unintent (Medication Adherence Rating Scale five items unintentional non-adherence subscale score: 5='adherent', <5='non-adherent').

Attendance measures: <100% appointment attendance in last 2-3/12 months NRS (%) (Single item appointment attendance in last 2-3/12 months Numerical Rating Scale percentage, binary cut-offs: 100%=adherent; <100%=non-adherent).

Mood and functioning: PHQ-8 (Patient Health Questionnaire 8-items: 0-4 'No significant depressive symptoms', 5-9 'mild depressive symptoms', 10-14 'moderate depressive symptoms', 15-19 'moderately severe depressive symptoms', 20-24 'severe depressive symptoms'; GAD-7 (Generalised Anxiety Disorder 7-items: 0-4 'Minimal', 5- 9'Mild', 10-14 'Moderate', 15-22 'Severe'; WSAS (Work and Social Adjustment Scale: 0-9 'Normal subclinical populations', 10-19 'Normal subclinical populations', 20-40 'moderately severe or worse psychopathology').

Psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (CompACT total sum score); CompACT total BA (CompACT Behavioral Awareness subscale) CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).

Statistical analyses: [1]t(334)=.032, p=.97, 95% CI= -4.70,4.55 two-tailed; [2]Male versus female (as too few expected counts for "other"): (χ^2 (1, 334)=.75, p=.38); [3]Likelihood ratio (1, 336)=1.94, p=.16); [4]White versus everything else (as too few expected counts for other groupings): Likelihood ratio(1, 335)=.38, p=.53); [5]t(261)=.40, p=.68, 95% CI=-.97,1.49 two-tailed; [6]'Working/in education' versus everything else (as too few expected counts for other categories): χ^2 (1, 309)=5.11, p=.02);

[7]'In a relationship' versus 'not in a relationship' (as too few expected counts for other categories): $\chi^2(1, 336)=.34$, $p=.56$); [8]$t(330)=-1.72$, $p=.08$, 95% CI=-5.60,.36 two-tailed; [9]$\chi^2(1, 335)=.80$, $p=.37$); [10]$t(333)=-2.59$, $p=.01$, 95% CI= -4.40, -.60 two-tailed; [11]$t(333)=-2.09$, $p=.03$, 95% CI= -3.68,-.11 two-tailed [12]$t(334)=-2.38$, $p=<.01$, 95% CI= -7.19-, -.68 two-tailed.

Table 14 provides a summary of primary LTCs reported by participants from the follow-up sample (see Appendix K for a more detailed summary). There was no significant association between proportion of people with Parkinson's disease who were adherent and non-adherent and all other LTCs.

Table 14: Primary LTC types of the follow-up sample across MARS-5 cut-offs (*n*=336)

	Adherent (according to MARS-5 cut-off) (*n*=49, 14.6%)	Non-adherent (according to MARS-5 cut-off) (*n*=287, 85.4%)	*p* value
Parkinson's Disease *vs.*	18 (36.7)	139 (48.6)	.12[1]
All other LTCs (%)	31 (63.3)	147 (51.4)	
Type of LTC by ICD-11 disease category			
Allergies	0	2 (.07)	
Autoimmune	10 (20.4)	71 (24.7)	
Birth defect	0	1 (0.3)	
Cancers (all types)	2 (4.1)	3 (1.0)	
Cardiovascular/Circulatory	6 (12.2)	12 (4.2)	
Endocrine	1 (2.0)	7 (2.4)	
Genitourinary	0	1 (0.3)	
Hereditary	1 (2.0)	9 (3.1)	
Immunodeficiency	4 (8.2)	7 (2.4)	
Infectious	1 (2.0)	0	
Inflammatory	1 (2.0)	11 (3.8)	
Neurodegenerative	22 (44.9)	142 (49.5)	
Trauma/injury	0	2 (0.7)	
Other conditions	1 (2.0)	18 (6.3)	
LTC not reported	0	1 (.03)	

Adherence measures: ICD-11 (WHO International Classification of Diseases, 11th Revision (ICD-11) MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent').

Statistical analyses: [1]χ^2 (1, 335)=2.36, *p*=.12.

3.2.5 Bivariate analyses adherence, psychological flexibility and mood and general functioning

Consistent with baseline estimates, all biserial relationships between PF processes at baseline and the dichotomised adherence outcomes at 3-months follow-up were in expected directions (Table 15). Intentional non-adherence showed only small significant associations with PF, and 'openness to experience' and 'behavioural awareness' subscales were unrelated. Similarly, unintentional non-adherence showed small or inconsistent associations with PF as measured by the AAQ-II, but not the CompACT. PF processes significantly predicted general functioning and anxiety and depression at follow-up in expected directions, showing mostly medium to large effects.

Table 15: Bivariate correlations (Bca 95% CIs) between baseline psychological flexibility and adherence and appointment attendance, and mood and general functioning measures at follow-up (sample sizes range from *n*=286 to *n*=336)

	MARS-5 Intent FU	MARS-5 Unintent FU	<100% App. 2-3 mo. FU	<100% App. 12 mo. FU	WSAS FU	PHQ-8 FU	GAD-7 FU	AAQ-II	CompACT total	CompACT total OE	CompACT total BA	CompACT total VA
MARS-total dich FU	*.53** (.46,.60)*	*.64** (.56,.72)*	*.03 (-.07,.13)*	*.15** (.07,.21)*	*.12* (.01,.23)*	*.17** (.08,.25)*	*.14** (.05,.21)*	*.16** (.07,.24)*	*-.10* (-.19,-.01)*	*-.08 (-.17,.01)*	*-.09 (-.19,.01)*	*-.10* (-.19,<-.01)*
MARS-5 Intent FU		*17** (.06,.29)*	*.01 (-.10,.13)*	*.15* (.04,.26)*	*.19** (.09,.29)*	*.22** (.11,.31)*	*.18** (.08,.28)*	*.16** (.06,.25)*	*-.11* (-.21,<-.01)*	*-.08 (-.19,.01)*	*-.06 (-.16,.05)*	*-.13* (-23,-01)*
MARS-5 Unintent FU			*.09 (-.01,.18)*	*.13 (<-.01,.19)*	*.10 (-.01,.20)*	*.18** (.08,.27)*	*.13* (.03,.22)*	*.12* (.02,.21)*	*-.09 (-.19,<.01)*	*-.07 (-.17,.02)*	*-.08 (-.17,.01)*	*-.08 (-.18,<.01)*
<100% App. 2-3 mo. FU				*.561** (.43,.68)*	*.03 (-.07.15)*	*.09 (-.02.21)*	*.08 (-.03,.20)*	*.13* (.01,.24)*	*-.11 (-.23,.01)*	*-.07 (-.18,.05)*	*-.02 (-.13,.08)*	*-.18** (-.31,-.05)*
<100% App. 12 mo. FU					*.19 (.08,.31)*	*.30 (.19,.42)*	*.24 (.12,.37)*	*.25 (.14,.37)*	*-.25 (-.36,-.14)*	*-.19 (-.31,-.08)*	*-.18 (-.29,-.07)*	*-.24** (-.36,-.12)*
WSAS FU						.64** (.57,.70)	.46** (.37,.55)	.52** (.43,.60)	-.39** (-.47,-.29)	-.31** (-.41,-.20)	-.31** (-.40,-.20)	-.37** (-.46,-.27)
PHQ-8 FU							.79** (.75,.84)	.70** (.62,.76)	-.60** (-.66,-.52)	-.53** (-.61,-.44)	-.47** (-.55,-.39)	-.46** (-.55,-.37)
GAD-7 FU								.70** (.63,.77)	-.62** (-.69,-.55)	-.59** (-.66,-.51)	-.50** (-.58,-.42)	-.41** (-.51,-.31)

Italics=point biserial Pearson's correlations; **Correlation is significant <.01 (2-tailed); *Correlation is significant <.05 (2-tailed); Bca 95% bootstrapped CI (bias corrected and accelerated *r* value 95% confidence intervals with 1000 samples).

Baseline psychological flexibility processes: AAQ-II (Acceptance and Action Questionnaire II); CompACT total (CompACT total sum score); CompACT total BA (CompACT Behavioral Awareness subscale); CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale).

Adherence and appointment attendance measures: All measures were coded 0='adherent', 1='non-adherent'. %App. 2-3 mo. FU (Single item percentage of appointment attendance in last 2-3 months numerical rating scale follow-up score, 100%=adherent, <100%=non-adherent"); %App. 12 mo. FU (Single item percentage of appointment attendance in last 12 months numerical rating scale follow-up score, 100%=adherent, <100%=non-adherent"). MARS-5 (Medication Adherence Rating Scale five items total score), MARS-total dich FU (MARS-5 total score at follow-up dichotomised), MARS-5 Intent FU (Medication Adherence Rating Scale five items intentional non-adherence subscale score at follow-up: 20 coded as 0='adherent', <20 1= 'non-adherent'); MARS-5 Unintent FU (Medication Adherence Rating Scale five items unintentional non-adherence subscale score at follow-up: 5 coded as 0='adherent', <5 coded as 1='non-adherent),

Mood and functioning: PHQ-8 total FU (Patient Health Questionnaire 8-items at follow-up), GAD-7 FU (Generalised Anxiety Disorder scale 7-items at follow-up); WSAS FU (Work and Social Adjustment Scale at follow-up).

3.2.6 Binomial regressions intentional and unintentional non-adherence

A data-driven approach was taken with regards to inclusion of covariates in hierarchical binomial regression models, where only demographic and disease variables significantly related with non-adherence outcomes at the bivariate level (p<.05) at baseline were entered in the first step. Therefore, each model included slightly different variables. Mood measured by the PHQ-8 (baseline M=8.45, SD=6.24; follow-up M=8.28, SD=6.22: t(334)=-8.04, p=.44, 95% CI=-.25,60, two-tailed) and GAD-7 (baseline M=6.14, SD=5.83 follow-up M=6.04, SD=5.84: t(335)=.50, p=.61, 95% CI= -.30, .52, two-tailed) did not significantly change over time. Therefore, baseline values where relevant were entered in the first step of the regression. PF processes measured by the CompACT significantly improved over time (baseline M=83.07, SD=21.41, follow-up M=89.59, SD=23.95: t(335)=-8.37, p<.01, 95% CI=-8.05, -4.9, two-tailed), including the BA (baseline M=16.73, SD=6.07, follow-up M=17.91, SD=7.42: t(335)=-3.62, p<.01, 95% CI=-1.82-.54, two-tailed) and VA subscales (baseline M=31.56, SD=7.49, follow-up M=36.46, SD=8.21: t(335)=-14.06, p<.01, 95% CI=-5.58,-4.21, two-tailed). PF processes were entered in the following step to assess their predictive power on non-adherence after demographic and disease variables were accounted for.

The first logistic regression satisfied diagnostic assumptions and tested the components of the PF model in predicting intentional non-adherence at 3-month follow-up controlling for relevant demographic and disease variables (Table 16). Demographic and disease variables accounted for (8.3%) (Nagelkerke R^2=.083) of the variance in *intentional* non-adherence but did not significantly improve the model fit ($\chi^2(9)=15.89$, p=.06. Specifically, only more years since diagnosis (OR=1.04, 95% CI=[1.00, 1.07]) was associated with increased odds of intentional non-adherence. Adding PF processes did not significantly improve the model fit ($\Delta\chi^2$ (2)=2.59, p=.27), only explaining a further 1.4% (Nagelkerke ΔR^2=.014) of the variance.

Table 16: Multiple binomial logistic regression to predict intentional non-adherence at 3-months follow-up (MARS-5)

Step 1: Baseline demographic and disease variables	*n*=254			R^2=.083
($\chi^2(9)$=15.89, *p*=.06				
-2LL=314.34 ($\chi^2(8)$7.5, *p*=.48)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Gender[1]	-.08	-.73, .58	.91	.48, 1.73
Age	<-.01	-.03, .01	.99	.97, 1.01
Relationship status[2]	-.08	-.78, .54	.92	.49, 1.73
Years of education	.01	-.06, .10	1.01	.94, 1.09
LTC type[3]	-.20	-1.11, .62	.81	.37, 1.75
More than one LTC	.58	<-.01, 1.28	1.78	.98, 3.25
Years since diagnosis	.03*	<.01, .08*	1.04	1.00, 1.07
Depression (PHQ-8)	.01	-.06, .09	1.01	.94, 1.08
Anxiety (GAD-7)	.02	-.06, .12	1.02	.95, 1.11
Step 2: Baseline psychological flexibility processes				R^2=.097
$\Delta\chi^2$ (2)=2.59, *p*=.27				
-2LL=311.74 ($\chi^2(8)$7.63, *p*=.47)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	.02	-.02, .07	1.02	.97, 1.07
Valued Action (CompACT total VA)	-.02	-.07, .03	.97	.93, 1.02

Adherent=0, Non-adherent=1; [1]Female=0 with "other" case excluded; [2]In a relationship=0; [3]Parkinson's disease =0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit), *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples); *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total VA (CompACT Valued Action subscale); PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items)

The second logistic regression satisfied diagnostic assumptions and tested the components of the PF model in predicting *unintentional* non-adherence at 3-month follow-up controlling for relevant demographic and disease variables (Table 17). Demographic and disease variables were entered in the first step and PF scores in the second step. Demographic and disease

variables accounted for 11.7% (Nagelkerke R^2=.117) of the variance in unintentional non-adherence, significantly improving the model fit (χ^2 (6)=26.18 (p<.01). Having LTCs other than Parkinson's disease (OR=.44, 95% CI=[.23,.84]) was associated with decreased odds of unintentional non-adherence. Adding PF processes did not significantly improve the model fit ($\Delta\chi^2$ (2)=.003 (p=.95), nor did it explain any further variance (Nagelkerke ΔR^2=0).

Table 17: Multiple binomial logistic regression to predict unintentional non-adherence at 3-months follow-up (MARS-5)

Step 1: Baseline demographic and disease variables	n=303		$\boldsymbol{R^2}$=.117	
χ^2 (6)=26.18 (p<.001)				
-2LL=344.17 (χ^2(8)6.95, p=.54)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Occupational status[1]	.26	-.40, .86	1.30	.73, 2.32
LTC type[2]	-.81*	-1.53, -.21*	.44	.23, .84
Years since diagnosis	.01	-.01, .05	1.01	.98, 1.04
More than one LTC	.30	-.28, .93	1.36	.76, 2.42
Depression (PHQ-8)	.08*	.03, .14*	1.08	1.03, 1.13
Country of residence (UK vs. all other countries)[3]	-.70	-1.77, .27	.49	.18, 1.29
Step 2: Baseline psychological flexibility processes			$\boldsymbol{R^2}$=.117	
$\Delta\chi^2$ (1)=.003(p=.95)				
-2LL=344.16 (χ^2(8)4.38, p=.82)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	<.01	-.03, .04	1.00	.96, 1.03

Adherent=0, Non-adherent=1; [1]Working=0; [2]Parkinson's disease=0; [3]UK=0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples); *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total BA (CompACT Behavioural Awareness subscale); PHQ-8 total (Patient Health Questionnaire 8-items).

3.2.7 Binomial regressions routine appointment attendance

The third logistic regression did not satisfy the linearity of the logit assumption for the CompACT 'behavioural awareness' (p=.05), so should be interpreted with caution in testing baseline validated PF measures in predicting nonattendance to related health care appointments in the last 2-3 months (i.e. anything less than 100%) at 3-month follow-up controlling for relevant demographic and disease variables (Table 18). Demographic and disease variables accounted for 3.9% (Nagelkerke R^2=.039) of the variance in nonattendance in the last 2-3 months but did not significantly improve the model fit ($\chi^2(3)=6.85$, p=.077). Having more than one LTC (OR=1.99, 95% CI=[1.01, 3.94]) was associated with increased odds of nonattendance. Adding PF processes did not significantly improve the model fit ($\Delta\chi^2(4)=8.41$ (p=.07, 2LL= 249.82), explaining a further 4.7% (Nagelkerke ΔR^2=.047) of the variance. However, consistent with baseline analyses, engaging in valued action (OR=.93, 95% CI=[.89,.98]) was associated with decreased odds of non-attendance.

Table 18: Multiple binomial logistic regression to predict appointment nonattendance in the last 2-3 months at 3-month follow-up.

Step 1: Baseline demographic and disease variables	*n*=286			$\boldsymbol{R^2}$=.039
χ^2 (3) = 6.85 (*p*=.07)				
-2LL = 246.90 (χ^2(8)11.96, *p*=.15)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
More than one LTC	.69*	.052, 1.50*	1.99	1.01, 3.94
Depression (PHQ-8)	<.01	-.07, .08	1.00	.92, 1.08
Anxiety (GAD-7)	.02	-.05, .10	1.02	.94, 1.11
Step 2: Baseline psychological flexibility processes				$\boldsymbol{R^2}$=.086
$\Delta\chi^2$ (4) = 8.41 (*p*=.07)				
-2LL=249.82 (χ^2(8)14.95, *p*=.06)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	.02	-.03, .08	1.02	.97, 1.08
Openness to Experience subscale (CompACT total OE)	.01	-.03, .06	1.01	.97, 1.06
Behavioural awareness (CompACT total BA)	.01	-.05, .08	1.01	.95, 1.08
Valued Action (CompACT total VA)	-.06*	-.12, -.01*	.93	.89, .98

Adherent=0, Non-adherent=1; [1]Female=0 with "other" case excluded; [2]White=0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples); *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total BA (CompACT Behavioral Awareness subscale); CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale; PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items)

The final logistic regression satisfied diagnostic assumptions and tested the components of the PF model in predicting nonattendance to related health care appointments in the last *12 months* (i.e. anything less than 100%) controlling for relevant demographic and disease variables (Table 19). Demographic and disease variables accounted for 19.0% (Nagelkerke R^2=.190) of the variance in nonattendance in the last 12 months, significantly improving the model fit (χ^2(7)=38.18 (p<.01). Being older (OR=.96, 95% CI=[.94,.99]) was associated with

decreased odds of nonattendance. Adding PF processes did not significantly improve the model fit ($\Delta\chi^2(4)=7.12$, $p=.13$, 2LL= 239.77), explaining a further 3.3% (Nagelkerke $\Delta R^2=.033$) of the variance and none of the processes were related.

Table 19: Multiple binomial logistic regression to predict appointment nonattendance in the last 12 months at 3-month follow-up.

Step 1: Baseline demographic and disease variables	*n*=323		***R*²**=.190	
$\chi^2(7) = 38.18$ ($p<.01$)				
-2LL = 246.90 ($\chi^2(8)4.22$, $p=.83$)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Age	-.03*	-.06, <-.01*	.96	.94, .99
Gender[1]	-.22	-1.39, .66	.80	.33, 1.94
More than one LTC	.76	-.02, 1.67	2.15	.98, 4.69
LTC type[2]	.09	-1.05, 1.20	1.09	.40, 2.98
Years since diagnosis	<-.01	-.04, .03	.99	.96, 1.03
Depression (PHQ-8)	.02	-.07, .09	1.02	.94, 1.10
Anxiety (GAD-7)	.07	<-.01,.17	1.07	.99, 1.16
Step 2: Baseline psychological flexibility processes			***R*²**=.223	
$\Delta\chi^2(4) = 7.12$ ($p=.13$)				
-2LL = 239.77 ($\chi^2(8)46.44$, $p=.59$)				
	b	**Bca 95% CI**	**OR**	**OR 95% CI**
Psychological inflexibility (AAQ-II)	-.02	-.08, .03	.97	.92, 1.03
Openness to Experience subscale (CompACT total OE)	.01	-.04, .06	1.01	.96, 1.05
Behavioural awareness (CompACT total BA)	-.03	-.12, .04	.97	.90, 1.04
Valued Action (CompACT total VA)	-.06	-.13, <.01	.93	.88, .98

Adherent=0, Non-adherent=1; [1]Female=0 with "other" case excluded; [2]Parkinson's Disease=0; χ^2 Chi-squared goodness of fit; $\Delta\chi^2$ (Chi-squared goodness of fit); *b*= beta value; Bca 95% bootstrapped CI (bias corrected and accelerated beta value 95% confidence intervals with 1000 samples);; *beta is significant <.05 (2-tailed); OR (standardized odds ratio); OR 95% CI (standardized odds ratio 95% confidence intervals); -2LL(-2 Log Likelihood statistic); R^2 (Nagelkerke R^2 / pseudo R^2); AAQ-II (Acceptance and Action Questionnaire II); CompACT total BA (CompACT Behavioral Awareness subscale); CompACT total OE (CompACT Openness to Experience subscale); CompACT total VA (CompACT Valued Action subscale; PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items)

Chapter 4: Discussion

This final chapter will first provide a brief summary of the main findings from the literature review and empirical study. Novel contributions of the project will then be highlighted. This will be followed by a discussion of the theoretical utility and implications of the PF model in conceptualising and treating non-adherence in people with LTCs in relation to previous literature. Potential limitations of the thesis will then be discussed. Finally, possible avenues for future research and clinical practice to improve our understanding and treatment of non-adherence are provided.

4.1 Summary of main findings

The current thesis aimed to apply and evaluate the utility of a new conceptual model – psychological flexibility – to understand treatment non-adherence in people with LTCs and inform the development of novel intervention targets to improve adherence in the future. Chapter 1 began by introducing treatment non-adherence as a multifaceted problem, highlighting important challenges with operationalising this complex construct. It also provided a critical summary of the evidence for several different psychological approaches aiming to conceptualise and improve non-adherence, including the theory of planned behaviour, common sense model of illness perceptions and necessity concerns framework. However, the overall explanatory power of these models were shown to be modest and interventions stemming from them demonstrated limited efficacy. The review also illustrated that no single theory provided a comprehensive explanation of adherence that fully integrates all potentially important psychosocial variables in the literature. The broadly applicable and potentially modifiable

processes within ACT's PF model were identified as an alternative way of integrating existing variables to conceptualise non-adherence in people with LTCs but had received less research attention to date. Further longitudinal investigation and the development of new momentary measurements of PF, adherence and emotional functioning was warranted.

The large longitudinal study presented in Chapter 2 tested key elements of the PF model. Adherence and attendance outcomes showed poor convergence overall and unintentional non-adherence was more common than intentional non-adherence. Findings identified mostly small, significant bivariate cross-sectional relationships between PF and self-reported adherence and routine appointment attendance outcomes, emotional and general functioning. Specifically, as predicted, greater psychological inflexibility was associated with lower levels of adherence and appointment attendance and poorer functioning in people with LTCs. PF processes were more related to intentional than unintentional non-adherence, where only the CompACT and its behavioural awareness subscale (i.e. 'aware' sub-process) were significantly related to unintentional non-adherence. Furthermore, PF was not significantly associated with adherence outcomes and appointment attendance at baseline after controlling for demographic and disease variables, indicating few differences between non-adherence subtypes.

Longitudinal bivariate relationships between PF at baseline and adherence and appointment attendance outcomes at three months were largely consistent with baseline analyses. However, the magnitude of these relationships were generally smaller and not all reached statistical significance. Specifically, the AAQ-II was significantly related to unintentional non-adherence at three months but unrelated at baseline, while the opposite was true for the CompACT. Only bivariate relationships between PF measured using the AAQ-II and valued action subscale of the CompACT (i.e. 'engaged' sub-process) adherence and appointment attendance in the last two-three months remained significant. However, only the valued action subscale retained significance in relation to appointment attendance within the last twelve months. Overall, the

AAQ-II showed slightly larger associations with adherence and attendance, and mood, outcomes compared to the CompACT. While it has been argued that the AAQ-II may reflect a measure of generalised emotional distress (Wolgast, 2014) and might artificially enhance its explanatory power, the magnitude of correlations with key outcome variables were consistently smaller than the PHQ-8 and the GAD-7. An unexpected finding was that PF processes measured using the CompACT (i.e. behavioural awareness and valued action subscales) significantly improved over the three-month period, despite mood and other outcomes remaining unchanged. However, this might reflect measurement error or a characteristic of self-selected participants within the follow-up sample.

Baseline self-reports of PF did not significantly predict adherence and appointment attendance outcomes at three months follow-up, indicating few differences between non-adherence subtypes, after controlling for demographic and disease variables. Taken together, PF processes only accounted for a very small non-significant proportion of the variance. Consistent with a previous cross-sectional study investigating PF in relation to antiretroviral therapy non-adherence in people with HIV (Harrison et al., 2019, unpublished) and studies examining the application of social cognitive models to understand non-adherence behaviour (Brandes & Mullan, 2014; Rob Horne et al., 2013; Rich et al., 2015), current findings indicate PF processes (as measured here) have limited explanatory power in understanding non-adherence in people with LTCs. One possible reason for this finding is that the AAQ-II and CompACT are not LTC or adherence specific, but rather measure more general patterns of behaviour, and therefore may be less sensitive for, or understandable to, people living in these different contexts. Relatedly, the sample included a wide range of conditions that come with different adherence behaviour demands. Specifically, some adherence behaviours may be considered minimal, whilst others considerably more intrusive, perhaps depending on the type/stage of disease. In addition, some adherence behaviours are required to halt progression of a disease, whilst others target symptom relief. Arguably, different LTCs will be associated

with different numbers of appointments, where some people may be seen more frequently than others, potentially adding significant variability in regression analyses.

The study identified a range of demographic and disease factors related to adherence and appointment attendance at the bivariate level. However, subsequent regression analyses revealed there were more potent demographic and disease predictors of adherence outcomes cross-sectionally and longitudinally. Specifically, more years since diagnosis was significantly associated with greater likelihood of intentional non-adherence, whilst having Parkinson's disease and higher levels of depression were associated with an increased likelihood of unintentional non-adherence. In addition, being older was a significant predictor of poor attendance to routine clinical appointments over the last twelve months at three months follow-up, but cross-sectional relationships were not consistent with this finding. Low mood at baseline was significantly associated with greater likelihood of poor appointment attendance outcomes cross-sectionally but was not a significant predictor at follow-up. This difference is unlikely to be attributable to improvements in mood, which appeared stable over time. These findings emphasise the potential importance of contextual factors and need for context-specific measures of PF to improve prediction. However, significant relationships between increased age and having Parkinson's disease with unintentional non-adherence, might also support the idea that being more forgetful is more likely to be a cause than a form of experiential avoidance (i.e. being 'closed') *per se*.

4.2 Contributions to the literature

The current thesis makes a distinct contribution to the literature. This is the first study investigating the potentially important role of PF processes in predicting self-reported intentional and unintentional non-adherence and routine health care appointment attendance in

people with a range of LTCs. Therefore, it improves on previous cross-sectional studies in the area (e.g., Harrison et al., 2019, unpublished), providing insight into the potential role of PF in predicting adherence and attendance outcomes over time. The survey showed that self-reported PF was a relatively weak predictor of self-reported adherence and appointment attendance outcomes and certain demographic and disease factors have a potentially significant role to play in predicting non-adherence.

4.3 Theoretical implications

4.3.1 Theoretical implications of our understanding of PF and ACT

The introduction outlined the potential applicability of the PF model as a way to conceptualise and treat non-adherence in LTCs. The longitudinal survey findings show PF processes have some, albeit limited, explanatory power in understanding self-reported non-adherence (intentional r=.11-.16; unintentional r=.09-.12) and appointment attendance outcomes (2 to 3 months r=.11-.13; 12 months r=.25) at the bivariate level. These findings were largely consistent with other psychological models in the literature, including the self-regulation model (r=.02-0.12), necessity-concerns framework (OR=.50-1.74) and theory of planned behaviour (r=.30). Therefore, at present there is no clear indication that elements drawn from any single candidate theory are necessarily more important.

This study found only small relationships between self-reported non-adherence, appointment attendance and emotional and general functioning, contrasting with the expectation that non-adherence triggers low mood and reduces functioning or vice-a-versa. However, consistent with the LTC literature (Graham et al., 2016; Kashdan & Rottenberg, 2010; Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016) the finding that PF processes share significant medium to large

bivariate relationships with emotional functioning suggests the model has some transdiagnostic utility in predicting other important domains of functioning and helping people with LTCs better manage their distress to increase values-based activity. Many trials in these reviews show that PF is a clinically relevant change process, such that increased PF leads to improvements in mood (Graham et al., 2016). Given that distress predicts non-adherence and PF correlates strongly with mood in the current study, it could be that increasing PF leads to improvements in mood, which in turn may reduce non-adherence behaviour. This might explain why ACT shows promising preliminary outcomes in adherence in people with LTCs (Moitra et al., 2011; Nelson et al., 2014) and psychosis (Spidel et al., 2018), but currently it remains unclear whether these improvements are achieved through targeting mood rather than adherence directly.

There are potential theoretical gaps in the PF model and/or measures used here that may have accounted for the limited explanatory power in predicting adherence and attendance outcomes. First, PF is based on RFT, which provides a universal explanation of how naturally occurring human verbal behaviour processes interact with arbitrary language conventions in the social context, which can come to dominate our private experience (Torneke, 2010). RFT argues this learning can potentially influence our behaviour, including whether people with LTCs adhere or not. However, RFT's operant explanation is less specific about how an individual's established pattern of behaviour might be influenced by, or coincide with, ideas from other psychological models, such as personality, pre-existing vulnerabilities, critical life events and trauma, and acquired or developmental neurocognitive impairments. Unlike CBT, ACT also de-emphasises the importance of collaboratively developing a tailored conceptual model to help understand the client's past experience and/or schema to contextualise their present strengths and difficulties as a basis for further intervention. However, it has been argued that the same verbal processes in RFT will also influence the way clinicians and researchers come to talk about, create and evaluate psychological constructs. This can often occur in absence of any underlying ontological and epistemological assumptions or overarching basic level theory, or

without evaluating the constructs' validity *and* utility at an applied level (McCracken & Morley, 2014). For instance, to date there is still limited evidence testing whether sharing a detailed conceptual model incorporating precipitating/vulnerability and other psychological factors correlates with better treatment outcomes (Bieling & Kuyken, 2003; Johnstone, 2018).

Relatedly, current findings might also suggest that PF processes as measured in the current study are too 'broad brush' to predict more discreet non-adherence and appointment attendance behaviours, reflecting only some among many other valued actions or goals of an individual. Currently, PF measures remain intra-personal and trait-based. As mentioned previously, researchers could either try to develop more context-sensitive idiographic and/or momentary measures, which would fit with PF/ACT's focus on behaviours in context. Alternatively, efforts could focus on adopting a COM-B approach by looking at PF's relationship to non-adherence in combination with a range of other psychological variables drawn from other candidate models, such as specific beliefs about illness or treatments (Karekla, Karademas, & Gloster, 2018). This 'lumping' approach might artificially improve the predictive power of models, but equally risk contradicting underlying theoretical assumptions (Harrison et al., 2017). Additionally, over-focusing on narrower cognitive treatment targets could also potentially overlook broader contextual factors/life circumstances that might be influencing a person's non-adherence behaviour (e.g. loss/bereavement, family or relationship problems, access to health care). However, recent evidence of merging more theoretically consistent approaches/techniques, such as ACT and MI, show promising outcomes in other areas (Ehman & Gross, 2019).

Second, bivariate correlations in the baseline analysis indicated certain socio-demographic contextual factors were related to non-adherence, including being in a relationship. This finding contrasted with a recent study examining similar relationships in people with HIV indicating

being single was a potent predictor of non-adherence to anti-retroviral therapy (Harrison et al., 2019). It is also unclear contextually *how* or *why* being 'in a relationship' or 'not' might exert influence on a person's non-adherence behaviour, and if and how social processes specifically contribute to poor adherence through the lens of PF. The current sample was older and therefore being in a relationship incorporated people who have experienced death of spouse or divorce, as well as being single. Although ACT is fundamentally a relational therapy that seeks to understand the person's broader life context, it is usually confined to the client-therapist relationship (Harris, 2009; Hayes et al., 1999). Unlike systemic and family-based approaches (Carr, 2000; Dallos & Stedmon, 2006), the PF model and the overly intra-personal PF measures are less explicit about how to understand complex social-contextual processes that may influence non-adherence and how we might intervene at a broader systems level.

ACT attempts to contextualise a person's behavioural patterns as either "workable" or "unworkable", which could potentially inform values-based goals about socialising or connecting more with others. For instance, taking one's medication may in some cases be required in order to achieve such goals, and yet the same treatments may trigger unpleasant side effects that act as barriers to action. However, social-oriented values-based goals or actions in ACT are typically individually-derived and attempts to achieve them may not necessarily be met with positively reinforcing responses, understanding or reciprocation from others. This might explain why some researchers highlight the importance of perceived or actual stigma as being bigger drivers of non-adherence than general psychological factors in certain LTCs (Fekete, Williams, & Skinta, 2018; Rachlis, Mills, & Cole, 2011). Therefore, only assessing an individual's intra-personal PF processes (as measured here) and targeting these in ACT in isolation may be too insensitive to identify or address workable or unworkable contextual-relational patterns (and, e.g., stigma) and exert a limited impact clinically. Future theoretical and intervention developments incorporating social processes (e.g. shared values-based goals and experiential avoidance) may enhance the utility of PF in adherence. Family based ACT

interventions have been argued to be more applicable particularly in young people who are non-adherent to medications (Hadlandsmyth et al., 2013). Such developments could potentially involve obtaining outcomes of the individual's family, carer, or friends. However, this may be particularly problematic if the individual experiences unchangeable complex social circumstances and/or social dynamics in the home or work contexts (e.g. an unsupportive, or overly solicitous, partner/carer, colleague or health care provider). Unfortunately, the current study did not successfully recruit adolescents with LTCs as initially planned, therefore the applicability of PF to understand non-adherence in this subgroup remains unclear.

Third, the sample included people with a range of LTCs who are likely to be prescribed a variety of different treatments, indicating that more years since diagnosis and LTC type were consistent predictors over time. However, potential distinctions between biomedical factors in the PF model also remain unclear. Despite being promoted as a transdiagnostic approach, which is largely supported by a recent study including only people with HIV (Harrison et al., 2019, unpublished), the varied and complex nature of treatment regimens and their biological impact on the body cannot easily be explained by PF. Future studies could explore potential differences between specific LTCs, co-morbidity (Williams et al., 2008) and treatments in conjunction with PF processes to identify at risk groups. For example, the over-use of pain relief medications observed in chronic pain are also a form of non-adherence behaviour that will likely differ to other LTCs (Harrison, Graham, & McCracken, 2017). It might also be helpful to explore potential differences within LTCs, for example testing stage of disease progression, use of polypharmacy and whether there are short and long-term psychological consequences of following regimens that range in complexity and method of administration (e.g., painful injectables like disease modifying treatments in MS: Remington, Rodriguez, Logan, Williamson, & Treadaway, 2013).

Fourth, it could be argued that PF, as measured in the current broad LTC sample, does not incorporate enough disease-specific biological processes to explore the interaction between aspects of all three elements in the broader "biopsychosocial" framework (Engel, 1977). As newer adherence technologies emerge to support more objective ways of measuring adherence, aspects of biological processes may be more easily incorporated in PF and adherence studies. However, theoretically PF prioritises behavioural processes that have broad applicability in measuring with precision, predicting and influencing outcomes (Hayes, Pistorello, & Levin, 2012), and whilst it acknowledges neuro- and physiological processes are important, it does not deem these variables as directly modifiable through treatments like ACT. To date, no studies have examined the relationship between PF processes, adherence and neurophysiological or physiological variables in LTCs. Therefore, investigating relationships between PF and physiology processes may be an interesting avenue for future research.

A related point is that Parkinson's disease and higher levels of depression were significant predictors of unintentional non-adherence (i.e. forgetting) in the sample. Acute or chronic neurocognitive changes are common in these and other LTC groups and often associated with non-adherence (Lovejoy & Suhr, 2009). A recent HIV sample reported significant medium sized relationships between perceived cognitive problems and unintentional non-adherence (Harrison et al., 2019, unpublished). However, no studies have explored potential moderating relationships between actual neurocognitive impairments in the context of PF and adherence relationships and whether they are modifiable as part of an ACT intervention, or whether an adjunctive neurorehabilitation component focussing on remedial and compensatory strategies may be optimal.

4.3.1 Theoretical implications of our understanding of adherence

Eighty-eight percent of the baseline sample were estimated to be non-adherent, according to the binary cut-offs of the MARS-5, whilst 84.6% reported they attend 100% of their medical appointments. The high percentage of non-adherers according the MARS-5 is almost double the proportion of estimates recorded in previous studies in the LTC literature, which range from 25% to 50% (Coleman et al., 2012; DiMatteo, 2004b; DiMatteo, Giordani, Lepper, & Croghan, 2002; Haynes, 2001; Osterberg & Blaschke, 2005). Aside from possible self-selection bias and poor stability of the binary cut-offs score over time, one possible reason for this could be that the sample was predominantly comprised of older people with Parkinson's disease, who might experience challenges with memory and increased use of polypharmacy at this later life stage. However, a related issue could also be that the items used within the MARS-5 significantly contributed to variability in the data when applied to such a diverse sample of people with different LTCs and corresponding treatment regimens. For instance, a person with comorbidities and multiple treatment regimens at timepoint one may have answered items at timepoint two with a different condition and medications in mind. Additionally, participant's interpretation and response of items on the MARS-5, such as "I adjust the dosage of my medication", may also have captured either a person's tendency to alter their medication use against (or in line with) their doctor's advice, depending on the specific treatment or condition they are referring to.

Despite the relatively small relationships between self-reported adherence and general functioning, there is also an implicit assumption in most adherence, concordance or compliance research that non-adherence and symptom exacerbation, or illness deterioration, will equate to reduced engagement in meaningful activities and QoL. This prevailing view is perhaps unsurprising from a 'common sense' point of view, but also given that historically a significant

proportion of adherence research has been funded by pharmaceutical companies. However, the PF and ACT literature indicates that people can live valued lives despite the presence and progression of difficult symptoms and prognoses, especially when adaptations to valued-activity are modified to account for such changes (Graham et al., 2016). Typically, adherence is the goal, but it may be that unpleasant side-effects and poor prognosis influence a person's informed and valued choice to not adhere, whilst at the same time continuing to pursue other valued activities. For example, taking breast cancer hormone therapies that reduce the chance of cancer recurrence may for some people cause extreme side effects that adversely affect their QoL (e.g. significant pain, sexual dysfunction etc.) Therefore, it could be at times more in line with the person's values to be non-adherent and accept they have a slightly increased chance of disease recurrence in order to have a better QoL, rather than a greater chance of quantity of life. This would suggest that greater PF may not necessarily relate 100% to higher rates of adherence. Ultimately, PF and ACT may still potentially be a useful approach to support people in developing an awareness of the consistency (or lack of consistency) between their values and behaviour, rather than specifically targeting PF with the sole aim of improving adherence.

4.4 Limitations

The current study has several limitations, which are outlined in the following section.

First, longitudinal studies are useful to quantify temporal relationships between self-reported PF, adherence and attendance, and general and emotional functioning. However, causation cannot strictly be inferred, since changes in other exogeneous factors or contextual processes may have exerted influence on participants reporting of PF and adherence behaviour during the three-month period (Cole & Maxwell, 2003). However, evidence from ACT-based

interventions targeting adherence offer preliminary support for the idea that PF processes could be modified to improve adherence in the context of LTCs (Moitra & Gaudiano, 2016; Nelson et al., 2014).

Second, the importance of non-significant PF predictors may also be underestimated due to common-method variance and conceptual overlap with other psychological/emotional processes in some regression models. However, sensitivity analyses were conducted with anxiety and depression removed from these analyses, revealing only modest change in effect sizes. Relatedly, CFAs tested the validity of proposed factor structures in all PF, adherence and emotional and general functioning variables, but standard hierarchical regression analyses were used to assess predictive relationships, which do not account for measurement structure overlap or error accrued by scale items (MacKenzie & Podsakoff, 2012). Another issue was that the data-driven, rather than strictly theoretically-driven, approach informing the inclusion of covariates and predictors within the regression models meant they were not directly comparable, and the differing number of variables may have inadvertently advantaged or disadvantaged particular models.

Third, the use of two timepoints over a three-month period reflected a compromise between the primary and secondary aims. However, this relatively short timescale precludes clear interpretation of relationships over a longer follow-up period. Another issue is that two timepoints have been described as insufficient to be a robust longitudinal design for two reasons. First, any change reflects "only an increment of difference between the two times and does not evaluate if change was steady or delayed, or whether it plateaued and then changed again" (Ployhart & Vandenberg, 2010, p.97). Second, true change and measurement error may be confounded, such that true change is assumed when in fact measurement error suppresses scores at baseline and increases them at follow-up (Ployhart & Vandenberg, 2010). Relatedly, Ployhart

et al. (Ployhart & Vandenberg, 2010) also suggest at least three timepoints is optimal for increasing precision of reliability estimates and temporal ordering of variables for mediational analyses. However, as this study was exploratory in nature no mediational hypotheses were tested.

4.4.1 Sampling

The online study was successful in recruiting people with LTCs with a range of demographic and disease characteristics from a range of voluntary sector organisations, but none were recruited via the National Health Service (NHS). Therefore, the health status and diagnosis of participants in the sample could not be confirmed by a medical professional and self-selection bias is likely. Another challenge with self-selection bias in online adherence research specifically is that participants may be inherently more responsive and adherent, representing only a small proportion of the larger LTC population who may be harder to reach.

Relatedly, the sample was unusual in that 41.0% percent of participants were diagnosed with Parkinson's disease, in their mid-fifties, and predominantly English-speaking UK residents. However, no sensitivity analyses were conducted to directly compare adherence, and the relationship between PF and adherence, of people with Parkinson's Disease with other LTCs. The sample was therefore less representative of people with other LTCs and adolescents, despite efforts to recruit for an adolescent version of the survey, and the fact that UK has a different health care access context compared to other countries. Additionally, the study did not explore polypharmacy, which is more common in older people with LTCs (Marcum & Gellad, 2012). This may have contributed significant variability to the regression analyses data since participants may have responded to the MARS-5 quite differently, where for example, they

defer to an average rating for all regimens or for one only, and/or provide ratings for different treatments at the two time points.

Although the initial sample size for the study was large and cross-sectional and longitudinal analyses were arguably sufficiently powered (Faul et al., 2009), the attrition rate was relatively high (48.0%) and there was no way of enumerating response rates, which may limit generalisability of findings. The study was hypothesis-driven using pre-registration to avoid data fishing. However, the number of correlations explored in combination with the initially large sample size may have resulted in detecting spurious or artificially inflated effects. Another issue is that the range of LTCs and reduced sample size at follow-up meant that prediction models precluded potential moderation and subgroup effects, where combining all LTCs into one group may lose potentially important distinctions. However, the study was exploratory in nature and no specific hypotheses about subgroups were identified *a priori.*

4.4.2 Self-report of adherence, attendance and disease characteristics

In addition to theoretical limitations of PF outlined, there may be other possible reasons why PF processes showed small correlations with self-reported non-adherence and appointment attendance outcomes in this study related to measurement error.

First, the online survey format precluded the use of more objective measures of adherence and self-reporting biases commonly highlighted in the adherence literature (Horne, 2006) would likely have significantly under- or possibly over-estimated the rate of actual rates of non-adherence. Responses on the appointment attendance scales may not necessarily reflect a person's choice, since more severely disabled participants may want to attend face-to-face

medical appointments but may struggle to do so. Additionally, the longitudinal analyses meant that the retrospective twelve months attendance outcome reflected behaviours that pre-dated the baseline score.

Second, the 'near perfect' categorical anchors of adherence used for the MARS-5 will have likely reduced precision, having indicated that 88.5% of sample were unintentionally non-adherent, which potentially reflects a gross overestimate compared to previous adherence studies. Therefore, it follows that cut-offs applied to intentional and unintentional non-adherence will likely have impacted on the precision and accuracy of 'caseness' within the regression models and predictive accuracy of PF and other variables.

Third, poor convergence between self-reported adherence on the MARS-5 and new attendance outcomes raises the question of whether either were adequately measuring adherence and health utilisation in the current sample. This was supported by confirmatory factor and test-re-test analyses, which indicated the MARS-5 may not be accurately measuring what it intends to measure in this sample, nor is it optimally reliable over time. In contrast, the single-item attendance outcomes could not be factor-analysed, were skewed and therefore categorised into binary cut-offs similar to the MARS-5 but showed moderate levels of stability over time. The near perfect cut-offs used for both measures might therefore not have sufficiently captured variability in PF or emotional and general functioning. However, the new attendance scales were designed to reduce participant burden and the MARS-5 was used to capture pragmatic adherence subcategories, where other scales did not differentiate between intentional and unintentional non-adherence and/or were too costly (Morisky et al., 1986). Despite these limitations, the MARS-5 and appointment attendance scales offered a universal, albeit with potentially debatable validity, way of quantifying adherence across LTCs. Support for both measures were that relationships with key variables mostly fell in expected directions and

potential lack of measurement precision might suggest the magnitude of these effects were underestimated.

Fourth, the MARS-5 adherence did not specify a time-frame. It is therefore plausible that participants provided an average rating over a self-selected timeframe. Arguably, problems with retrospective bias can also arise with measures that specify historical timeframes (Moskowitz & Young, 2006).

A further limitation was that the study used non-validated self-report questions about participant's LTCs that did not distinguish between disease severity and/or disease-specific functioning using validated measures. In addition, disease variables (e.g. disease duration and number of LTCs) may also have been susceptible to either exaggeration or under-reporting by participants. However, obtaining confirmation by medical professionals about participant's disease subtype or severity, relapse status and treatment regimens (and related allergies or adverse reactions to them) on entry to the study would have provided greater accuracy. However, obtaining this information would also have been costly and time consuming, potentially increasing participant burden and adding increasing complexity to statistical analyses.

4.4.3 Self-report psychometric instruments

A final limitation relates to the self-reported questionnaires used to assess PF, mood and general functioning constructs in the longitudinal study. Most scales included in the adult sample have been used in other LTC samples, but few of them have been properly validated. Attempting to validate new momentary measures against established measures that have yet to

be fully validated in LTC samples may undermine convergent, criterion and predictive validity. However, efforts were made to confirm the validity of all scales using CFA methods. These suggested it was unclear if the underlying constructs identified in a previous validation sample for the CompACT were indicated based on more established fit indices, though the goodness of fit criteria designed to test ordinal data was acceptable (Francis et al., 2016).

Despite this, all psychological scales showed acceptable internal consistencies and test-re-test reliabilities, although significant life events that might explain reliable change over the three-month period could not be ruled-out. Additionally, all scales produced correlations with adherence and appointment attendance outcomes and emotional and general functioning in hypothesised directions, consistent with previous PF correlational (Cheung & Mak, 2016; Kamody et al., 2017) and ACT-based intervention literature (Moitra & Gaudiano, 2016; Nelson et al., 2014) supporting criterion and predictive validity. Discriminant validity of established scales was not examined in the current study, but the varied magnitude of correlations between mood and PF with adherence and attendance outcomes provided some preliminary support for the idea that measures tapped overlapping but distinct constructs.

As mentioned previously, PF measures may have been too ‘broad brush’ to capture variability in more discreet adherence behaviours. Therefore, an important challenge for measurement development in PF and adherence research is deciding whether to use more established generic intra-personal PF measures or develop LTC and/or non-adherence-specific PF scales that is sufficiently sensitive to context, but equally does not inadvertently overlap with behavioural descriptions in self-reported adherence instruments.

A further limitation is that other than self-reported anxiety and depression, the questionnaire did not ask participants about other emotions, such as anger, or ask about other mental health

difficulties using a valid and reliable self-report instruments (e.g., Zimmerman & Mattia, 2001) or clinician diagnostic interviews (e.g., First, Gibbon, Spitzer, Benjamin, & Williams, 1997). Therefore, other mental health difficulties were not controlled for statistically or by exclusion, which may also contribute to non-adherence.

4.5 Future directions and clinical implications

The previous section highlights several methodological issues that future research should attempt to address. With these in mind, the current thesis identifies several important avenues for future research summarised in the following section.

Future studies examining temporal relationships between PF and adherence and appointment attendance outcomes may benefit from the following:

First, sufficiently powered temporal designs should either incorporate three or preferably more timepoints to capture true change over time (Ployhart & Vandenberg, 2010) to further examine theoretically-informed interrelationships (i.e. mediation) between PF, general and emotional functioning with more objective valid and reliable adherence measures. Alternatively, temporal designs could also include sufficiently powered EMA studies or RCTs. The secondary aim of the current study incorporated feedback from experts by experience and preliminarily validated the new ultra-brief momentary/state scales of PF, mood and adherence for people with LTCs with some success. Relatedly, when assessing test-re-test reliability future research could also explore responsiveness, by asking participants questions about key life events over the study period (e.g. disease activity/relapse, change in medication, uptake of psychological or psychiatric treatments) that might provide some understanding of why changes

might have occurred. Conducting sensitivity analysis with only those people who are stable over time may also be informative.

Second, given the possible variance between and within LTC groups, and their respective treatments and use of polypharmacy, it might also be helpful to limit samples to specific LTCs to ensure they are sufficiently representative. Efforts should also be made to conduct future studies with adolescents and adults separately as there are likely to be important distinctions.

Third, using structural equation modelling procedures (Anderson & Gerbing, 1988) to first factor-analyse observed variables and then use these models to estimate temporal relationships between more objective adherence and healthcare utilisation outcomes in conjunction with emotional, physical and social-role functioning outcomes might tell us more about these interrelationships. SEM methods could also determine the unique contribution of separate models to directly compare them head-to-head or in combination. Such analyses could also incorporate theoretically informed mediation, moderation, subgroup and/or sensitivity analyses to test if key demographic and disease variables identified in the current study (i.e. age, depression, perceived or actual neurocognitive impairments, LTC type and perhaps country of residence) differentially influence these relationships to identify at risk groups. Equally, latent class analysis may be useful in this regard (Tyndall et al., 2018).

Fourth, valid and more objective measures of adherence and health care utilisation, such as nebuliser microchips used in cystic fibrosis (Latchford et al., 2009), MEMS® and others obtained via existing medical records (e.g. actual health care appointment attendance and relevant biomarkers), could be triangulated with self-report instruments. Self-reported adherence measures should be validated for specific LTCs with established non-adherence cut-offs and ideally specify a specific timeframe to improve precision to an extent. For example, specific number of doses skipped in HIV may be more important in relation to $CD4^+$ counts and

functioning than anchors used in the MARS-5. The current study suggests using adherence instruments that distinguish intentional and unintentional non-adherence may be less important in relation to PF. However, better validated measures incorporating these constructs might be clinically meaningful and help to clarify differences in PF-adherence and health care utilisation relationships across demographic and disease variables, such as age, years since diagnosis, LTC type and depression.

Given that self-report adherence data is commonly negatively skewed and often results in the use of relatively arbitrary categories of adherence and non-adherence by researchers (see email communication from Professor Rob Horne Appendix L), one alternative approach might be to conduct receiver operating characteristic (ROC) analyses (Hajian-Tilaki, 2013) as part of a self-reported adherence measure's validation study, which could involve setting it against more objective measures of adherence to determine more meaningful cut-offs to improve convergent validity.

Fifth, it may be useful to include more than one overall measure of PF in a given study to further clarify the factor structure of scales like the CompACT in LTCs. Alternatively, other scales specific to each aspect of the six-process model are also available to use showing good psychometric properties (e.g., Cardaciotto, Herbert, Forman, Moitra, & Farrow, 2008; Gillanders et al., 2014; Trompetter et al., 2013; Zettle et al., 2018).

Sixth, one way to overcome measurement problems and aggregation bias (Johnston & Johnston, 2013) might be to use more objective ecological momentary assessments of adherence in conjunction with preliminarily validated momentary measures of PF and mood that were developed as part of the current study's secondary aim. Briefly, two new 3-item daily and hourly PF scales showed acceptable psychometric properties for potential use in EMA designs. Alternatively, other momentary measures informed more directly by general RFT processes are

also available (Levin, Krafft, Pierce, & Potts, 2018; Pierce & Levin, 2019) and possible alternatives to self-report have been recently proposed (Newsome, Newsome, Fuller, & Meyer, 2018). Other ACT researchers have also highlighted how EMA could potentially capture dynamic changes over time and across contexts (e.g. using emerging smartphone application technologies), including potential effects of periodic and cumulative non-adherence in the context mental health (Moitra & Gaudiano, 2016) and LTCs. EMA methods also examine within-individual and group-level relationships between variables in conjunction with relevant events or changes in routine (Hektner et al., 2007). An important step in developing the 3-item PF momentary scales as part of the secondary aim of the current project has been consulting with people with LTCs when co-constructing ultra-brief momentary measures for people with LTCs to ensure measure content is understandable[3]. However, using additional methods, such as Delphi and/or think aloud approaches, might be helpful to capture patient and clinicians lived-experience or views of the scales in greater depth to further inform the measure development process.

Finally, depending on the outcome of these preclinical studies, it might be more economically viable to develop and evaluate briefer ACT-based interventions for people with LTCs to address non-adherence. These could potentially be delivered via minimal face-to-face or telephone and/or email support by clinical psychologists and/or other HCPs. Specifically, Focused ACT (FACT) works on the assumption that the modal frequency of psychological sessions is one, and therefore FACT is specifically designed to shift PF processes in the context of brief health care consultations (Strosahl, Robinson, & Gustavsson, 2012). However, arguably it may also be important to evaluate the feasibility and efficacy of standard-length ACT interventions for adherence in specific LTCs prior to embarking on this work.

3 While outside the scope of this thesis, these findings will be published at a later date.

Such an intervention could potentially be supplemented by a guided self-help web-based platform to improve access that is informed by a more reliable clinical assessment process. The current study findings indicate that it may be important to screen service-users for other potentially important contextual factors, such as age, duration of illness, depression neurocognitive impairments, LTC type and relationship status. Individuals with these characteristics may require a simpler approach, more time to complete sessions, remedial or compensatory strategies (e.g. simple smartphone reminders) to support homework completion and promote adherence (Alfonsson, Englund, & Parling, 2019) and/or a higher intensity intervention. Interventions such as FACT may have useful applications in adherence but need to be preliminarily evaluated in case-series studies, and feasibility and definitive RCTs to ensure they acceptable to people with LTCs and cost-effective. Orienting HCPs to ACT ideas via a brief clinician training may also improve delivery and facilitation of informed-consent and collaborative decision-making processes in consultation with people with LTCs (Conn et al., 2015; Levin, Herbert, & Forman, 2017). Competency assessment and regular supervision ideally provided by a clinical health psychologist may further support therapist's fidelity to the model.

4.6 Conclusions

This initial investigation found limited evidence for a contribution of PF model to explanations of non-adherence in LTCs. The two classifications of adherence did not appear to have any clear differential psychological responses associated with them. Given that ACT seeks directly to improve PF, the present study does not suggest that ACT is more suitable than existing behaviour change approaches informed by social cognitive models. However, this study is the first longitudinal evaluation of PF and further research with more sensitive

adherence and context-sensitive PF measurements and methodologies may give more precise evaluations on which to base future trials or clinical practice.

The study identifies significant methodological problems. However, whilst adherence appears to be multifactorial in nature, findings suggest that ACT may have a small role in helping improve non-adherence in LTCs, but that contextual factors, such as being older, in a relationship, having a longer disease duration, depression and cognitive impairments, should first be considered within an intervention. However, in the current study relationships between mood and PF were medium to strong, consistent with established evidence showing interventions targeting PF can improve mood in the wider LTC and mental health literature. Therefore, ACT's efficacy could reduce non-adherence via improvements in mood.

Less research has been conducted to support the idea that ACT-based approaches may improve adherence outcomes as compared to general and emotional functioning, which might be transferrable to a range of treatments. Currently, studies focusing specifically on adherence are mostly small, uncontrolled and have not measured PF processes as part of mediation analyses. Assessment of key therapeutic mechanisms in larger trials after EMA investigations could further clarify the idiographic and group-level utility of PF model. Moderation analyses will help determine who may benefit and identify at risk groups. In practice, such approaches aim to assist people in opening-up to thoughts and feelings related to non-adherence to pursue valued actions or goals. It might be that designing and evaluating either separate or integrated theories, and corresponding treatment approaches, may lead to more effective psychological interventions for adherence in LTCs in the future.

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Appendix A
Search strategy for literature review

Databases: Medline, PsychInfo, EMBASE December 2017 and April 2019.

1. Adherence/ OR
2. Medication adherence.mp. OR
3. Adherence.mp. OR
4. Non$adherence.mp. OR
5. Compliance/ OR
6. Compliance.mp. OR
7. Concordance/ OR
8. Concordance.mp.

9. Psychotherapy/ OR
10. Psycho*.mp. OR
11. Social cognitive.mp. OR
12. Behavio$r change.mp. OR
13. Acceptance and Commitment Therapy/

14. Chronic health conditions/ OR
15. Chronic illness/ OR
16. Long-term health conditons.mp.

17. 1 to 8 AND 9 to 12 AND 13 to 15

Appendix B
Faculty of Medicine and Health Research Office School of Medicine Research Ethics Committee Letter of Ethical Approval

Faculty of Medicine and Health Research Office
School of Medicine Research Ethics Committee (SoMREC)

Room 9.29, level 9
Worsley Building
Clarendon Way
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United Kingdom

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19 June 2018

Dr Anthony Harrison
Psychologist in Clinical Training
Institute of Health Sciences
Clinical Psychology Training Programme
School of Medicine, Level 10 Worsley Building,
Clarendon Way Leeds LS2 9NL

Dear Anthony

Ref no: **MREC17-068**

Title: **Exploring longitudinal relationships between new ecological momentary assessment (EMA) and existing group-based measures of psychological flexibility, medication adherence and general functioning in adolescents and adults with long-term health conditions (LTCs): A proof of concept and preliminary measure validation study**

(Short title: Medication Adherence in Physical health conditions (MAP) study)

Your research application has been reviewed by the School of Medicine Ethics Committee (SoMREC) and we can confirm that ethics approval is granted based on the following documentation received from you and subject to the following condition *which must be fulfilled prior to the study commencing:*

Evidence of gatekeeper permission from the recruitment organisations must be submitted

Document	*Version*	*Date Submitted*
Ethical_Review_Form_ThesisHarrison A FINAL v3	3.0	18/06/2018

Appendix 1: Study Advertisements v3	3.0	18/06/2018
Appendix 2: Welcome message on Bristol Online Survey (BOS) for adolescents (aged 16-17) and adults v3	3.0	18/06/2018
Appendix 3: Adolescent (aged 16-17) and adult participant information sheet on Bristol Online Survey (BOS) v3	3.0	18/06/2018
Appendix 4: Welcome message on Bristol Online Survey (BOS) parental consent (adolescents aged 13-15) v3	3.0	18/06/2018
Appendix 5: Parental participant information sheet on Bristol Online Survey (BOS) v3	3.0	18/06/2018
Appendix 6: Adolescent (aged 13-15) participant information sheet on Bristol Onlin Survey (BOS) v3	e 3.0	18/06/2018
Appendix 7: BOS questionnaires: Adults (18+) version v3 15/06/18	3.0	18/06/2018
Appendix 8: BOS questionnaire: Adolescents (13 to 17) version v3 15/06/18	3.0	18/06/2018

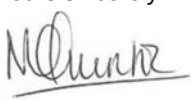
Please notify the committee if you intend to make any amendments to the original research ethics application or documentation. All changes must receive ethics approval prior to implementation. Please contact the Faculty Research Ethics Administrator for further information (fmhuniethics@leeds.ac.uk)

Ethics approval does not infer you have the right of access to any member of staff or student or documents and the premises of the University of Leeds. Nor does it imply any right of access to the premises of any other organisation, including clinical areas. The committee takes no responsibility for you gaining access to staff, students and/or premises prior to, during or following your research activities.
Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, risk assessments and all other documents relating to the study. This should be kept in your study file, which should be readily available for audit purposes. You will be given a two week notice period if your project is to be audited.

It is our policy to remind everyone that it is your responsibility to comply with Health and Safety, Data Protection and any other legal and/or professional guidelines there may be.

We wish you every success with the project.

Yours sincerely



Dr Naomi Quinton, Co-Chair, SoMREC, University of Leeds
(Approval granted by Co-Chair Dr Naomi Quinton on behalf of the committee).

Appendix C
Participant Information Sheets

C.1 Adolescent (aged 16-17) and adult participant information sheet on Online Surveys

INFORMATION SHEET FOR PARTICIPANTS

YOU CAN PRINT A COPY OF THIS INFORMATION SHEET OR YOU CAN REQUEST THAT WE CAN SEND YOU A VERSION TO YOUR EMAIL

Medication Adherence in Physical health conditions (MAP) study

We would like to invite you to take part in a research study conducted by Leeds University. The study will investigate people's experiences of taking medication for physical health conditions. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with family members or friends if you wish. Please contact the research team if anything is unclear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Who is conducting, organising and funding the study?

This project is being conducted by Dr. Anthony Harrison (Principal Investigator), Psychologist in Clinical Training at the University of Leeds. The study is being conducted as part of Anthony's doctoral studies along with his supervisors, Dr. Christopher Graham and Dr. Gary Latchford (Chief Investigator). It is an unfunded study, forming part of Anthony's Doctorate in Clinical Psychology at Leeds University.

What is the purpose of the study?

Previous research has shown that people living with illness may not always take prescribed medication to manage their condition. How people think and feel is related to whether they take medication or not, where most studies have focused on people's mood or beliefs about their medication or illness specifically. However, little research has explored how people relate to their thinking, and how certain types of behaviour might also impact on how they take their medication. We are interested in how people with chronic health conditions respond to taking their medication, how much it affects them, and how they deal with it on the day-to-day. Better understanding how people with chronic health conditions relate to their thinking about medication, and how they behave, will help researchers develop new treatments aiming to support people living with illness.

Why have I been chosen?

You have been approached about this study because you are 16 years old or older and have a physical health condition and have been prescribed medication to manage it. We have invited people with a variety of conditions to take part in the project.

Do I have to take part?

No. It is up to you to decide whether to take part or not. If you are interested in taking part, we will ask you to tick a box conforming your consent prior to completing the survey. You are free to change your mind and to withdraw at any time. This will not in any way affect your standard of care.

What will happen to me if I take part?

If you agree to take part after reading this information sheet you can access the online questionnaire directly by continuing with this survey.

The survey will ask you questions about your health condition and how it affects your life, experiences of taking medication, and how you relate to your thoughts, feelings and behaviours, and should take around twenty minutes to complete. You can save a partially completed questionnaire and complete it later if you wish. If you submit a partially completed questionnaire, where possible your information will still be used in our data analysis, unless you request contact us to withdraw your data.

We will ask you to tell us if you wish to complete the questionnaire again at three months. This will allow us to see if and how your experience changes over time. We will ask for your email address at the end of the questionnaire so we can send you the second questionnaire link via email. You can withdraw your data for either the first or second questionnaire up until the final analysis date (01.03.2019) and it will not be used in the final analysis. You will need to contact us directly to request this using the same email address you entered at the start of either questionnaire. If you do not provide us with your email address at the start of either questionnaire your data cannot be withdrawn once submitted because it will be unidentifiable, and we will be unable to link your first questionnaire to your second questionnaire. It is optional to provide your name and email address. Please be aware that if you decide to provide your name and/or email address to receive the follow-up questionnaire and/or results of the study, your questionnaire will not be anonymous.

Will You Compensate Me for My Time?

Unfortunately, this is unfunded study therefore we cannot compensate you for your time. While we very much appreciate your help, and you may find the experience useful, you will not benefit financially from the project. However, at the conclusion of the study, we will send a summary of the results online so you can view the main findings.

Are there any costs?

The questionnaire will take between 20-30 minutes of your time, so other than your time and effort there are no other costs to you associated with the project.

What are the possible disadvantages and risks of taking part?

The risks involved in participating are minimal. It is possible that you might find it distressing to reflect on questions in relation to your own lived experiences of your illness and taking medication. If you get upset, you can skip questions, take a break or decide not to continue with the survey. Should you become unduly distressed during or after completion of the questionnaire and continue to feel this way, we suggest you access sources of support, including your doctor, but also a family member or friend. For any other queries about completing the survey please contact Anthony directly at umamh@leeds.ac.uk, Clinical Psychology Training Programme, Institute of Health Sciences School of Medicine, Level 10 Worsley Building, Clarendon Way, Leeds LS2 9N.

What are the possible benefits of taking part?

There will be no direct benefits to you for taking part in this study. However, the answers that you give will provide the researchers with more information about medication use for people with health conditions. This information may help to improve the treatment of people with illness in the future. In addition, some people may find it helpful or interesting to reflect on how their health condition and medication use affects them. On completing the project, we can send you a summary of our findings if you prefer.

If this study has harmed you in any way…

In the unlikely event that you are unhappy with the way that the project is conducted complaint mechanisms are available to you. In the first instance please contact Dr. Gary Latchford g.latchford@leeds.ac.uk. If you are not satisfied with this process, we advise you contact Clare Skinner, Head of Research Integrity and Governance c.e.skinner@leeds.ac.uk

Will my taking part in the study be kept confidential?

Yes. All information about your participation in this study will be kept confidential in accordance with the Data General Data Protection Regulations 2018. The completed questionnaire data will be downloaded onto a secure university computer. Only the researchers will have access to the computer, which will have a password to protect all confidential files.

Any personal details or identifiable information will be removed and contact details will be stored separately on another password protected file Your information will only be available to members of the research team and will only be used for the purposes of the current study. The data will be kept securely at Leeds University. It will be destroyed three years after the research has finished, and your contact details will be destroyed once results are sent to you should you opt-in for this.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time without having to give a reason even if you decide to take part initially. However, your data cannot be withdrawn once the results have been analysed and written up (01.035.2019).

What will happen to the results of the study?

The results of this study may be published in scientific journals and at medical and psychological academic conferences. You will not be identified in any report or publication. A lay summary of our findings can be emailed to you if you prefer.

Who has reviewed the study?

The study has been reviewed by the University of Leeds School of Medical Research Ethics Subcommittee (SoMREC) (Ref: MREC17-068)

I understand that by that by ticking "I agree" and completing and submitting this questionnaire I am consenting to participate in the study	☐ I agree

C.2 Parental participant information sheet on Online Surveys

UNIVERSITY OF LEEDS

INFORMATION SHEET FOR PARENTS OF ADOLESCENT PARTICIPANTS

YOU CAN PRINT A COPY OF THIS INFORMATION SHEET OR YOU CAN REQUEST THAT WE SEND YOU A VERSION TO YOUR EMAIL

Medication Adherence in Physical health conditions (MAP) study

We would like to invite your child to take part in a research study conducted by Leeds University. The study will investigate young people's experiences of taking medication for physical health conditions. Before you decide whether you want your child to take part, it is important for you to understand why the research is being done and what their participation will involve. Please take time to read the following information carefully and discuss it with family members or friends if you wish. Please contact the research team if anything is unclear or if you would like more information. Take time to decide whether or not you wish for your child to take part. Thank you for reading this.

Who is conducting, organising and funding the study?

This project is being conducted by Dr. Anthony Harrison (Principal Investigator), Psychologist in Clinical Training at the University of Leeds. The study is being conducted as part of Anthony's doctoral studies along with his supervisors, Dr. Christopher Graham and Dr. Gary Latchford (Chief Investigator). It is an unfunded study, forming part of Anthony's Doctorate in Clinical Psychology at Leeds University.

What is the purpose of the study?

Previous research has shown that young people living with illness may not always take prescribed medication to manage their condition. How young people think and feel is related to whether they take medication or not, where most studies have focused on their mood or beliefs about their medication or illness specifically. However, little research has explored how people relate to their thinking, and how certain types of behaviour might also impact on how they take their medication. We are interested in how young people with chronic health conditions respond to taking their medication, how much it affects them, and how they deal with it on the day-to-day. Better understanding how young people with chronic health conditions relate to their thinking about medication, and how they behave, will help researchers develop new treatments aiming to support them living with illness.

Why has my child been chosen?

You have been approached about this study because your child has a physical health condition and has been prescribed medication to manage it. We have invited young people with a variety of conditions to take part in the project.

Does my child have to take part?

No. It is up to you and your child to decide whether to take part or not. If you are interested in your child taking part, we will ask you to tick a box conforming your consent prior to getting their consent before they complete the survey. You are both free to change your mind and to withdraw at any time. This will not in any way affect your child's standard of care.

What will happen to my child if they take part?

If you agree for your child to take part after reading this information sheet and reviewing the questionnaire in the following pages you will be asked to submit a consent form and provide an electronic signature at the end. At which point, your child can then access the online questionnaire directly by following a weblink provided. It may be helpful to discuss participation in the study with your child/children prior to them agreeing to participate.

The survey will ask your child questions about their health condition and how it affects their life, experiences of taking medication, and how it relates to their thoughts, feelings and behaviours. It should take around twenty minutes to complete. Your child can save a partially completed questionnaire and complete it later if they wish. If your child submits a partially completed questionnaire, where possible their information will still be used in our data analysis, unless you or they contact us to request we withdraw their data.

We will ask your child if they wish to complete the questionnaire again at three months. This will allow us to see if and how their experience, changes over time. We will ask for their email address at the end of the questionnaire so we can send the second questionnaire link to them via email. You or your child can withdraw their data for either the first or second questionnaire up until the final analysis date (01.03.2019) and it will not be used in the final analysis. They or you will need to contact us directly to request this using the same email address they or you entered at the start of both questionnaires. If your child or you do not provide us with your email address at the start of either questionnaire their data cannot be withdrawn once submitted because it will be unidentifiable, and we will be unable to link your child's first questionnaire to their second questionnaire. It is optional to provide your name and email address. Please be aware that if you decide to provide your name and/or email address to receive the follow-up questionnaire and/or results of the study, your questionnaire will not be anonymous.

Will you compensate me or my child for our time?

Unfortunately, this is unfunded study therefore we cannot compensate for you or your child's time. While we very much appreciate your help, and your child may find the experience useful, your child will not benefit financially from the project. However, at the conclusion of the study, we can send a summary of the results to you via email so you can view the main findings.

Are there any costs?

The questionnaire will take between 20-30 minutes of your child's time, so other than their time and effort there are no other costs to you associated with the project.

What are the possible disadvantages and risks of taking part?

The risks involved in participating are minimal. It is possible that you and your child might find it distressing to reflect on questions in relation to your own lived experiences of your illness and taking medication. If your child gets upset, they can skip questions, take a break or decide not to continue with the survey. Should you or your child become unduly distressed during or after viewing or completing the questionnaire and continue to feel this way, we suggest you access sources of support, including your GP or current NHS clinician/s, NHS 111 (Tel: 111), or other organisations, such as The Samaritans (Tel: 116 123). For any other queries about completing the survey please contact Anthony directly at umamh@leeds.ac.uk, Clinical Psychology Training Programme, Institute of Health Sciences School of Medicine, Level 10 Worsley Building, Clarendon Way, Leeds LS2 9N.

What are the possible benefits of taking part?

There will be no direct benefits to your child for taking part in this study. However, the answers that they give will provide the researchers with more information about medication use for young people with health conditions. This information may help to improve the treatment of young people with illness in the

future. In addition, some young people may find it helpful or interesting to reflect on how their health condition and medication use affects them. On completing the project, we can send you a summary of our findings if you prefer.

If this study has harmed your child in any way…

In the unlikely event that you are unhappy with the way that the project is conducted complaint mechanisms are available to you. In the first instance please contact Dr. Gary Latchford g.latchford@leeds.ac.uk. If you are not satisfied with this process, we advise you contact Clare Skinner, Head of Research Integrity and Governance c.e.skinner@leeds.ac.uk

Will my child's data be kept confidential?

Yes. All information about your child's participation in this study will be kept confidential in accordance with the General Data Protection Regulations 2018. The completed questionnaire data will be downloaded onto a secure university computer. Only the researchers will have access to the computer, which will have a password to protect all confidential files.

Any personal details or identifiable information will be removed and contact details will be stored separately on another password protected file. Your child's information will only be available to members of the research team and will only be used for the purposes of the current study. The data will be kept securely at Leeds University. It will be destroyed three years after the research has finished, and your contact details will be destroyed once results are sent to you should you opt-in for this.

What will happen if I don't want to carry on with the study?

You and your child are free to withdraw from the study at any time without having to give a reason even if you decide to take part initially. However, your child's data cannot be withdrawn once the results have been analysed and written up (01.03.2019).

What will happen to the results of the study?

The results of this study may be published in scientific journals and at medical and psychological academic conferences. Your child will not be identified in any report or publication. A lay summary of our findings can be emailed to you if you prefer.

Who has reviewed the study?

The study has been reviewed by the University of Leeds School of Medical Research Ethics Subcommittee (SoMREC) (Ref: MREC17-068).

Please now review the questionnaire in the following pages using the "Back" and "Next" function at the bottom of each page. At the end of the questionnaire you will be asked to submit a consent form and provide an electronic signature. At which point your child can then access the online questionnaire directly by following the weblink provided.

[After survey review]

I understand that by ticking "I agree" and submitting this form I am consenting to my child's/children's participation in the study	☐ I agree

Providing your contact email is optional. However, providing your email will mean we can withdraw your child's and your data before the final analysis date if you wish (01.03.2019). We could also send you the results of this study and news about related future studies. **IMPORTANT**: If your child does not provide your (or their own) email address in their second questionnaire in 3 months, we will be unable to link it up with their data from the first questionnaire.
Your email address:
Your child's full name:
On submitting your parental consent, please advise your child that they can now complete their consent form and survey on their own: [Link to adolescent version of survey]

C.3 Adolescent (aged 13-15) participant information sheet on Online Surveys

UNIVERSITY OF LEEDS

INFORMATION SHEET FOR PARTICIPANTS

YOU CAN PRINT A COPY OF THIS INFORMATION SHEET OR YOU CAN REQUEST THAT WE SEND YOU A VERSION TO YOUR EMAIL

Medication Adherence in Physical health conditions (MAP) study

Hi! My name is Dr. Anthony Harrison. I'm a researcher and psychologist doing my clinical training at Leeds University. Right now, I'm trying to learn more about how young people take their medications for their illness. I would like to ask you to help me by being in a study, but before I do, I want to explain what will happen if you decide to help me. So please take time to read the below information and discuss it with family members or friends if helpful. Thank you for reading this!

If you want to take part, you can go ahead and complete the questionnaire after reading this page, which will ask you about how you think and feel about taking medications for your health condition, and how deal with it from day-to-day. There are no right or wrong answers! It should take about 20 to 30 minutes to finish. You can save a nearly finished questionnaire and complete it later if you want. If you submit a half-completed questionnaire, your information will probably still be used in our data analysis, unless you tell us to take it out. We will send a reminder to your email asking you to complete the same questionnaire again in three months to help us to see if things change over time for you. You can take out your data up until 01.03.2019 and it will not be used in the final analysis. If you want to take it out, you will need to contact me using your same email address you enter below. If you do not share your email address with me your data cannot be taken out once you submit this questionnaire because I won't know who you are! You don't have to provide your name and email address. Please be aware that if you decide to share your name and/or email address to get the follow-up questionnaire and/or results of the study, your questionnaire will not be anonymous.

There are no costs to taking part, other than your time and effort. By being in the study, you will help me understand why young people take or don't take medication for their physical health condition.

You might find thinking about some of the questions upsetting. If you get upset, you can skip questions, take a break or decide not to carry on with the questionnaire. Should you become really upset during or after completing the questionnaire, and continue to feel this way, we suggest you ask you or your parent / guardian to contact your doctor, or NHS 111 (Telephone: 111), or other services like The Samaritans (Telephone: 116 123). If you have any other questions about the survey please contact me directly at umamh@leeds.ac.uk or Clinical Psychology Training Programme, Institute of Health Sciences School of Medicine, Level 10 Worsley Building, Clarendon Way, Leeds LS2 9N.

There will be no direct benefits for you taking part in this study (e.g. we can't give you any money), but the answers that you give will give me with more information about medication use for young people with health conditions. This information may help to make treatments for young people better in the future. Also, some young people may find it helpful or interesting to think about how their health condition and medication use makes them think, feel and behave. We can also send you a summary of our findings if you like.

Your parents/guardian will not know what you have said in the questionnaire. When I tell other people about my study, I will not use your name, and no one will be able to tell who I'm talking about. Your questionnaire

data will be downloaded onto a secure Leeds University computer. Only me and my team will get onto the computer, and we will use a password-protected files. All your information will be deleted after 3 years. Your contact details will be destroyed as soon as the once results are sent to you should you want them.

Your parent / guardian has said it's okay for you to be in my study. But if you don't want to be in the study, you don't have to be. What you decide won't make any difference to the care you receive for your health condition. I won't be upset, and no one else will be upset, if you don't want to be in the study. If you want to be in the study now but change your mind later, that's okay. You can stop at any time. If there is anything you don't understand you should tell me so I can explain it to you.

The results of this study may be written-up in scientific journals and at medical and psychological conferences. You will not be identified in any report or publication. We can send you a copy of our findings if you like.

The questionnaire has been seen by the University of Leeds University Ethics Committee who said they thought it was fine (Reference number: MREC17-068).

You can ask me questions about the study. If you have a question later that you don't think of now, you can email me or ask your parents to call me or send me an email.

Do you have any questions for me now? If so please email me: umamh@leeds.ac.uk

Would you like to be in my study and answer some questions about your how you take your medication?

I understand that by that by ticking "I agree" and completing and submitting this questionnaire I am consenting to participate in the study	☐ I agree

Appendix D
Final Online Survey questionnaire for Adults (18+) version

Demographic and illness information

Please feel free to take a break at any point. You can save your progress at the bottom of each page using the **'Finish Later'** button on each questions page of the survey.

Questions About Your Illness:	
What physical health condition do you have that you need to take medication for? If you have more than one, please indicate which you consider to be your primary illness. (This was a drop-down menu of all physical health conditions, including an "other" option)	
Do you have more than one physical health conditions listed?	**Please tick**
Yes	☐
No	☐
When was your long-term health condition diagnosed? (DD/MM/YY):	
Are you prescribed medications for your illness?	**Please tick**
Yes	☐
No (please do not continue with this survey)	☐

Questions About You:	
What is your age (years):	
How do you identify your gender?	**Please tick**
Female	☐
Male	☐
Other gender identity (please specify):	☐

What is your ethnicity?			
☐ White - English / Welsh / Scottish / Northern Irish / British / Irish /Gypsy or Irish Traveller / Any Other White background	☐ Mixed / Multiple ethnic group - White and Black Caribbean / White and Black African / White and Asian / Any Other Mixed / multiple ethnic background	☐ Asian / Asian British – Indian / Asian British – Pakistani / Asian British – Bangladeshi / Asian British – Chinese / Asian British - Any other Asian background	☐ Black / African / Caribbean / Black British – African / Black British – Caribbean / Black British – Any other Black
		☐ Other ethnic group – Arab Other ethnic group – Any other ethnic group	☐ Not known / not provided

In what country do you currently live? (This was a drop-down menu of all countries)	
What is your present relationship status?	**Please tick**
Single	☐
Married / Civil partnership	☐
Widowed	☐
Separated / Divorced	☐
Co-habiting / Living together	☐
Other (please state):	☐

How many years of education have you completed: _____ (*Years)*	
Which of the following best describes your current occupational status?	**Please tick**
Employed outside the home, full-time	☐
Employed outside the home, part-time	☐
Self-employed	☐
Homemaker	☐
Retired	☐
Medically retired	☐
Unemployed	☐
Full / part-time student	☐
Other (please state):	☐

Work and Social Adjustment Scale (WSAS)
(Mundt, Marks, Shear, & Greist, 2002)

Questions about your illness:

Physical health conditions sometimes affect people's ability to do certain day-to-day tasks. To rate problems related to your illness please look at each statement below and use the scale provided to indicate how much your illness impairs your ability to carry out the activity.

Because of my illness my **ability to work/study** is impaired. '0' means 'not at all impaired' and '8' means very severely impaired to the point I can't work.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness my **home management** (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness my **social leisure activities** (with other people e.g. parties, bars, clubs, outings, visits, dating, home entertaining) are impaired.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness, my **private leisure activities** (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness, my ability to form and maintain **close relationships** with others, including those I live with, is impaired.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**

Medication Adherence Report Scale 5-items (MARS-5)
(Horne, Hankins, & Jenkins, 2001).

Questions about your medication for your illness:

Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines**. For each statement, please tick the box which best applies to you.**

	Never	Seldom	Sometimes	Often	Always
I forget to take my medication					
I adjust the dosage of my medication					
I stop using my medication for a while					
I decide to skip my medication doses					
I take fewer tablets than prescribed to me					

New non-validated single-item daily momentary numerical rating scale for self-reported adherence

In your view, how good have you been at taking your medications for your illness on time and as prescribed Today. Please rate on a scale of 0 (not good at all) to 10 (extremely good):

0	1	2	3	4	5	6	7	8	9	10

Please indicate if not applicable: ☐

New non-validated single-item hourly momentary numerical rating scale for self-reported adherence

Over the past hour, in your view how good have you been at taking your medications for your illness on time and as prescribed. Please rate on a scale of 0 (not good at all) to 10 (extremely good):

0	1	2	3	4	5	6	7	8	9	10

Please indicate if not applicable: ☐

New non-validated scales exploring health care utilisation as a proxy of adherence

In the last two to three months, what percentage of routine appointments for your illness have you attended?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Please indicate if not applicable: ☐

In the last year, what percentage of routine appointments for your illness have you attended?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Please indicate if not applicable: ☐

Acceptance and Action Questionnaire (AAQ-II)
(Bond et al., 2011)

Questions about your thinking and how you're feeling more generally:

Below you will find a list of statements. Please indicate how true each statement is for you by selecting the relevant box.

	Never true	Very seldom true	Seldom true	Sometimes true	Frequently true	Almost always true	Always true
1. My painful experiences and memories make it difficult for me to live a life that I would value.	1	2	3	4	5	6	7
2. I'm afraid of my feelings.	1	2	3	4	5	6	7
3. I worry about not being able to control my worries and feelings.	1	2	3	4	5	6	7
4. My painful memories prevent me from having a fulfilling life.	1	2	3	4	5	6	7
5. Emotions cause problems in my life.	1	2	3	4	5	6	7
6. It seems like most people are handling their lives better than I am.	1	2	3	4	5	6	7
7. Worries get in the way of my success.	1	2	3	4	5	6	7

Comprehensive assessment of Acceptance and Commitment Therapy processes (CompACT)
(Francis, Dawson and Golijani-Moghaddam, 2016)

Please rate the following 23 statements using the scale below:

	Strongly disagree	Moderately disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Moderately agree	Strongly agree
1. I can identify the things that really matter to me in life and pursue them	0	1	2	3	4	5	6
2. One of my big goals is to be free from painful emotions	0	1	2	3	4	5	6
3. I rush through meaningful activities without being really attentive to them	0	1	2	3	4	5	6
4. I try to stay busy to keep thoughts or feelings from coming	0	1	2	3	4	5	6
5. I act in ways that are consistent with how I wish to live my life	0	1	2	3	4	5	6

6. I get so caught up in my thoughts that I am unable to do the things that I most want to do	0	1	2	3	4	5	6
7. I make choices based on what is important to me, even if it is stressful	0	1	2	3	4	5	6
8. I tell myself that I shouldn't have certain thoughts	0	1	2	3	4	5	6
9. I find it difficult to stay focused on what's happening in the present	0	1	2	3	4	5	6
10. I behave in line with my personal values	0	1	2	3	4	5	6
11. I go out of my way to avoid situations that might bring difficult thoughts, feelings, or sensations	0	1	2	3	4	5	6
12. Even when doing the things that matter to me, I find myself doing them without paying attention	0	1	2	3	4	5	6

13. I am willing to fully experience whatever thoughts, feelings and sensations come up for me, without trying to change or defend against them	**0**	**1**	**2**	**3**	**4**	**5**	**6**
14. I undertake things that are meaningful to me, even when I find it hard to do so	**0**	**1**	**2**	**3**	**4**	**5**	**6**
15. I work hard to keep out upsetting feelings	**0**	**1**	**2**	**3**	**4**	**5**	**6**
16. I do jobs or tasks automatically, without being aware of what I'm doing	**0**	**1**	**2**	**3**	**4**	**5**	**6**
17. I am able to follow my long terms plans including times when progress is slow	**0**	**1**	**2**	**3**	**4**	**5**	**6**
18. Even when something is important to me, I'll rarely do it if there is a chance it will upset me	**0**	**1**	**2**	**3**	**4**	**5**	**6**

19. It seems I am "running on automatic" without much awareness of what I'm doing	**0**	**1**	**2**	**3**	**4**	**5**	**6**
20. Thoughts are just thoughts – they don't control what I do	**0**	**1**	**2**	**3**	**4**	**5**	**6**
21. My values are really reflected in my behaviour	**0**	**1**	**2**	**3**	**4**	**5**	**6**
22. I can take thoughts and feelings as they come, without attempting to control or avoid them	**0**	**1**	**2**	**3**	**4**	**5**	**6**
23. I can keep going with something when it's important to me	**0**	**1**	**2**	**3**	**4**	**5**	**6**

New 9-item daily momentary Psychological Flexibility scale of "Open, Aware, Engaged" to be statistically reduced to 3 items.

Below you will find a list of statements. Please indicate how true each statement is for you by selecting the relevant number.

Today:

	Not at all					Some-what					Very much
1. I struggled to control my thoughts or feelings	0	1	2	3	4	5	6	7	8	9	10
2. I put a lot of effort into making my thoughts or feelings stop or go away*	0	1	2	3	4	5	6	7	8	9	10
3. I got upset with myself for having certain thoughts or feelings.	0	1	2	3	4	5	6	7	8	9	10
4. I thought about things that happened in the past or worried about the future, instead of what was happening at the time.	0	1	2	3	4	5	6	7	8	9	10
5. I found it difficult to stay focused on what was happening in the present	0	1	2	3	4	5	6	7	8	9	10
6. I did jobs or tasks automatically, without being aware of what I was doing	0	1	2	3	4	5	6	7	8	9	10
7. I stopped doing things that were important to me when I felt bad.	0	1	2	3	4	5	6	7	8	9	10

8. My worries and fears got in the way of doing the things that mattered to me.	0	1	2	3	4	5	6	7	8	9	10
9. I got so wrapped up in what I was thinking or feeling that I couldn't do the things that mattered to me.	0	1	2	3	4	5	6	7	8	9	10

New 9-item hourly momentary Psychological Flexibility scale of "Open, Aware, Engaged" to be statistically reduced to 3 items.

Within the last hour or so:

	Not at all					Some-what					Very much
1. I struggled to control my thoughts or feelings	0	1	2	3	4	5	6	7	8	9	10
2. I put a lot of effort into making my thoughts or feelings stop or go away*	0	1	2	3	4	5	6	7	8	9	10
3. I got upset with myself for having certain thoughts or feelings.	0	1	2	3	4	5	6	7	8	9	10
4. I thought about things that happened in the past or worried about the future, instead of what was happening at the time.	0	1	2	3	4	5	6	7	8	9	10
5. I found it difficult to stay focused on what was happening in the present	0	1	2	3	4	5	6	7	8	9	10

6. I did jobs or tasks automatically, without being aware of what I was doing	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
7. I stopped doing things that were important to me when I felt bad.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
8. My worries and fears got in the way of doing the things that mattered to me.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
9. I got so wrapped up in what I was thinking or feeling that I couldn't do the things that mattered to me.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Patient Health Questionnaire 8-items (PHQ-8)
(Kroenke, et al. 2009; Johnson, 2002)

Over the last 2 weeks, how often have you been bothered by the following problems? *(Please indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling asleep or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite and overeating	0	1	2	3
6. Feeling bad about yourself – or that you're a failure and let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading a newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being also fidgety or restless that you have been moving around a lot more than usual.	0	1	2	3

Generalised Anxiety Disorder Scale 7 items (GAD-7)
(Spitzer, Kroenke, Williams, & Löwe, 2006; Mossman et al, 2017).

Over the last 2 weeks, how often have you been bothered by the following problems? *(Please indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen?	0	1	2	3

Modified daily version of the Patient Health Questionnaire 2 items (PHQ-2) (Kroenke, Spitzer, & Williams, 2003)

How often have you been bothered by the following problems today? *(Please indicate your answer)*	Not at all			Very much
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

Modified hourly version of the Patient Health Questionnaire 2 items (PHQ-2) (Kroenke, Spitzer, & Williams, 2003)

Over the last hour or so, how often have you been bothered by the following problems? *(Please indicate your answer)*	Not at all			Very much
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

Modified daily version of the Generalised Anxiety Disorder (GAD-2) scale (Skapinakis, 2007)

How often have you been bothered by the following problems today? *(Please indicate your answer)*	Not at all			Very much
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3

Modified hourly version of the Generalised Anxiety Disorder (GAD-2) scale (Skapinakis, 2007)

Over the last hour or so, how often have you been bothered by the following problems? *(Please indicate your answer)*	Not at all			Very much
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3

Appendix E
Final Online Survey questionnaire for Adolescent (13-17) version

Demographic and illness information

Please feel free to take a break at any point. You can save your progress at the bottom of each page using the **'Finish Later'** button on each questions page of the survey.

Questions About Your Illness:	
What physical health condition do you have that you need to take medication for? If you have more than one, please indicate which you consider to be your primary illness. (This was a drop-down menu of all physical health conditions, including an "other" option)	
Do you have more than one physical health conditions listed?	**Please tick**
Yes	☐
No	☐
When was your physical health condition diagnosed? (DD/MM/YY):	
Are you prescribed medications for your illness?	**Please tick**
Yes	☐
No (please do not continue with this survey)	☐

Questions About You:	
What is your age (years):	
How do you identify your gender?	**Please tick**
Female	☐
Male	☐
Other gender identity (please specify):	☐

What is your ethnicity?			
☐ White - English / Welsh / Scottish / Northern Irish / British / Irish /Gypsy or Irish Traveller / Any Other White background	☐ Mixed / Multiple ethnic group - White and Black Caribbean / White and Black African / White and Asian / Any Other Mixed / multiple ethnic background	☐ Asian / Asian British – Indian / Asian British – Pakistani / Asian British – Bangladeshi / Asian British – Chinese / Asian British - Any other Asian background	☐ Black / African / Caribbean / Black British – African / Black British – Caribbean / Black British – Any other Black
		☐ Other ethnic group – Arab Other ethnic group – Any other ethnic group	☐ Not known / not provided

In what country do you currently live? **(This will be a drop-down menu of all countries)**	
What is your present relationship status?	**Please tick**
Single	☐
In a relationship	☐
Other (please state):	☐

How many years of education have you completed: _____ (*Years)*	
Which of the following best describes your current education status?	**Please tick**
Full-time student	☐
Part-time student	☐
Homeschooled	☐
Other (please state):	☐

New modified version of the Work and Social Adjustment Scale for adolescents (WSAS) (Mundt, Marks, Shear, & Greist, 2002)

Questions about your illness:

Illnesses sometimes affect people's ability to do certain day-to-day tasks. To rate problems related to your illness please look at each statement below and use the scale provided to indicate how much your illness affects your ability to carry out the activity.

Because of my illness my **ability to study** is badly affected. '0' means 'not at all a problem' and '8' means "very severely" affected to the point I can't study.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness my attention to **home tasks** (e.g. cleaning tidying my room) is badly affected.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness my **social leisure activities** (with other people e.g. parties, outings, visits, dating, having people over) are badly affected.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness, my **private leisure activities** (done alone, such as reading, playing, walking alone) are badly affected.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**
Because of my illness, my ability to form and keep **close relationships** with others, including those I live with, is badly affected.								
0 Not at all	**1**	**2 Slightly**	**3**	**4 Definitely**	**5**	**6 Markedly**	**7**	**8 Very Severely**

Medication Adherence Report Scale 5-items (MARS-5)
(Horne, Hankins, & Jenkins, 2001).

Questions about your medication for your illness:

Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines**. For each statement, please select the box which best applies to you.**

	Never	Seldom	Sometimes	Often	Always
I forget to take my medication					
I adjust the dosage of my medication					
I stop using my medication for a while					
I decide to skip my medication doses					
I take fewer tablets than prescribed to me					

New non-validated single-item daily momentary numerical rating scale for self-reported adherence

In your view, how good have you been at taking your medications for your illness on time and as prescribed Today. Please rate on a scale of 0 (not good at all) to 10 (extremely good):

0	1	2	3	4	5	6	7	8	9	10

Please indicate if not applicable: ☐

New non-validated single-item hourly momentary numerical rating scale for self-reported adherence

Over the past hour, in your view how good have you been at taking your medications for your illness on time and as prescribed. Please rate on a scale of 0 (not good at all) to 10 (extremely good):

0	1	2	3	4	5	6	7	8	9	10

Please indicate if not applicable: ☐

In the last two to three months, roughly what percentage of routine appointments for your illness have you attended?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Please indicate if not applicable: ☐

New non-validated scales exploring health care utilisation as a proxy of adherence

In the last year, roughly what percentage of routine appointments for your illness have you attended?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Please indicate if not applicable: ☐

Avoidance and Fusion Questionnaire for Youth 8-items (AFQ-Y-8)
(Greco, Lambert, & Baer, 2008)

We want to know more about what you think, how you feel, and what you do. Read each sentence. Then, select a number between 0-4 that tells how true each sentence is for you.

	Not at all True	A little True	Pretty True	True	Very True
1. My life won't be good until I feel happy.	0	1	2	3	4
2. My thoughts and feelings mess up my life.	0	1	2	3	4
3. The bad things I think about myself must be true.	0	1	2	3	4
4. If my heart beats fast, there must be something wrong with me.	0	1	2	3	4
5. I stop doing things that are important to me whenever I feel bad.	0	1	2	3	4
6. I do worse in school when I have thoughts that make me feel sad.	0	1	2	3	4
7. I am afraid of my feelings.	0	1	2	3	4
8. I can't be a good friend when I feel upset.	0	1	2	3	4

Child and Adolescent Mindfulness Measure (CAMM)
(Greco, Baer, & Smith, 2011)

We want to know more about what you think, how you feel, and what you do. **Read** each sentence. Then, select the number that tells **how often each sentence is true for you.**

	Never True	Rarely True	Some-times True	Often True	Always True
1. I get upset with myself for having feelings that don't make sense.	0	1	2	3	4
2. At school, I walk from class to class without noticing what I'm doing.	0	1	2	3	4
3. I keep myself busy so I don't notice my thoughts or feelings.	0	1	2	3	4
4. I tell myself that I shouldn't feel the way I'm feeling.	0	1	2	3	4
5. I push away thoughts that I don't like.	0	1	2	3	4
6. It's hard for me to pay attention to only one thing at a time.	0	1	2	3	4
7. I get upset with myself for having certain thoughts.	0	1	2	3	4
8. I think about things that have happened in the past instead of thinking about things that are happening right now.	0	1	2	3	4
9. I think that some of my feelings are bad and that I shouldn't have them.	0	1	2	3	4
10. I stop myself from having feelings that I don't like.	0	1	2	3	4

New 9-item daily momentary Psychological Flexibility scale of "Open, Aware, Engaged" to be statistically reduced to 3 items.

Below you will find a list of statements. Please indicate how true each statement is for you by selecting the relevant number.

Today:

	Not at all					Some-what					Very much
1. I struggled to control my thoughts or feelings	0	1	2	3	4	5	6	7	8	9	10
2. I put a lot of effort into making my thoughts or feelings stop or go away*	0	1	2	3	4	5	6	7	8	9	10
3. I got upset with myself for having certain thoughts or feelings.	0	1	2	3	4	5	6	7	8	9	10
4. I thought about things that happened in the past or worried about the future, instead of what was happening at the time.	0	1	2	3	4	5	6	7	8	9	10
5. I found it difficult to stay focused on what was happening in the present	0	1	2	3	4	5	6	7	8	9	10
6. I did jobs or tasks automatically, without being aware of what I was doing	0	1	2	3	4	5	6	7	8	9	10
7. I stopped doing things that were important to me when I felt bad.	0	1	2	3	4	5	6	7	8	9	10

8. My worries and fears got in the way of doing the things that mattered to me.	0	1	2	3	4	5	6	7	8	9	10
9. I got so wrapped up in what I was thinking or feeling that I couldn't do the things that mattered to me.	0	1	2	3	4	5	6	7	8	9	10

New 9-item hourly momentary Psychological Flexibility scale of "Open, Aware, Engaged" to be statistically reduced to 3 items.

Within the last hour or so:

	Not at all					Some-what					Very much
1. I struggled to control my thoughts or feelings	0	1	2	3	4	5	6	7	8	9	10
2. I put a lot of effort into making my thoughts or feelings stop or go away*	0	1	2	3	4	5	6	7	8	9	10
3. I got upset with myself for having certain thoughts or feelings.	0	1	2	3	4	5	6	7	8	9	10
4. I thought about things that happened in the past or worried about the future, instead of what was happening at the time.	0	1	2	3	4	5	6	7	8	9	10
5. I found it difficult to stay focused on what was happening in the present	0	1	2	3	4	5	6	7	8	9	10
6. I did jobs or tasks automatically, without being aware of what I was doing	0	1	2	3	4	5	6	7	8	9	10
7. I stopped doing things that were important to me when I felt bad.	0	1	2	3	4	5	6	7	8	9	10

8. My worries and fears got in the way of doing the things that mattered to me.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
9. I got so wrapped up in what I was thinking or feeling that I couldn't do the things that mattered to me.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Patient Health Questionnaire 8-items Adolescent version taken from the 9 item (PHQ-A)

(Johnson, 2002)

Instructions: How often have you been bothered by each of the following symptoms during the **past two weeks**? For each symptom put an "X" in the box beneath the answer that best describes how you have been feeling.				
(Please indicate your answer)	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling down, depressed, irritable or hopeless?	0	1	2	3
2. Little interest or pleasure in doing things?	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much?	0	1	2	3
4. Poor appetite, weight loss, or overeating?	0	1	2	3
5. Feeling tired, or having little energy?	0	1	2	3
6. Feeling bad about yourself – or feeling that you are a failure and let yourself or your family down?	0	1	2	3
7. Trouble concentrating on things like school work, reading, or watching TV	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. **Or the opposite – being also fidgety or restless that you have been moving around a lot more than usual.**	0	1	2	3

Generalised Anxiety Disorder Scale 7 items (GAD-7)
(Spitzer, Kroenke, Williams, & Löwe, 2006; Mossman et al, 2017).

Over the last 2 weeks, how often have you been bothered by the following problems? *(Please indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen?	0	1	2	3

Modified daily version of the Patient Health Questionnaire 2 items (PHQ-2) (Kroenke, Spitzer, & Williams, 2003)

How often have you been bothered by the following problems today? *(Please indicate your answer)*	Not at all			Very much
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

Modified hourly version of the Patient Health Questionnaire 2 items (PHQ-2) (Kroenke, Spitzer, & Williams, 2003)

Over the last hour or so, how often have you been bothered by the following problems? *(Please indicate your answer)*	Not at all			Very much
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

Modified daily version of the Generalised Anxiety Disorder (GAD-2) scale (Skapinakis, 2007)

How often have you been bothered by the following problems today? *(Please indicate your answer)*	Not at all			Very much
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3

Modified hourly version of the Generalised Anxiety Disorder (GAD-2) scale (Skapinakis, 2007)

Over the last hour or so, how often have you been bothered by the following problems? *(Please indicate your answer)*	**Not at all**			**Very much**
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3

Appendix F
Email communication from Doctor Nima Moghaddam regarding sample descriptive data for CompACT total and subscale scores with only 20.0% scale item missing

Nima Moghaddam <NMoghaddam@lincoln.ac.uk>

Reply all

Mon 07/01, 15:49

Anthony Harrison

Research Project

Flag for follow up. Completed on 30 January 2019.

You replied on 07/01/2019 21:59.

Hi Anthony,

There's a collaborative European project that is handling missing CompACT data in a way that resembles your second approach: Allowing for 25% missing item-level data and using mean (versus total) scores – they're using the Mean function in SPSS syntax, which will automatically divide by the number of valid values (adjusting the item-count for items with missing data).

It would be possible to empirically test a few imputation methods (within a sub-set of complete data: comparing methods to see which provides the best approximation of values obtained with the complete data [as a benchmark]) but we think the mean-scoring approach would be defensible. For reference, here are the descriptive stats for the CompACT when mean-scored (0-6 scale) in our original (general population) sample (N = 352):
Openness to Experience: Mean = 3.18; SD = 1.30
Behavioural Awareness: Mean = 3.40; SD = 1.37
Valued Action: Mean = 4.76; SD = 0.88
CompACT Total (Psych Flex): Mean = 3.78; SD = 0.91

Best wishes,

Nima

Appendix G

Initial 22-items for new momentary Psychological Flexibility "Open, Aware, Engaged" questionnaire (daily/hourly versions were identical)

Below you will find a list of statements. Please indicate how true each statement is for you by selecting the relevant number.

Today / Within n the last hour or so:

	Not at all					Some-what					Very much
OPEN / CLOSED											
1. I tried to distract myself from thinking about upsetting things	0	1	2	3	4	5	6	7	8	9	10
2. I kept myself busy so I didn't notice my thoughts or feelings.	0	1	2	3	4	5	6	7	8	9	10
3. I struggled to control my thoughts or feelings	0	1	2	3	4	5	6	7	8	9	10
4. I put a lot of effort into making my thoughts or feelings stop or go away*	0	1	2	3	4	5	6	7	8	9	10
5. I worked hard to stop upsetting feelings	0	1	2	3	4	5	6	7	8	9	10
6. I pushed away thoughts and feelings that I didn't like.	0	1	2	3	4	5	6	7	8	9	10
7. I got upset with myself for having certain thoughts or feelings.	0	1	2	3	4	5	6	7	8	9	10
8. I got upset and bothered by my feelings or thoughts	0	1	2	3	4	5	6	7	8	9	10

9. I thought that some of my feelings are bad and that I shouldn't have them.	0	1	2	3	4	5	6	7	8	9	10
10. I told myself that I shouldn't have certain thoughts or feelings	0	1	2	3	4	5	6	7	8	9	10
11. I stopped myself from having feelings that I didn't like.	0	1	2	3	4	5	6	7	8	9	10
12. I went out of my way to avoid situations that might bring difficult thoughts, feelings, or sensations in my body											
AWARE / UNAWARE											
13. I thought about things that happened in the past or worried about the future, instead of what was happening at the time.	0	1	2	3	4	5	6	7	8	9	10
14. I rushed through activities that I care about without really paying attention to them	0	1	2	3	4	5	6	7	8	9	10
15. Even when doing things that mattered to me, I found myself doing them without paying attention	0	1	2	3	4	5	6	7	8	9	10
16. I found it difficult to stay focused on what was happening in the present	0	1	2	3	4	5	6	7	8	9	10
17. I did jobs or tasks automatically, without being aware of what I was doing	0	1	2	3	4	5	6	7	8	9	10
ENGAGED / DISENGAGED											

18. I stopped doing things that were important to me when I felt bad.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
19. My worries and fears got in the way of doing the things that mattered to me.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
20. I got so wrapped up in what I was thinking or feeling that I couldn't do the things that mattered to me.	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
21. I didn't act in ways that fit with how I want to live my life	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
22. Even when an activity was important to me, I didn't do it because I thought it would upset me	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Appendix H

Feedback from adult and adolescent participants regarding the initial 22-items for the new momentary Psychological Flexibility "Open, Aware, Engaged" questionnaire (face validity)

Person (LTC; adult or adolescent)	Rachel Sawyer (Inflammatory Bowel Disease; adult)	Alison Potts (TBI and carer for mother with psychosis; adult)	Sarah Bittlestone (Multiple Sclerosis; adult)	Maisie Stewart (Endocrine disorder; adolescent)	Elom Nyonator (Chronic constipation; adolescent)
Ranking of items					
1 (most important)	21	3	4	18	3
2	15	16	16	12	7
3	20	7	17	22	12
4	16	13	18	20	10
5	14	17	20	19	16
6	19	19	21	17	17
7	17	1	1	15	18
8	18	10	6	3	21
9	22	12	7	4	15
10	13	19 (repeat)	19	6	13
11	7	4	3	14	14
12	3	9	8	8	22
13	8	15	10	7	1
14	12	22	**11**	10	2

15	9	18	12	13	19
16	6	14	13	**11**	20
17	5	**11**	14	5	4
18	4	8	22	9	6
19	**11**	20	15	2	5
20	1	5	9	16	8
21	10	6	2	21	9
22 (least important)	2	21	5	1	**11**

Appendix I
Confirmatory Factor Analyses Results for Established Measures at Baseline

Measure	Estimator	*n*	Number of factors tested	Item	STDY Estimate	SE	R^2	SE	Absolute model fit indices (goodness of fit value cut-offs)				
									RMSEA (<.06)	TLI (>.95)	CFI (>.95)	SRMR (<.08)	WRMR (>1)
MARS-5	MLR	545	1: Adherence	1	.42	.04	.17	.04	.11	.85	.92	.04*	NA
				2	.50	.04	.25	.05					
				3	.78	.03	.61	.05					
				4	.82	.03	.68	.05					
				5	.74	.03	.55	.05					
AAQ-II	WLSMV	555	1: PF	1	.82	.01	.68	.02	.20	.96*	.97*	NA	1.57*
				2	.90	<.01	.81	.01					
				3	.90	<.01	.81	.01					

				4	.88	.01	.78	.02					
				5	.87	.01	.76	.01					
				6	.85	.01	.72	.02					
				7	.87	.01	.75	.02					
CompACT	WLSMV	478	1: OE	2	.46	.03	.21	.03	.15	.72	.75	NA	2.75*
				4	.54	.03	.29	.03					
				6	.79	.02	.63	.03					
				8	.56	.03	.31	.03					
				11	.77	.02	.59	.03					
				13	.67	.02	.45	.03					
				15	.50	.03	.25	.03					
				18	.71	.02	.51	.03					
				20	.63	.02	.40	.03					
				22	.72	.02	.52	.03					
			2: BA	3	.68	.02	.46	.03					
				9	.83	.02	.69	.03					

				12	.80	.02	.65	.03					
				16	.65	.02	.42	.03					
				19	.65	.02	.42	.03					
			3: VA	1	.73	.02	.54	.04					
				5	.72	.02	.52	.03					
				7	.57	.03	.33	.03					
				10	.36	.04	.13	.02					
				14	.52	.03	.27	.03					
				17	.79	.02	.62	.03					
				21	.50	.03	.25	.03					
				23	-.18	.03	.03	.01					
CompACT	WLSMV	478	1: PF	2	.44	.03	.20	.03	.16	.68	.71	NA	2.96*
				4	.52	.03	.27	.03					
				6	.77	.02	.60	.03					
				8	.54	.03	.30	.03					
				11	.75	.02	.56	.03					

13	.65	.02	.42	.03
15	.49	.03	.24	.03
18	.69	.02	.48	.03
20	.61	.02	.38	.03
22	.70	.02	.49	.03
3	.62	.02	.38	.03
9	.74	.02	.55	.03
12	.74	.02	.53	.03
16	.58	.02	.34	.03
19	.59	.02	.34	.03
1	.65	.02	.42	.03
5	.62	.02	.39	.03
7	.49	.03	.24	.03
10	.28	.03	.07	.02
14	.44	.03	.19	.02
17	.68	.02	.47	.03

				21	.43	.03	.18	.03					
				23	-.21	.03	.04	.01					
WSAS	WLSMV	551	1: Functioning	1	.86	.01	.73	.01	.15	.99*	.96*	NA	.62
				2	.92	<.01	.85	.01					
				3	.92	<.01	.85	.01					
				4	.90	<.01	.81	.01					
				5	.82	.01	.67	.02					
PHQ-8	WLSMV	543	1: Depression	1	.85	.01	.72	.02	.11	.95*	.97*	NA	1.33*
				2	.81	.02	.66	.03					
				3	.68	.02	.46	.03					
				4	.79	.02	.62	.03					
				5	.80	.02	.64	.03					
				6	.83	.02	.70	.03					
				7	.68	.02	.46	.04					
				8	.59	.03	.35	.04					
GAD-7	WLSMV	555	1: Anxiety	1	.89	.01	.80	.020	.12	.98*	.99*	NA	1.08*

2	.96	<.01	.93	.013
3	.94	<.01	.90	.014
4	.83	.01	.69	.028
5	.67	.03	.45	.040
6	.76	.02	.58	.034
7	.83	.01	.69	.032

STDY estimate (Mplus standardises estimates using the variances of observed outcome and latent variables only).
Good fit indices: CFI (Comparative Fit Index); RMSEA (Root Mean Square Error of Approximation); SRMR (Standardized Root Mean Square Residual) ; TLI (Tucker Lewis Index); WRMR (Weighted Root Mean Square Residual).
Established measures: AAQ-II (Acceptance and Action Questionnaire II); CompACT (Comprehensive assessment of Acceptance and Commitment Therapy processes); BA (CompACT Behavioral Awareness subscale); OE (CompACT Openness to Experience subscale); VA (CompACT Valued Action subscale); PHQ-8 total (Patient Health Questionnaire 8-items), GAD-7 (Generalised Anxiety Disorder scale 7-items); WSAS (Work and Social Adjustment Scale).

Appendix J
Primary LTC types of the baseline sample across MARS-5 cut-offs (*n*=695)

	Adherent (according to MARS-5 cut-off) (*n*=80, 11.5%)	Non-adherent (according to MARS-5 cut-off) (*n*=617, 88.5%)	*p* value
Parkinson's Disease *vs.*	36 (45.0)	250 (40.6)	.45[1]
All other LTCs (%)	44 (55.0)	366 (59.4)	
Type of LTC by ICD-11 disease category			
Allergies (incl. vasculitis)	1 (1.3)	3 (0.5)	
Autoimmune	20 (25.0)	157 (25.4)	
Ankylosing spondylitis*	0	1 (0.2)	
Arthritis	0	4 (0.6)	
Autoimmune polyendocrine syndromes	0	2 (0.3)	
Coeliac disease	0	1 (0.2)	
Hashimoto's thyroiditis	5 (6.3)	13 (2.1)	
Inflammatory bowel disease	0	1 (0.2)	
Lupus erythematosus	2 (2.5)	45 (7.3)	
Microscopic Colitis	0	1 (0.2)	
Mucous membrane pemphigoid	0	1 (0.2)	
Rheumatoid arthritis, other inflammatory polyarthropathies and systematic connective tissue	1 (1.3)	47 (7.6)	
Thyroid disease	8 (10.0)	29 (4.7)	
Ulcerative colitis	1 (1.3)	8 (1.3)	
*Also, disease of the musculoskeletal system and connective tissue			
Birth defect	0	2 (0.3)	

Spina bifida	0	1 (0.2)
Williams syndrome	0	1 (0.2)
Cancers (all types)	3 (3.8)	9 (1.5)
Cardiovascular/Circulatory	7 (8.8)	39 (6.3)
Atrial fibrillation	1 (1.3)	0
Coronary heart disease	0	3 (0.5)
Heart failure	1 (1.3)	1 (0.2)
Hypertension	2 (2.5)	3 (0.5)
Postural orthostatic tachycardia syndrome	2 (2.5)	32 (5.2)
Sick sinus syndrome	1 (1.3)	0
Endocrine	0	18 (2.9)
Addison's disease	0	1 (0.2)
Diabetes Type I*	0	15 (2.4)
Diabetes Type II*	0	2 (0.3)
*Also, metabolic		
Genitourinary		
Endometriosis	0	2 (.03)
Hereditary	0	29 (4.7)
Charcot-Marie-Tooth disease*	0	4 (0.7)
Cystic fibrosis	0	1 (0.2)
Ehlers–Danlos** syndrome (various types)	0	20 (2.9)
Eczema	0	2 (0.3)
Myotonia congenita	0	1 (0.2)
Panhypopituitarism***	0	1 (0.2)
*Also, degenerative; **metabolic; ***endocrine		
Immunodeficiency	6 (7.5)	11 (1.8)
Common variable immunodeficiency	0	1 (0.2)
HIV/AIDS	6 (7.5)	10 (1.6)
Infectious		
Bronchiectasis	0	2 (.03)
Inflammatory	1(1.3)	18 (2.9)

Antiphospholipid syndrome	0	1 (0.2)
Asthma	0	8 (1.3)
Behçet's disease	0	2 (0.3)
Chronic obstructive pulmonary disease	1 (1.3)	1 (0.2)
Myositis (polymyositis and dermatomyositis)	0	1 (0.2)
Periodontal disease	0	1 (0.2)
Psoriasis	0	3 (0.5)
Ulcers	0	1 (0.2)
Neurodegenerative	41 (51.3)	263 (42.6)
Epilepsy	1 (1.3)	7 (1.1)
Multiple sclerosis*	4 (5.0)	6 (1.0)
Parkinson’s disease	36 (45.0)	250 (40.5)
*Also, autoimmune and inflammatory		
Neurology other	0	1 (0.2)
Myoclonus Dystonia		
Trauma/injury	0	6 (0.9)
Brain injury	0	3 (.05)
Cerebral palsy	0	2 (.3)
Progressive supranuclear palsy	0	1 (0.2)
Other conditions	1 (1.3)	55 (8.9)
Bile acid diarrhea	0	1 (0.2)
Chronic fatigue syndrome/Myalgic encephalomyelitis	0	7 (1.1)
Chronic pain	0	3 (0.5)
Fibromyalgia	0	9 (1.5)
Gastroesophageal Reflux Disease	0	1 (0.2)
Kidney disease	1 (1.3)	1 (0.2)
Migraine	0	32 (5.2)
Peripheral neuropathy	0	1 (0.2)
Bile acid diarrhea	0	1 (0.2)

LTC not reported	0	2 (.3)

Adherence measures: ICD-11 (WHO International Classification of Diseases, 11th Revision (ICD-11) MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent').
Statistical analyses: $^{1}\chi^{2}$ (1)=.57, *p*=45

Appendix K
Primary LTC types of the follow-up sample across MARS-5 cut-offs (n=336)

	Adherent (according to MARS-5 cut-off) (*n*=50, 14.9%)	Non-adherent (according to MARS-5 cut-off) (*n*=285, 81.5%)	*p* value
Parkinson's Disease *vs.*	19 (38.0)	138 (48.4)	.17[1]
All other LTCs (%)	31 (62.0)	147 (51.6)	
Type of LTC by ICD-11 disease category			
Allergies	0	2 (.07)	
Vasculitis			
Autoimmune	10 (20.4)	71 (24.7)	
Arthritis	0	1 (.03)	
Autoimmune polyendocrine syndromes	0	1 (0.3)	
Coeliac disease	0	1 (0.3)	
Hashimoto's thyroiditis	3 (6.1)	10 (3.5)	
Inflammatory bowel disease	1 (2.0)	3 (1.0)	
Lupus erythematosus	3 (6.1)	20 (7.0)	
Rheumatoid arthritis, other inflammatory polyarthropathies and systematic connective tissue	0	20 (7.0)	
Thyroid disease	2 (4.1)	12 (4.2)	
Ulcerative colitis	1 (2.0)	3 (1.0)	
*Also, disease of the musculoskeletal system and connective tissue			
Birth defect	0	1 (0.3)	
Spina bifida			
Cancers (all types)	2 (4.1)	3 (1.0)	
Cardiovascular/Circulatory	6 (12.2)	12 (4.2)	
Atrial fibrillation	1 (2.0)	0	
Coronary heart disease	0	1 (0.3)	

Heart failure	0	2 (0.7)
Hypertension	3 (6.1)	0
Postural orthostatic tachycardia syndrome	1 (2.0)	9 (3.1)
Sick sinus syndrome	1 (2.0)	0
Endocrine	1 (2.0)	7 (2.4)
Addison's disease	0	1 (0.3)
Diabetes Type I*	1 (2.0)	5 (1.7)
Diabetes Type II*	0	1 (0.3)
*Also, metabolic		
Genitourinary	0	1 (0.3)
Endometriosis		
Hereditary	1 (2.0)	9 (3.1)
Charcot-Marie-Tooth disease*	1 (2.0)	2 (0.7)
Ehlers–Danlos** syndrome (various types)	0	6 (2.1)
Panhypopituitarism***	0	1 (0.3)
*Also, degenerative; **metabolic; ***endocrine		
Immunodeficiency	4 (8.2)	7 (2.4)
Common variable immunodeficiency	0	1 (0.3)
HIV/AIDS	4 (8.2)	6 (2.1)
Infectious	1 (2.0)	0
Bronchiectasis		
Inflammatory	1 (2.0)	11 (3.8)
Asthma	0	5 (1.7)
Behçet's disease	0	1 (0.3)
Chronic obstructive pulmonary disease	1 (2.0)	1 (0.3)
Periodontal disease	0	1 (0.3)
Psoriasis	0	2 (0.7)
Ulcers	0	1 (0.3)
Neurodegenerative	22 (44.9)	142 (49.5)
Epilepsy	1 (2.0)	0
Multiple sclerosis*	3 (6.1)	3 (1.0)

Parkinson's disease	18 (36.7)	139 (48.4)
*Also, autoimmune and inflammatory		
Trauma/injury	0	2 (0.7)
Brain injury	0	2 (0.7)
Other conditions	1 (2.0)	18 (6.3)
Chronic fatigue syndrome/Myalgic encephalomyelitis	0	1 (0.3)
Chronic pain	0	1 (0.3)
Fibromyalgia	0	3 (1.0)
Gastroesophageal Reflux Disease	0	1 (0.3)
Kidney disease	1 (2.0)	0
Migraine	0	11 (3.8)
Peripheral neuropathy	0	1 (0.3)
LTC not reported	0	1 (.03)

Adherence measures: ICD-11 (WHO International Classification of Diseases, 11th Revision (ICD-11) MARS-5 (Medication Adherence Rating Scale five items total score: 25='adherent' and <25 'non-adherent').
Statistical analyses: $^{1}\chi^{2}$ (1)=.62, p=.17

Appendix L
Email communication from Professor Rob Horne regarding distribution of MAR-S 5 data

Hi Anthony,

Sorry for the radio licence my end
I have been meaning to contact you and to support your work with MARS.
I disagree with Durand et al on this point. The argument for using continuous data above dichotomised is a good general principle as dichotomising loses information. However, in the case of self-report adherence scores I think we. need to take a more pragmatic approach. The data is typically highly negatively skewed and transformations do not solve the problem. From a pragmatic point of view, we are often interested in separating samples into high vs low adherence and can do this on the basis of frequency distribution of scale scores within that sample.

Of course its better if we don't have to do this as a continuous measure of degrees of adherence is better. BUT and it's a big one, self-repots are flawed and do not provide the degree of accuracy and reliability to justify such a 'purist' approach.

Would it be helpful to arrange a telcon to discusses your data and these issues in more detail?

With best wishes
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